

CLINICAL REVIEW

Clinical Review Section

were 12-17 years of age. There were 5 patients in the desloratadine group and 8 patients in the placebo group who were 65 years of age or older (v44, p59).

The primary efficacy variable was the average AM/PM instantaneous (point-in-time, NOW) total symptom score (TSS), excluding nasal congestion in terms of change from baseline over 4 weeks of treatment compared to the change seen with placebo. No statistically significant difference was seen between the group that received desloratadine and the group that received placebo over the four weeks of treatment or at any other time point, i.e. days 1, 2, 3, 4 and periods days 1-8, 9-15, 16-22 or 23-29 (v44, p61). There was no significant difference in the results dependent on gender, age or race. There was no significant difference in interpretation of the data based on analysis of data from the EES of patients (V44, p61, t11). It should be noted that the baseline scores were statistically significantly different between the two treatment groups ($p = 0.002$). The mean score for the desloratadine group was 10.28 and the mean score for the placebo group was 11. Since the placebo group had more severe symptoms, it is possible that these patients had more room for improvement, contributing to the lack of any statistically significant difference between the two treatment groups after treatment. Whether this imbalance contributed to the failure to show efficacy for desloratadine in this study or not, this study does not support the efficacy of desloratadine for the treatment of PAR.

In terms of other efficacy variables, there was no efficacy demonstrated for desloratadine for reflective AM/PM TSS, total nasal symptom score (TNSS), either NOW or reflective, total non-nasal symptom score (TNNSS), either NOW or reflective, TSS AM or PM, either NOW or reflective or for any specific symptom either NOW or reflective. Although there were too few patients 12-17 years of age and 85 years of age and older to reach any conclusion about the data in these subsets of patients, there was significantly greater improvement after administration of desloratadine in these age groups than after administration of placebo (32% and 34% improvement, respectively compared to 17% and 3% improvement, respectively)(v44, p155, 157, t1,3). Of those centers with at least 5

CLINICAL REVIEW

Clinical Review Section

patients, desloratadine was more effective at 12 and placebo was more effective at 16 centers.

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CLINICAL REVIEW

Clinical Review Section

Mean changes based on ITT population

Parameter	DCL change from baseline	placebo change from baseline	DCL percent change	p value
TSS AM/PM NOW * days 1-29	- 3.3	- 3.5	31.1%	0.49
TSS AM/PM NOW # days 1-29	- 3.6	- 3.9	29.2%	0.39
TSS AM/PM reflect * days 1-29	- 3.9	- 4.0	35.4%	0.87
TSS AM/PM reflect # days 1-29	- 4.3	- 4.3	33.2%	0.73
TSS AM NOW * days 1-29	- 3.1	- 3.4	28.8%	0.34
TSS AM reflective + days 1-29	- 3.8	- 3.9	34.3%	0.88
TNSS AM/PM NOW + days 1-29	- 2.0	- 2.1	27.6%	0.63
TNSS AM/PM reflective + days 1- 29	- 2.4	- 2.3	33.2%	0.88
TNSS AM/PM NOW # days 1-29	- 2.3	- 2.4	26.4%	0.45
TNSS AM/PM # reflective days 1-29	- 2.7	- 2.7	30.6%	0.86
TNSS AM/PM NOW days 1-29	- 1.3	- 1.4	31.3%	0.41
TNSS AM/PM reflective days 1-29	- 1.6	- 1.6	37.5%	0.58
Rhinorrhea AM/PM NOW days 2-29	- 0.47	- 0.51	22%	0.35
Nasal congest AM/ PM NOW days 2-29	- 0.29	- 0.36	12%	0.083 favoring placebo
Nasal itch AM/PM NOW days 2-29	- 0.58	- 0.56	34%	0.70
Sneezing AM/PM NOW days 2-29	- 0.50	- 0.49	31%	0.83
Itch eyes AM/PM NOW days 2-29	- 0.49	- 0.52	28%	0.56
Tearing eyes AM/ PM NOW days 2-29	- 0.40	- 0.47	20%	0.13
PND AM/PM NOW days 2-29	- 0.44	- 0.50	22%	0.19
Itch ears AM/PM NOW days 2-29	- 0.44	- 0.45	32%	0.95
Overall condition at endpoint	- 0.60	- 0.59	-----	0.71
Therapeutic response at endpoint	3.31	3.47	-----	< 0.001

- excluding nasal congestion # including nasal congestion

CLINICAL REVIEW

Clinical Review Section

efficacy conclusion: This study failed to show the efficacy of desloratadine in the treatment of PAR, based on the primary efficacy outcome variable or any other objective assessment.

Safety:

Adverse events: Of adverse events that occurred in 2% or more of patients in either treatment group, there was a 2% or greater incidence in the desloratadine group compared to the placebo group of dryness of the mouth (4%) and dizziness (2.3%)(v44, p80, t21), and only the dryness of the mouth was considered treatment related. There were no treatment-related or severe adverse events that occurred significantly more in the desloratadine group than in the placebo group. A greater percentage of patients discontinued treatment because of adverse events in the placebo group than in the desloratadine group. There were no significant differences based on race, gender or age, although the difference in reports of dryness of the mouth, noted above, was driven by this occurrence in females.

Laboratory tests: There was no median change in any laboratory value in the group that received desloratadine that was clinically significantly different from baseline or from the placebo group (v46, p687-693) in terms of the overall study population. Nor was there any significant difference in the percentage of patients who shifted from normal at baseline to significantly abnormal after treatment for any parameter (v46, p765-69). There was a significant median decrease in platelets in the desloratadine group (31)(v46, p708) compared to the placebo group, in patients 65 years or older (n = 4). There were no clinically significant differences based on gender or race. No significant changes from a normal value at baseline to a value outside the normal reference range was seen for any laboratory test in the desloratadine group that was not also seen in the placebo group. For example, one patient who received desloratadine had an increase in SGPT from 34 U/L at baseline to 298 U/L after treatment, associated with an increase in SGOT from 25 U/L to 117 U/L. On the other hand, one patient who received placebo had an increase in SGOT from 22 U/L to 199 U/L after treatment. There was one placebo patient who had a baseline SGOT of 226 U/L and SGPT of 606 U/L (v44, p 95, t28). The sponsor should be asked to explain why

CLINICAL REVIEW

Clinical Review Section

this patient was included in the study and whether there were other obvious examples of such dismal failure of study adherence by investigators, that could raise questions about the validity of the safety data from this study.

Vital signs: There were no significant mean changes in systolic or diastolic blood pressure, pulse rate or respiration after treatment with desloratadine overall. There were no significant differences based on gender, age or race, with the exception that in Hispanic patients, there was an increase from 23% to 25% of patients who had a systolic blood pressure less than 100 mm Hg compared with a decrease from 26% to 18% in patients who received placebo (v46, p814). In addition, there were 6 Caucasians who had a pulse rate < 50 bpm after treatment with desloratadine (2 patients at baseline), compared with no placebo patients (2 patients at baseline)(v46m p823). The clinical significance, if any, of these findings is unclear.

ECGs: Using Bazett's correction, there was mean increase of 2.4 msec in the group that received desloratadine compared to a mean increase of 0.8 msec in the group that received placebo (v46, p872). The biggest difference in mean QTc interval change based on Bazett's correction was in African-American patients (n = 14) where there was a mean increase of 7.2 msec in the group that received desloratadine compared to an increase of 4.8 msec in the placebo group (v46, p875). The percentage of patients in the active treatment and placebo groups who had an increase in the QTc interval of 15% or more was comparable using both the Bazett and the Fridericia correction. (v46, p877). A QTc interval was considered normal if it was 430 msec or less in males and 450 msec or less in females. There were 3 patients in the desloratadine group and 2 patients in the placebo group who had a change from baseline of > 60 msec, all of whom had a normal value at baseline (v46, p881).

☛ **Safety conclusion:** Based on the parameters that were performed in this study, desloratadine has been shown to be safe for administration to patients with PAR.

2. Studies evaluating Clarinex for rhinitis with concomitant asthma:

CLINICAL REVIEW

Clinical Review Section

- a. **Study 214:** 24 centers; 37 centers when combined with study 216; The centers in study 216 were distributed to studies 214 and 215 as indicated in the amendment of 24 November 1999. Studies 214, 215, and 216 were identically designed studies. Because of low enrollment and revised sample size requirements the 3 studies were condensed into 2 studies, 214 and 215. After discussion with Biostatistics, this was performed in an acceptable manner.

Number of patients: 501; 168 received DCL, 170 received montelukast and 163 received placebo; 166 DCL patients and 150 placebo patients were included in the ITT analysis while 156 of the DCL patients and 153 of the placebo patients were included in the efficacy analysis

Age range: 15-75 years; there were 9 patients 65 years of age or older, 3 in the desloratadine group, 4 in the placebo group and 3 in the montelukast group.

Patient population: SAR and asthma; across treatments, 62-70% of patients in the study were female and 77-79% were Caucasian. There was no significant difference in gender or race in the treatment groups. The duration of SAR varied from 2-73 years across treatment groups, while the duration of asthma varied from < 1-73 years. There was no significant difference between treatment groups in regard to either the duration of SAR or the duration of asthma.

Study design: multicenter, randomized, double-blind, placebo controlled, active treatment controlled parallel study

Drug administration: 5 mg DCL once daily; montelukast 10 mg once daily

Periods of study: randomized treatment once daily for 4 weeks

Parameters evaluated: There were co-primary efficacy variables; average reflective AM/PM TSS for SAR change from baseline over the first two weeks of the study compared to placebo; and FEV-1 change from baseline over the 4 weeks of the study compared to placebo. Secondary variables included total asthma symptom scores and nasal, non-nasal and individual symptoms associated with SAR on a reflective and point-in-time assessment by the patient; QOL, overall condition of SAR and asthma and response to therapy; safety variables included AEs, 12 lead ECGs, VS, and laboratory tests;

CLINICAL REVIEW

Clinical Review Section

evaluation occurred at screening, baseline and after 7, 14, 21, and 28 days of treatment.

Study results:

Database: Of the patients who received placebo, 9% discontinued because of treatment failure, compared to 4% of patients treated with DCL and 2% of patients treated with montelukast.

Discontinuation because of adverse event was 4% in the placebo group and 2% in each of the active treatment groups. There were 6% of the DCL group, compared to 6% in the montelukast group and 4% in the placebo group that had protocol deviations that resulted in their exclusion from the efficacy-evaluable subset of patients. A comparable percent of patients in each of the three treatment groups did not meet the entrance criteria for the study but there were only 6 patients, 3 in the SAR efficacy-evaluable and 3 in the asthma efficacy-evaluable population, all in the DCL group, that used unacceptable concomitant medications (v27, p65-67, t8-10). None of these differences are likely to have significantly influenced the study results.

Two data sets were analyzed; an intent-to-treat population and an efficacy-evaluable population. The intent-to-treat population included all patients who were randomized, while the efficacy population included all patients who were randomized and met the eligibility criteria and could be evaluated based on inclusion/exclusion criteria, compliance and concomitant medication use. Of the patients evaluated for SAR, there were 168, 170, and 163 patients receiving desloratadine, montelukast and placebo, respectively in the intent-to-treat population and 156, 158, and 153 patients receiving desloratadine, montelukast and placebo, respectively in the efficacy subset. The distribution of patients was not significantly different in terms of evaluation of patients for asthma (v27, p67-70, t11-13).

In the efficacy subset, all patients were at least 80% compliant.

CLINICAL REVIEW

Clinical Review Section

Efficacy

The primary efficacy variable for SAR was the change from baseline in total reflective symptom scores for days 1-15 compared to placebo. The primary efficacy variable for asthma was the change from baseline in FEV-1 averaged over weeks 1-4 compared to placebo.

In terms of total symptom scores for SAR, there was a statistically significantly greater mean reduction in symptoms seen in desloratadine group than in the placebo group at all time points based on reflective or point-in-time assessment, except for the last week of treatment ($p = 0.12$). This statistically significant difference began as early as the first day of treatment using the intent-to-treat population (see table below)(v27, p72, t14).

The lack of any significant difference in terms of mean total symptom scores based on either reflective or point-in-time assessment between desloratadine and placebo during days 23-29 of the study was due to the significant improvement of patients receiving placebo during that time period, i.e. due to a greater placebo effect during the last week of treatment, which could have coincided with the end of the pollen season. The subset of patients 12-17 years of age ($N = 13$) had more improvement relative to placebo because there was less placebo effect. Patients 65 years of age and older ($N = 4$) also appeared to show more improvement than younger patients (v27, p 264-266) . The small number of patients in each of these subgroups does not allow any clinically meaningful conclusions to be drawn from these databases. There was no statistically significant difference between desloratadine and montelukast at any time point and the montelukast group did significantly better than the placebo group at all time points. No significant differences were seen in response to treatment based on gender, age, or race (v27, p. 267-270).

In terms of mean total AM/PM reflective nasal symptom scores for SAR including nasal congestion (v27, p310) (see table below), improvement after administration of desloratadine was statistically significantly greater than placebo for the first two weeks of the study ($p < 0.001$) but not for the last two weeks of the study ($p = 0.14$). This

CLINICAL REVIEW

Clinical Review Section

was due to a significantly greater placebo effect during the last two weeks of the study. The same effect was seen to a lesser degree in evaluating total non-nasal symptom scores, i.e. mean improvement in the group that received desloratadine was not statistically significantly different than was seen in the placebo group during the last week of the study ($p = 0.08$)(v27, p314). In regard to means for individual nasal symptoms, there was no statistically significant difference between desloratadine and placebo for any nasal symptom during the last two weeks of treatment; rhinorrhea ($p = 0.14$), nasal congestion ($p = 0.28$), nasal itching ($p = 0.25$), sneezing ($p = 0.17$)(v27, p317-322).

In terms of change in mean FEV-1, there was no statistically significant difference noted between either desloratadine and placebo or desloratadine and montelukast (v27, p74, t15). No significant differences were seen in response to treatment based on gender, age, or race. There was a statistically significantly greater reduction in mean total and individual asthma symptoms compared to placebo, except for dyspnea (see table below)(v27, p336-341). As with upper respiratory symptoms, significant improvement was only seen for the first two weeks of the study.

The clinical significance of the differences in mean symptom improvement of SAR and asthma in the desloratadine and the placebo groups is open to question. In terms of individual nasal symptoms, mean improvement for the desloratadine group compared to the placebo group was 0.24 greater for sneezing, 0.25 greater for nasal itching, 0.18 greater for nasal congestion, and 0.20 greater for rhinorrhea during the first two weeks of the study (days 1-15), when the maximum effect of desloratadine was seen (v27, p 316-321). These symptoms were recorded using a categorical scale of 0-3. The results are consistent with the change seen in mean total symptom scores, where there was a 1.92 greater improvement in mean total symptom score after desloratadine than was seen after placebo. Since there were 8 symptoms included in the total symptom score, there is an average mean improvement in each symptom of 0.24. In this reviewer's opinion, this amount of improvement is not clinically significant.

CLINICAL REVIEW

Clinical Review Section

There was no significant mean difference in improvement of lower respiratory symptoms in the group that received desloratadine and the group that received montelukast, except for dyspnea where there was significantly more improvement with montelukast than with desloratadine (v27, p336-341). Mean AM and PM PEFr and other pulmonary function tests averaged over 4 weeks of treatment showed no statistically significant difference in change from baseline for the desloratadine and the placebo groups. There was no statistically significant difference between the desloratadine and the placebo groups in terms of overall condition of asthma ($p = 0.4$), therapeutic response of asthma ($p = 0.3$), or the total domain of the asthma-specific QOL assessment ($p = 0.1$).

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CLINICAL REVIEW

Clinical Review Section

Parameter	DCL change from baseline	placebo change from baseline	DCL percent change	p value
TSS AM/PM NOW * Days 1-15	- 3.7	- 2.2	29.3%	< 0.001
TSS AM/PM NOW # Days 1-15	- 4.2	- 2.5	28.2%	< 0.001
TSS AMPM reflect * Days 1-15	- 4.3	- 2.6	32.6%	< 0.001
TSS AMPM reflect # Days 1-15	- 4.9	- 3.0	31.3%	< 0.001
TSS AM/PM reflect Day 1	- 3.1	- 1.1	20.6%	< 0.001
TSS AM NOW * Days 2-15	- 3.9	- 2.2	27%	< 0.001
TSS AM NOW Day 2	- 2.6	- 0.9	19%	< 0.001
TNSS reflect Days 1-15	- 2.3	- 1.4	27.5%	< 0.001
TNSS reflect Day 1	- 1.5	- 0.7	18%	0.003
TNNSS reflect Days 1-15	- 2.57	- 1.54	35%	< 0.001
TNSS AM/PM NOW Days 1-15	- 1.95	- 1.25	35%	0.003
TNNSS AM/PM NOW days 1-15	- 2.19	- 1.25	31%	< 0.001
Nasal congestion reflect days 1-15	- 0.56	- 0.38	23.5%	0.006
Rhinorrhea AM/PM reflect – days 1-15	- 0.55	- 0.35	24%	0.003
Nasal itching reflect days 1-15	- 0.61	- 0.36	30%	< 0.001
Sneezing AM/PM reflect days 1-15	- 0.59	- 0.35	27%	< 0.001
Itching eyes Reflective days 1-15	- 0.69	- 0.42	34%	< 0.001
Tearing eyes Reflective days 1-15	- 0.66	- 0.41	36%	< 0.001
Reddness eyes Reflective days 1-15	- 0.64	- 0.35	34%	< 0.001
Itching ears/palate Reflective days 1-15	- 0.58	- 0.37	34%	0.004
FEV-1; weeks 1-4	0.02	0.02	1%	0.91
TASS reflective Days 1-15	- 1.35	- 0.94	20%	0.02
Wheezing reflective Days 1-15	- 0.48	- 0.33	20%	0.03
Cough reflective days 1-15	- 0.42	- 0.27	12%	0.03
Dyspnea reflective days 1-15	- 0.46	- 0.34	20%	0.10

CLINICAL REVIEW

Clinical Review Section

Beta agonist use days 1-15	- 0.59	- 0.18	15%	0.03
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- excluding nasal congestion

including nasal congestion

NOW = point-in-time at the end of the dosing interval for days 2-15

TSS = total symptom score which includes nasal and non-nasal symptoms

AM/PM reflect = average of AM and PM 12 hour reflective scores

TNSS = total nasal symptom score

TNNSS = total non-nasal symptom score

TASS = total asthma symptom score

There was no significant improvement in overall condition of SAR evaluated jointly by the patient and the investigator, after administration of desloratadine in comparison with placebo at any time during the 4 weeks of treatment ($p = 0.192$). The group that received montelukast did not have any significantly different response than the group that received desloratadine ($p = 0.7$). There was no significant improvement in therapeutic response of SAR evaluated jointly by the patient and the investigator, after administration of desloratadine in comparison with placebo at any time during the 4 weeks of treatment ($p = 0.1$). The group that received montelukast showed no statistically significant difference from the group that received desloratadine ($p = 0.07$). Evaluation of overall QOL for SAR showed more improvement after administration of desloratadine than was seen after administration of placebo ($p = 0.04$), although eye symptoms after desloratadine were not statistically significantly different from placebo ($p = 0.09$).

Overall, in terms of efficacy, based on the data from this study:

1. A dose of 5 mg of desloratadine was significantly more efficacious than placebo in reducing symptoms of SAR, when analyzed from both a reflective and point-in-time standpoint. Significant improvement was seen as early as the first day of treatment for total symptoms, nasal symptoms, non-nasal symptoms and all individual symptoms except for nasal congestion. The effectiveness of this dose of desloratadine was demonstrated over the entire treatment interval based on scores at the end

CLINICAL REVIEW

Clinical Review Section

of the dosing interval that were significantly lower than were seen after placebo administration.

2. A dose of 5 mg of desloratadine produced mixed results in terms of its effect on the lower respiratory tract. It is not possible to make a claim for the efficacy of desloratadine in the treatment of asthma because there was not a significant effect on pulmonary function and change from baseline in FEV-1 was the primary efficacy variable. On the other hand, except for dyspnea, significantly greater improvement was seen in the desloratadine group in terms of total asthma symptoms, wheezing, cough and beta agonist use. These results are consistent with other data described in the literature that demonstrate an effect of antihistamines on lower respiratory symptoms without an effect on pulmonary function

Safety: 97% of the patients who were randomized to receive desloratadine in this study received desloratadine for at least 2 weeks. 92% received desloratadine for at least 4 weeks and 67% received desloratadine for 5 weeks.

Adverse Events:

The overall incidence of adverse events was 37% in the DCL group, 39% in the montelukast group and 36% in the placebo group (v27, p 105). There were 12 patients who discontinued treatment because of adverse events, 3 in the desloratadine group. Fatigue, headache and diarrhea were seen slightly more in the desloratadine group than in the placebo group (v27, p107, t34). The difference in the incidence of these adverse events was not clinically important. The incidence of adverse events was similar in males and females and there were not an adequate number of patients to reach any conclusions about adverse events in younger or older patients or in non-Caucasians. One patient, a 46 year old Hispanic woman, who received desloratadine developed chest pain one day after initiating treatment, considered possibly related to the study drug and was discontinued from the study (v27, p114-115, t38).

Treatment-related adverse events were reported by 16% of the DCL group, 12% of the montelukast group, and 14% of the placebo group. Fatigue was the only adverse event considered treatment-

CLINICAL REVIEW

Clinical Review Section

related that occurred more frequently in the desloratadine group than in the placebo group (v27, p109, t35).

Severe adverse events occurred in 9% of the DCL group, 4% of the montelukast group and 9% of the placebo group. There was no severe adverse event with a greater incidence in the desloratadine group than in the placebo group (v27, p111, t37).

Laboratory results: The sponsor defined a clinically significant result as a blood chemistry 2.6 times or greater the upper limit of the NRR, a hemoglobin concentration less than 9.4 g/dL, a platelet count less than 74,000/uL or a WBC of less than 2900/uL (v27, p118).

There were 2 patients, one in the desloratadine group and one in the placebo group who had SGOT and/or SGPT value within the normal reference range (NRR) at baseline who had an increase after treatment to a value above the NRR. The patient who received desloratadine was 28 year old Caucasian male whose SGPT was 27 U/L at baseline and increased to 239 U/L after treatment (N = 0-45U/L). Ten days after discontinuing treatment his SGPT was 51 U/L. The patient who received placebo was a 15 year old female whose SGPT was 17 U/L at baseline and increased to 348 U/L after treatment. Two weeks after discontinuing treatment, her SGPT was 36 U/L. She also had an increase in SGOT from 17 to 192 U/L which came down to 22 U/L two weeks after discontinuing treatment (v27, p119, t40). It is possible that a component of the drug product other than the active drug producing this increase in liver function enzymes. This could explain these findings in both the active treatment group and the placebo group.

Vital signs: There were no clinically significant mean changes in vital signs in any of the treatment groups. There were 6 patients who had a heart rate 90 bpm or greater after administration of desloratadine compared with one patient at baseline in this treatment group. In the montelukast group there were 6 patients at baseline and 5 after treatment and in the placebo group there were 4 patients at baseline and 6 after treatment who had a heart rate of this degree (v30, p1066). This difference from baseline in heart rate for the desloratadine group occurred predominantly among Caucasian

CLINICAL REVIEW

Clinical Review Section

women in the 18-65 year age group (v30, p1071). The clinical significance of this finding, if any, is unclear.

ECGs: There were no clinically significant changes noted on ECGs. There was a mean decrease in QTc interval in the group that received desloratadine of 1.5 msec using the Fridericia correction, compared with a mean decrease of 5.2 msec in the group that received placebo (v27, p123, t42). Of the patients that received desloratadine, 97% had a QTc interval within 10% of baseline and one patient had an increase between 10-15% of baseline. In the same group, the number of patients who had an mean increase in ventricular rate of at least 10% was comparable to the number of patients who had such an increase in the placebo and montelukast groups (v27, p 125, t43) There was an 8 msec mean increase in the QT interval and a 4 msec mean increase in the QTc interval in patients 12-17 years of age and a 4 msec mean increase in the QT interval and a 9 msec increase in the QTc interval (using Bazett's correction) in Hispanic patients after receiving desloratadine, whereas in other age and ethnic groups there was a mean decrease in the QT interval after receiving desloratadine (V30, p1103, 1109). The clinical significance of this finding, if any, is unclear. There were no patients who had a 15% or greater increase in the QTc interval (using either method of correction) after receiving desloratadine. There was one patient who had a prolonged QTc interval (defined as > 450 msec in males and > 470 msec in females) after receiving desloratadine.

Overall, the safety of desloratadine has been demonstrated in this study.

- b. Study 215: 32 centers; 22 centers from study 215 and 19 centers from study 216; the centers in study 216 were distributed to studies 214 and 215 as indicated in the amendment of 24 November 1999. Studies 214, 215 and 216 were identically designed studies. Because of low enrollment and revised sample size requirements, the 3 studies were condensed into 2 studies, 214, and 215. After discussion with Biostatistics, this was performed in an acceptable manner.**

CLINICAL REVIEW

Clinical Review Section

Number of patients: 423; 143 received DCL, 141, received montelukast and 139 received placebo; 140 of the DCL patients and 138 of the placebo patients were included in the ITT analysis while 136 of the DCL patients and 132 of the placebo patients were included in the efficacy analysis

Age range: 15-68 years

Patient population: SAR and asthma

Study design: multicenter (32 centers), randomized, double-blind, placebo-controlled, active treatment controlled, parallel study

Drug administration: DCL 5 mg once daily; montelukast 10 mg once daily

Periods of study: randomized treatment for 4 weeks

Parameters evaluated: There were co-primary outcome variables: average AM/PM TSS for SAR change from baseline over the first 2 weeks of the study compared to placebo; and FEV-1 change from baseline over the 4 weeks of the study compared to placebo; secondary variables included nasal, non-nasal and individual symptoms assessed by patient evaluation on a reflective and point-in-time basis; asthma symptom scores, QOL, overall condition of SAR and asthma and response to therapy; safety variables included AEs, Vs, 12 lead ECGs and lab tests; evaluation was made at screening, baseline and after 7, 14, 21 and 28 days of treatment.

Study results:

Efficacy: No statistically significant difference was demonstrated between desloratadine and montelukast at any time point during the 4 weeks of randomized treatment in regard to the primary outcome variable for SAR.

A statistically significant difference between desloratadine and placebo in terms of mean AM/PM reflective TSS for SAR, analyzing the ITT patient population, was noted over the primary evaluation

CLINICAL REVIEW

Clinical Review Section

period (days 1-15) as well as on day 1 ($p = 0.04$) and day 2 ($p = 0.02$), but not days 3 or 4 ($p = 0.07$) or over the entire 4 weeks of treatment ($p = 0.06$) (v33, p72, t14).

No significant differences were noted based on gender, age or race in terms of the primary outcome variable.

There was a statistically significant difference in terms of mean AM TSS evaluated at a point in time over days 2-15 and 2-29, as well as on day 2, approximately 24 hours after the first dose ($p = 0.006$) (v33, p76, t16). This effect was lost by day 4 ($p = 0.16$). Montelukast was not significantly different than placebo at any time point in terms of AM TSS NOW ($p = 0.3-0.7$).

Both desloratadine and montelukast were statistically more effective than placebo for the period 1-15 days, in terms of nasal congestion (v33, p77, t17).

There was a statistically significant difference between desloratadine and placebo for days 1-15 in regard to mean AM/PM reflective score for total nasal symptom scores ($p = 0.006$) (v33, p79, t18). There was a 25% reduction in total nasal symptoms in the group that received desloratadine compared to a 17% reduction in the group that received placebo. A statistically significant difference between desloratadine and placebo was not noted on day 1 ($p = 0.08$) but was noted on day 2 ($p = 0.007$). There was no statistically significant difference between montelukast and desloratadine noted over the 4 weeks of the study, except on day 3. On the other hand, there was no statistically significant difference between montelukast and placebo at any time point during the study. The differences in mean reduction in total nasal symptoms noted between desloratadine and placebo are of questionable clinical significance.

In terms of total mean reflective non-nasal symptom scores, the only statistically significant difference between any of the treatment groups was between desloratadine and placebo on day 1 ($p = 0.03$) (v33, p80, t19).

CLINICAL REVIEW

Clinical Review Section

There was a statistically significantly greater, but not a clinically significantly greater mean improvement in all individual nasal symptoms in the group that received desloratadine compared to the group that received placebo. There was no statistically significant difference between desloratadine and placebo in terms of ocular symptoms (v33, p82, t20).

Therefore, this study does not support a claim for ocular symptoms associated with allergic rhinitis.

The overall condition of the patients SAR was evaluated jointly by the investigator and the patient using a categorical scale of 0-3 with 0 being none and 3 being the most severe. The overall condition of the patient was assessed at baseline, weekly throughout the study and at endpoint and was averaged over the 4 weeks of the study. At no time point was there any statistically significant difference between either the desloratadine or montelukast group and the placebo group (v33, p85, t21).

Therapeutic response was evaluated jointly by the investigator and patient by comparing the patient's symptoms at the time of evaluation with their baseline symptoms, using a categorical scale of 1-5 with 1 being complete relief and 5 being treatment failure. Only when the evaluation was made after one week of treatment was there a statistically significant difference between either the desloratadine or the montelukast groups and the placebo group ($p = 0.03, 0.04$ respectively)(v33. p86, t22).

Health-related QOL assessment for allergic rhinitis evaluated 7 domains. There was no significant difference between either desloratadine or montelukast and placebo in regard to QOL assessment, including domains for nasal and ocular symptoms (v33. p88-89, t24, 25).

The primary outcome variable for asthma was change from baseline in FEV-1 averaged over the 4 weeks of the study. No significant difference between patients treated with desloratadine and patients treated with placebo was noted for mean change from baseline in FEV-1 ($p = 0.2$). The difference between the group that received

CLINICAL REVIEW

Clinical Review Section

montelukast and the group that received placebo was statistically significant for this parameter ($p < 0.001$) (v33, p74, t15). No significant differences were noted based on gender, age, or race.

Total asthma symptom scores evaluated reflectively over the preceding 12 hours showed no statistically or clinically significant mean difference between either the group that received desloratadine or the group that received montelukast and the group that received placebo at any time point (v33, p90, t26). The lack of response over the 4 weeks of the study to montelukast ($p = 0.39$), a drug approved for the management of asthma, raises questions about the validity of the data in this study.

In regard to individual asthma symptoms, there was no statistically significant mean difference between montelukast and placebo at any time point, again raising questions about the validity of this study (v33, p92, t27). There was a statistically significant mean difference between desloratadine and placebo only for difficulty breathing over the first two weeks of the study.

In addition, there was no significant difference noted in interference with sleep due to asthma symptoms, despite the fact that there was a 24% mean improvement in sleep disturbance in the desloratadine group compared with a 8% mean improvement in the placebo group. Sleep disturbance was evaluated on a 12 hour reflective basis in the morning. In the evening, interference with daily activities was evaluated. After two weeks of treatment both desloratadine and montelukast were significantly more effective in reducing interference by asthma symptoms with daily activities than was placebo ($p = 0.02$) (v33, p93).

There was no statistically or clinically significant difference between either the desloratadine group or the montelukast group and the placebo group in regard to AM or PM PEFr averaged over the 4 weeks of the study, based on daily measurements by patients (v33, p93).

A statistically significant decrease in the mean number of Proventil puffs per day was noted at all time points after the first day of

CLINICAL REVIEW

Clinical Review Section

treatment for the desloratadine and montelukast groups compared with placebo. The clinical significance of these differences is questionable (v33, p95, t28).

The overall condition of the patient's asthma was assessed jointly by the investigator and the patient, using a categorical scale of 0-3 with 0 being none and 3 being the most severe. A statistically significant mean difference was seen between the desloratadine group ($p = 0.004$) and the montelukast group ($p = 0.002$) compared to the placebo group over the 4 weeks of the study, driven by the response over the first two weeks of the study, since there was no statistically significant difference between the three groups over the last two weeks of the study (v33, p96, t29).

Therapeutic response was a joint evaluation by the patient and the investigator based on a categorical scale of 1-5, with 1 being complete relief of symptoms and 5 being treatment failure. A statistically significant mean difference between the desloratadine and montelukast groups was seen only over the first two weeks of the study (v33, p98, t30).

In terms of health-related QOL for asthma, no significant differences were observed between desloratadine or montelukast and placebo for any asthma domains at any time points (v33, p99-100, t31,32).

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CLINICAL REVIEW

Clinical Review Section

I. Mean change over days 1-15 in the study

Parameter	DCL change from baseline	placebo change from baseline	DCL percent improvement	p value
TSS AM/PM NOW* days 2-15	- 3.7	- 2.6	26.2%	0.02
TSS AM/PM NOW # Days 2-15	- 4.2	- 3.0	25.1%	0.01
TSS AMPM reflect * Days 1-15	- 3.8	- 2.9	27.3%	0.03
TSS AMPM reflect # Days 1-15	- 4.3	- 3.2	26.5%	0.02
TSS AM NOW * Days 2-15	- 3.5	- 2.5	23.9%	0.02
TNSS AM/PM reflect days 1-15	- 2.2	- 1.5	24.9%	0.006
TNNSS AM/PM reflect days 1-15	- 2.1	- 1.7	28.2%	0.09
Rhinorrhea AM/PM reflective; days 1-15	- 0.53	- 0.37	21.4%	0.02
Nasal cong AM/PM reflective days 1-15	- 0.54	- 0.35	21.1%	0.005
Nasal itch AM/PM reflective days 1-15	- 0.58	- 0.41	30%	0.02
Sneezing AM/PM reflective days 1-15	- 0.55	- 0.39	28.2%	0.02
Itching eyes AM/PM reflective days 1-15	- 0.55	- 0.47	27.2%	0.31
Tearing eyes AM/PM reflective days 1-15	- 0.54	- 0.47	26.3%	0.36
Red eyes AM/PM reflective days 1-15	- 0.48	- 0.35	28%	0.10
Itching ears AM/PM reflective days 1-15	- 0.57	- 0.39	29%	0.02
Overall condition SAR – avg 4 weeks	- 0.61	- 0.54	24%	0.43
Therapeutic response SAR – avg 4 weeks	3.41	3.59	----	0.09
FEV-1 averaged over 4 weeks	None	- 0.05	0.6%	0.20
TASS AM/PM reflective days 1-15	- 1.38	- 1.00	24%	0.06
Cough AM/PM reflective days 1-15	- 0.39	- 0.29	23%	0.16
Wheezing AM/PM reflective days 1-15	- 0.46	- 0.36	23%	0.17
Dyspnea AM/PM reflective days 1-15	- 0.53	- 0.35	25%	0.01
AM PEFr averaged over 4 weeks				

CLINICAL REVIEW

Clinical Review Section

Beta agonist use days 1-15	- 0.63	- 0.03	12%	0.002
Overall condition asthma avg 4 weeks	- 0.52	- 0.29	19.5%	0.004

Conclusion Efficacy: The efficacy of desloratadine in the treatment of nasal symptoms associated with SAR was demonstrated in this study. There was no efficacy demonstrated for ocular symptoms that are often associated with SAR. Although there was some indication of an effect of desloratadine on lower respiratory symptoms, objective assessments did not demonstrate any efficacy of desloratadine in the treatment of asthma.

Safety:

Adverse Events: The overall incidence of adverse events was 48% in the active treatment groups and 42% in the placebo group. Discontinuation of treatment due to an adverse event occurred in 3.5% of the desloratadine group and 3.6% of the placebo group.

Based on adverse events that were reported by 2% or more of patients, back pain, arthralgia, bronchitis, and pharyngitis were seen at least 2% more frequently in the desloratadine group compared to the placebo group (v33, p107, t34). Pharyngitis was considered to be treatment-related in 3 of the 9 patients who developed this adverse event after receiving desloratadine (v33, p109, t35).

There was a greater incidence of adverse events in female patients who received desloratadine (56%) compared to male patients (33%). There were no significant differences in the incidence of adverse events based on age or race. This was also true for the montelukast group.

One patient treated with desloratadine had a serious adverse event. This patient was a 25 year old Hispanic woman who developed severe chest pain after one week of treatment with desloratadine which was considered unrelated to the study drug and not cardiac in nature (v33, p113).

Laboratory tests: There were two patients who had elevated liver enzymes. One was a 27 year old American Indian who had an SGOT level of 25 U/L at baseline that rose to 186 U/L after 4 weeks of treatment with desloratadine.

CLINICAL REVIEW

Clinical Review Section

On the other hand, there was a 25 year old Caucasian woman who had a SGOT value of 40 U/L at baseline that increased to 150 U/L after receiving placebo for 4 weeks (v33, p117-118, t40). There were no mean or individual changes in laboratory tests that were clinically significant.

Vital Signs: There were no mean or individual changes in vital signs that were clinically significant.

ECGs: A 12 lead ECG was obtained at baseline and at the last study visit. All QTc intervals were recalculated using the Fridericia and Bazett corrections because different formulas were used at different centers to calculate intervals by computerized tracing machines. A 51 year old African-American woman had a QTc interval of 394 msec at baseline that increased to 520 msec after treatment with desloratadine. There was a mean decrease in the QTc interval using the Fridericia correction of 2.4 msec in the group that received desloratadine (v33, p 120-122, t42).

Conclusions safety: The safety of desloratadine has been demonstrated in this study.

3. Integrated Summary of Safety:

a. Adverse Events:

1. **Treatment-emergent AEs:** 41% of the patients who received DCL and 39% of the patients who received placebo in studies of allergic rhinitis.
2. **Treatment-related AEs:** 14% of the patients who received DCL and 12% of the patients who received placebo in studies of allergic rhinitis.
3. **Severe treatment-related AEs:** 2.5% of the patients who received DCL and 2.1% of the patients who received placebo in studies of allergic rhinitis
4. **Serious AEs:** 0.2% of the patients who received DCL and 0.3% of the patients who received placebo in studies of allergic rhinitis.
5. **Treatment-emergent AEs** reported by 2% or more of patients in either treatment group from the allergic rhinitis studies pooled: the largest difference between the DCL group and the placebo

CLINICAL REVIEW

Clinical Review Section

group was pharyngitis where 4.1% of the DCL group and 2.0% of the placebo group reported this AE.

6. **Adverse Cardiovascular events:** Based on an assessment of all studies evaluating allergic rhinitis, the percent and type of adverse cardiovascular events was similar for DCL and placebo.
7. **Hepatic adverse events:**
8. **Renal adverse events:**

b. Laboratory tests:

1. **Based on an assessment of the 3307 patients with allergic rhinitis, increased liver function tests were noted in 4 patients after receiving DCL and 3 patients after receiving placebo. There were 7 DCL patients and 8 placebo patients who had either a normal baseline liver function test that was elevated after treatment or had an elevated liver function test at baseline that increase further after treatment.**
2. **Renal function tests**

c. Vital signs:

1. **ECGs: Based on an assessment of all studies evaluating allergic rhinitis, QTc prolongation was noted in 2 patients treated with DCL. QTc intervals were recalculated using both the Fridericia and Bazett formula. There was no clinically significant change from baseline in mean QTc interval after administration of DCL, using either the Fridericia or Bazett correction. The same percentage of patients had a 10% or greater increase in the QTc interval after administration of DCL and placebo. Based on an assessment of all studies evaluating allergic rhinitis, tachycardia was noted in 3 patients treated with DCL and no placebo patients. There was no clinically significant change from baseline in mean ventricular rate after administration of DCL. A slightly higher percentage of patients had a 10-14% and a 20% or greater increase in ventricular rate after administration of DCL than after administration of placebo. DCL was given concomitantly with Prozac, Zithromax, and cimetidine.**

d. 4 month safety update:

CLINICAL REVIEW

Clinical Review Section

Included in this safety update were data from the following studies:

1. Study 1875, a 2 week study comparing 2 formulations of desloratadine D-24 (a combination of desloratadine and PSE) with PSE and desloratadine 5 mg per day given alone, in which 1495 adult patients with SAR were treated.
2. Study 1884, a 2 week study identical to study 1875, in which 1357 adult patients with SAR were treated.
3. Study 1546, a 2 week placebo-controlled study comparing desloratadine 5 mg per day to fexofenadine, in which 1043 adult patients with SAR were treated.
4. Study 1376, a 2 week placebo controlled study evaluating 5 mg of desloratadine daily in adolescent patients with SAR.
5. Study 222, a conjunctival challenge study preceded by 7 days of treatment with 5 mg per day of desloratadine in 22 adult patients with rhinoconjunctivitis.
6. Study 90, a single dose study of 21 patients in a hyperbaric chamber who received 5 mg of desloratadine, as well as Benadryl and placebo in a crossover study.

☛ adverse events: A “treatment-emergent adverse event” was defined as any adverse event that began on or after the first day of treatment through 30 days after the last day that the patient participated in the study. No adverse events were reported for studies 90 and 222.

There were no life-threatening or unique adverse events noted in the studies listed above. The most frequently reported adverse events in the two studies with desloratadine D-24 (1875, 1884) were headache, dry mouth and insomnia. There were no adverse events that occurred with significantly greater frequency in patients who received desloratadine compared with the other active treatments in these studies. Headache was the most frequently reported adverse event in studies 1546 and 1376, but the frequency of this adverse event, as well as other adverse events, was not significantly greater in

CLINICAL REVIEW

Clinical Review Section

patients who received desloratadine compared to patients who received fexofenadine or placebo.

There were no adverse events considered to be treatment-related that occurred with significantly greater frequency in patients who received desloratadine as compared to patients who received desloratadine D-24, PSE, fexofenadine or placebo. In study 1884, there were 6 patients who developed severe pharyngitis, 3 who received desloratadine D-24 and 3 who received desloratadine. Two of these adverse events were considered possibly related to the study medication by the investigator, in one patient who received desloratadine and one patient who received desloratadine D-24. Pharyngitis has occurred not infrequently in patients who have received desloratadine in other studies. The clinical significance of this finding is unclear.

Comparable or smaller numbers of patients who received desloratadine were discontinued from the studies listed above because of adverse events compared with patients who received other active treatment or placebo.

Laboratory tests: No clinically significant findings are reported in this 4 month safety update.

vital signs: No significant changes in vital signs was reported in this 4 month safety update.

ECGs: ECGs were done at baseline and at the end of randomized treatment in all the repetitive dose studies except for study 222. In studies 1875 and 1884, the mean change in ventricular rate was less in the group that received desloratadine than in the other active treatment groups. Using Bazett's correction, there was a 1.5 and 0.2 msec prolongation of the QTc interval after treatment with desloratadine in studies 1875 and 1884, respectively, compared with a mean prolongation of 3.8 to 7.4 msec with the other active treatment groups. There is a suggestion from study 1884, but not study 1875, that the greater mean prolongation of the QTc interval seen with desloratadine D-24 could be more than an additive effect. There were six patients, 4 of whom received desloratadine D-24 and

CLINICAL REVIEW

Clinical Review Section

2 who received PSE, in studies 1875 and 1884 who had a prolongation of the QTc interval based on the Fridericia correction.

A value > 450 msec for males and 470 msec for females was considered prolonged. One patient had a QTc interval of 389 msec at baseline and 506 msec after 2 weeks of treatment. Based on both the Fridericia correction and the Bazett's correction, there were fewer number of patients who received desloratadine, as compared to the other active treatment groups in studies 1875 and 1884 who had a 15% or greater increase in the QTc interval after treatment. In study 1546, the mean change in QTc interval using Bazett's correction was 0.2 msec, which was less than the change seen with placebo. Using Bazett's correction, there were fewer patients who received desloratadine who had a 15% or greater increase in the QTc interval than there were in the fexafenadine or placebo groups. In study 1376, the mean change in the QTc interval in the group that received desloratadine was 2 msec (Fridericia) and 3.6 msec (Bazett's) compared to 0.4 msec in the placebo group.

☛ spontaneous adverse event reporting: Out of 76 spontaneous reports, there were 6 that were considered serious, unexpected and possibly or probably related to administration of desloratadine. Three patients are of special note because they all developed throat pain or burning almost immediately after taking desloratadine. In one of these patients, this occurred after the tablet became lodged in her throat. After discussion with chemistry, there is no possible reason to suspect that desloratadine is unique in producing this type of reaction.

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Richard Nicklas
2/1/02 04:14:24 PM
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Badrul Chowdhury
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Please see my team leader memorandum dated January 28, 2002