PRODUCT MONOGRAPH
INCLUDING PATIENT MEDICATION INFORMATION

DESLORATADINE ALLERGY CONTROL

Desloratadine

Tablet, 5mg, Oral

House Standard

Histamine H1-Receptor Antagonist

PHARMASCIENCE INC.
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Date of initial Authorization:
SEP 22, 2011

Date of Revision:
SEP 12, 2023

Submission Control Number: 272961

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PART I: HEALTH PROFESSIONAL INFORMATION

1 INDICATIONS

DESLORATADINE ALLERGY CONTROL (desloratadine) tablets are indicated for:

- fast 24 hour and effective relief of multi nasal and non-nasal symptoms associated with allergic rhinitis, including sneezing, nasal discharge/rhinorrhea and itching, nasal congestion/stuffiness, itching of the palate and/or ears and/or throat and/or eyes and allergic cough, as well as burning, swollen, tearing and redness of the eyes.
- rapid and effective relief of symptoms associated with chronic idiopathic urticaria, such as pruritus and hives.

1.1 Pediatrics

Pediatrics (Tablets <12 years of age): The efficacy and safety of desloratadine Tablets in children under 12 years of age have not been established.

1.2 Geriatrics

Geriatrics (> 65 years of age): In a multiple dose study with desloratadine 5 mg, subjects >65 years of age (n=17) had AUC and C_{max} values 20% greater and plasma elimination half-life approximately 30% longer than in younger subjects; however, these changes are not considered to be clinically relevant and no dosage adjustment is warranted in this age subgroup (10.3 Pharmacokinetics / Elderly).

2 CONTRAINDICATIONS

- Patients who are hypersensitive to this drug or to any ingredient in the formulation or component of the container. For a complete listing, see 6 DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING.

3 SERIOUS WARNINGS AND PRECAUTIONS BOX

Serious Warnings and Precautions

- In the case of severe hepatic or renal insufficiency, use with caution.

4 DOSAGE AND ADMINISTRATION

4.1 Dosing Considerations

- In the case of severe hepatic or renal insufficiency, DESLORATADINE ALLERGY CONTROL should be used with caution.

4.2 Recommended Dose and Dosage Adjustment

- DESLORATADINE ALLERGY CONTROL (desloratadine 5 mg)
  Adults and children (12 years of age and older): One DESLORATADINE ALLERGY CONTROL (desloratadine) 5 mg tablet daily regardless of mealtime. For oral use

4.3 Administration

See 4.2 Recommended Dose and Dosage Adjustment.

4.4 Missed Dose

If you miss taking your dose on time, do not worry; take your dose when you remember. Do not exceed more than one dose in 24 hours.

5 OVERDOSAGE

In the event of overdose, consider standard measures to remove unabsorbed active substance. Symptomatic and supportive treatment is recommended. Desloratadine administered at a dose of 45 mg daily (nine times the clinical dose) for ten days showed no statistically or clinically relevant prolongation of the QTc interval. The mean changes in QTc were 0.3 msec and 4.3 msec for placebo and desloratadine, respectively (p=0.09; Lower confidence interval (LCI) = -0.6; Upper confidence interval (UCI) = 8.7).

Desloratadine is not eliminated by hemodialysis; it is not known if it is eliminated by peritoneal dialysis.

For management of a suspected drug overdose, contact your regional poison control centre.

6 DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING

Table 1 – Dosage Forms, Strengths, Composition and Packaging

Route of Administration	Dosage Form / Strength/Composition	Non-medicinal Ingredients
Oral	Tablet, 5 mg desloratadine	FD&C Blue No.2 aluminum lake, hypromellose, lactose, magnesium oxide, microcrystalline cellulose, polyethylene glycol, pregelatinized starch, titanium dioxide and zinc stearate

DESLORATADINE ALLERGY CONTROL 5 mg: Each blue, round, coated tablet debossed with “D” on one side of the tablet and plain on the other contains 5 mg of desloratadine.

Available in HDPE bottles of 180 tablets and in blister packs of 10, 20, 30, 50,70 and 80 tablets.

7 WARNINGS AND PRECAUTIONS

Please see 3 SERIOUS WARNINGS AND PRECAUTIONS BOX.

Hepatic/Biliary/Pancreatic

In a single-dose (7.5 mg) pharmacokinetic study, subjects with mild to severe hepatic dysfunction (n=4/group) had mean AUC and C_{max} values up to 2.4 times higher than healthy subjects (n=8); however, these findings are not considered to be clinically relevant.

Desloratadine 5mg was administered for 10 days to subjects with normal hepatic function (n=9) or moderate dysfunction (n=11). Subjects with hepatic dysfunction could experience a 3-fold increase in exposure (AUC) to desloratadine, but these findings are not considered to be clinically relevant.

Therefore, no dosage modification is recommended in individuals with hepatic dysfunction (see 10.3 Pharmacokinetics / Hepatic Dysfunction).

Neurologic

Desloratadine should be administered with caution in patients with a medical or family history of seizures. In particular, young children may be more susceptible to developing new seizures under desloratadine treatment. Healthcare providers may consider discontinuing desloratadine in patients who experience a seizure while on treatment.

Renal

In a single-dose (7.5 mg) pharmacokinetic study, subjects (n=25) with varying degrees of renal insufficiency (mild, moderate, severe and hemodialysis) had 1.7 to 2.5 fold increases in desloratadine mean AUC with minimal change in 3-hydroxy desloratadine concentrations. However, these findings are not considered to be clinically relevant (see 10.3 Pharmacokinetics / Renal Dysfunction).

In the case of severe renal insufficiency, DESLORATADINE ALLERGY CONTROL should be used with caution.

Respiratory

Use in Asthmatics: Desloratadine has been safely administered to patients with mild to moderate asthma (see 14 .1 Trial Design and Study Demographics / Efficacy in Seasonal Allergic Rhinitis: Patients with SAR and Concomitant Mild to Moderate Asthma & 14.2 Study Results / Efficacy in Seasonal Allergic Rhinitis: Patients with SAR and Concomitant Mild to Moderate Asthma).

Desloratadine did not cause exacerbation of asthma symptoms (see 10.2 Pharmacodynamics / Asthmatics).

7.1 Special Populations

7.1.1 Pregnant Women

Since no clinical data on exposed pregnancies are available with desloratadine, the safe use of desloratadine during pregnancy has not been established. The use of DESLORATADINE ALLERGY CONTROL during pregnancy is therefore not recommended.

No overall effect on rat fertility was observed with desloratadine at an exposure that was 34 times higher than the exposure in humans at the recommended clinical dose. No teratogenic or mutagenic effects were observed in animal trials with desloratadine (see 16 NON-CLINICAL TOXICOLOGY).

7.1.2 Breast-feeding

Desloratadine passes into breast milk; therefore, breast-feeding is not recommended in lactating women taking DESLORATADINE ALLERGY CONTROL.

7.1.3 Pediatrics

(Tablets <12 years of age): The efficacy and safety of desloratadine Tablets in children under 12 years of age have not been established.

7.1.4 Geriatrics

In a multiple dose study with desloratadine 5 mg, subjects >65 years of age (n=17) had AUC and C_{max} values 20% greater and plasma elimination half-life approximately 30% longer than in younger subjects; however, these changes are not considered to be clinically relevant and no dosage adjustment is warranted in this age subgroup (see 10.3 Pharmacokinetics / Elderly).

8 ADVERSE REACTIONS

8.1 Adverse Reaction Overview

No clinically relevant drug-related adverse effects including cardiovascular effects were observed with desloratadine in clinical trials.

Very rare cases of hypersensitivity reactions including anaphylaxis and rash have been reported during the marketing of desloratadine. In addition, cases of tachycardia, palpitations, psychomotor hyperactivity, seizures, elevations of liver enzymes, hepatitis, increased bilirubin, and increased appetite have been reported very rarely.

8.2 Clinical Trial Adverse Reactions

Because clinical trials are conducted under very specific conditions the adverse reaction rates observed in the clinical trials may not reflect the rates observed in practice and should not be compared to the rates in the clinical trials of another drug. Adverse drug reaction information from clinical trials is useful for identifying drug-related adverse events and for approximating rates.

The frequency of reasonably related undesirable effects is presented as the excess incidence in 1866 patients who received desloratadine 5 mg tablets compared to that seen in 1857 patients who received placebo in multiple-dose clinical trials evaluating the treatment of seasonal and allergic rhinitis and chronic idiopathic urticaria. The type and frequency of undesirable effects reported throughout the desloratadine allergic rhinitis and chronic idiopathic urticaria (CIU) clinical trials were comparable to those reported with placebo.

At the recommended dose of 5 mg daily, undesirable effects with desloratadine were reported in only 3% of patients in excess of those treated with placebo. No excess incidence of somnolence was reported in patients treated with desloratadine. Headache was reported in only 0.6% of patients in excess of those treated with placebo. The incidence of treatment-related adverse events reported by $\geq$ 1% of subjects treated with desloratadine 5 mg in multiple-dose clinical trials is presented in Table 2.

Table 2 - Incidence of Treatment-Related Adverse Events Reported by ≥2% of Subjects Treated with desloratadine 5 mg in Multiple-Dose Allergic Rhinitis and Chronic Idiopathic Urticaria Studies

	Desloratadine 5.0 mg n = 1866 (%)	**Placebo n = 1857 (%)**
No. of Subjects (%)[a] with Any Related Adverse Event[b]	**281 (15.1)**	**232 (12.5)**
Autonomic Nervous System Disorders	**51 (2.7)**	**36 (1.9)**
Dry mouth	49 (2.6)	34 (1.8)
Fatigue	33 (1.8)	12(0.6)
Body As a Whole-General Disorders	**124 (6.6)**	**88 (4.7)**
Headache	84 (4.5)	72 (3.9)
Psychiatric Disorders	**53 (2.8)**	**48 (2.6)**
Somnolence	36 (1.9)	35(1.9)

a: Number of subjects reporting related adverse events at least once during the study. Some subjects may have reported more than one adverse event.

b: Considered by the investigator to be possibly or probably related to treatment.

8.3 Post-Market Adverse Reactions

Very rare cases of hypersensitivity reactions, including anaphylaxis and rash have been reported during the marketing of desloratadine. In addition, cases of tachycardia, palpitations, psychomotor hyperactivity, somnolence, seizures, elevations of liver enzymes, hepatitis, increased bilirubin, and increased appetite have been reported very rarely.

9 DRUG INTERACTIONS

9.1 Drug Interactions Overview

Desloratadine taken concomitantly with alcohol did not potentiate the performance impairing effects of alcohol (see 10.2 Pharmacodynamics / Psychomotor Pharmacodynamics).

9.2 Drug-Behavioural Interactions

Effects on Ability To Drive And Use Machines: None (see 10.2 Pharmacodynamics / Psychomotor Pharmacodynamics).

9.3 Drug-Drug Interactions

No clinically relevant interactions with desloratadine were observed in clinical trials investigating the potential for interaction with azithromycin, erythromycin, ketoconazole, fluoxetine, and cimetidine.

In a multiple dose clinical trial, in which up to 20 mg of desloratadine was administered daily for 14 days to 49 healthy volunteers, no statistically or clinically relevant cardiovascular effects were observed. In another trial, desloratadine was administered at a dose of 45 mg daily (nine times the clinical dose) for ten days; no prolongation of the QTc interval was seen (see 5 OVERDOSAGE)

The potential for desloratadine to interact with ketoconazole (N=24), erythromycin (N=24), azithromycin (N=90), fluoxetine (N=54), and cimetidine (N=36) was investigated in separate interaction studies. Ketoconazole co-administered with desloratadine increased C_{max} and AUC values for desloratadine by 29% and 21% respectively, and 3-hydroxy desloratadine C_{max} and AUC values by 77% and 110%, respectively. Erythromycin co-administered with desloratadine increased the C_{max} and AUC values for desloratadine by 24% and 14%, respectively. The increases were 43% and 40%, respectively, for 3-hydroxy desloratadine. Azithromycin co-administered with desloratadine increased the C_{max} and AUC values for desloratadine by 15% and 5%, respectively. The increases were 15% and 4%, respectively, for 3-hydroxy desloratadine. Fluoxetine co-administered with desloratadine resulted in no change in the AUC of desloratadine and an increase of 15% in the C_{max} of desloratadine. The C_{max} and AUC values for 3-hydroxy desloratadine were increased by 17% and 13% respectively. Cimetidine co- administered with desloratadine increased C_{max} and AUC values by 12% and 19% respectively while the C_{max} and AUC of 3-hydroxy desloratadine were reduced by 11.2% and

2.8% respectively. However, as there was no evidence of change in the safety profile of desloratadine throughout these studies, the increases in plasma concentrations are not considered to be clinically relevant. In addition, no clinically relevant changes in electrocardiographic pharmacodynamics (QTc) were observed.

9.4 Drug-Food Interactions

There was no effect of food or grapefruit juice on the disposition of desloratadine (see 10.2 Pharmacokinetics / Effect of food).

9.5 Drug-Herb Interactions

Interactions with herbal products have not been established.

9.6 Drug-Laboratory Test Interactions

Interactions with laboratory test have not been established.

10 CLINICAL PHARMACOLOGY

10.1 Mechanism of Action

Desloratadine is a non-sedating long-acting antihistamine with selective peripheral H1-receptor antagonist activity, which has demonstrated antiallergic, antihistaminic, and anti -inflammatory activity.

Desloratadine does not exacerbate asthma.

Desloratadine is an active metabolite of loratadine that possesses qualitatively similar pharmacodynamic activity with a relative oral potency in animals 2.5 to 4 times greater than loratadine. In guinea pigs, the antihistamine effect after a single dose of desloratadine lasts 24 hours.

In addition to antihistaminic activity, desloratadine has demonstrated antiallergic and anti -inflammatory activity in a number of *in vitro* (mainly conducted on cells of human origin) and *in vivo* studies. These studies have shown that desloratadine inhibits the broad cascade of events that initiate and propagate allergic inflammation, including:

- the release of proinflammatory cytokines including IL-4, IL-6, IL-8 and IL-13,
- the release of important proinflammatory chemokines such as RANTES (Regulated upon Activation, Normal T-cell Expressed and Secreted),
- superoxide anion production by activated polymorphonuclear neutrophils,
- eosinophil adhesion and chemotaxis,
- the expression of the adhesion molecules such as P-selectin,

- IgE-dependent release of histamine, prostaglandin (PGD2) and leukotriene (LTC4)
- the acute allergic bronchoconstrictor response and allergic cough.

Desloratadine exhibits excellent receptor specificity for histamine H1-receptors. This selectivity together with a limited entry to the CNS accounts for the little or no sedation liability observed in clinical studies. Although antimuscarinic activity is significant from in vitro studies, this activity does not seem to be relevant in vivo where anticholinergic effects are only seen at very high doses, well in excess of the antihistamine dose.

10.2 Pharmacodynamics

After oral administration, desloratadine selectively blocks peripheral histamine H1-receptors as the drug is effectively excluded from entry into the central nervous system.

Wheal and Flare: Desloratadine 5mg was significantly better than placebo, as measured by a reduction in histamine-induced wheal and flare areas for all days tested (1, 7, 14, 21, 28). There was no evidence of tachyphylaxis over the 28-day dosing period.

Psychomotor Pharmacodynamics: Clinical trials have demonstrated that there was no difference in the incidence of somnolence in subjects treated with desloratadine 5 mg as compared to subjects treated with placebo.

No significant differences were found in the psychomotor test results between desloratadine and placebo groups, whether administered alone or with alcohol. Co-administration of alcohol with desloratadine did not increase the alcohol-induced impairment in performance or increase in sleepiness. No effects on the ability to drive and use machines have been observed. A single dose of desloratadine did not affect standard measures of flight performance including exacerbation of subjective sleepiness or tasks related to flying.

In a clinical study which utilized a 45 mg dose of desloratadine (nine times the clinical dose) (see *Cardiovascular Pharmacodynamics*), there were no reports of somnolence. In a separate randomized, single-dose, double-blind, placebo-controlled, 4-way crossover study, 25 healthy volunteers were treated with desloratadine 7.5 mg/juice, desloratadine 7.5 mg/alcohol in juice, placebo tablet/alcohol in juice and placebo tablet/juice. No significant differences were found in the psychomotor test results between desloratadine and placebo groups, whether given alone or with alcohol. In a study with desloratadine no effects on the ability to drive and use machines have been observed. In a separate study in normal volunteers administered a single dose of 5mg desloratadine, no effects on standard measures of flight performance were observed.

Drowsiness and somnolence, which affect psychomotor performance, have been reported with first generation antihistamines. The co-administration of alcohol with such products has resulted in further impairment of psychomotor performance. In a previous study, CLARITIN (loratadine) did not increase the alcohol-induced impairment in performance or increase in sleepiness.

Cardiovascular Pharmacodynamics: To confirm the cardiovascular safety of desloratadine, a study to evaluate the electrocardiographic effects of desloratadine in subjects (n=24) treated with 45 mg desloratadine (nine times the clinical dose) once daily for 10 days was conducted. The primary endpoint of this study was the difference between Baseline (Day -1) maximum ventricular rate, PR, QRS, QT and QTc intervals and the corresponding Day 10 maximum ECG parameters. At 9-fold the proposed clinical dose, there was no statistically or clinically relevant prolongation of the QTc interval. The mean changes in QTc were 0.3 msec and 4.3 msec for placebo and desloratadine, respectively (p=0.09; Lower confidence interval (LCI) = -0.6; Upper confidence interval (UCI) = 8.7). It should be noted that in a separate rising, multiple dose study in which up to 20 mg of desloratadine was administered daily for 14 days, no statistically or clinically relevant cardiovascular effects were observed.

Drug-Drug Interactions – two randomized, two-way crossover, third-party blind, multiple dose (10 days), placebo-controlled studies characterized the effect of CYP3A4 inhibitors ketoconazole (N=24) and erythromycin (N=24) on the pharmacokinetics and cardiovascular safety of desloratadine.

A third study (N=90) with similar design, except comparing parallel groups, investigated the effect of azithromycin, an azilide antibiotic that also inhibits CYP3A4, on the pharmacokinetics and cardiovascular pharmacodynamics of desloratadine.

Two additional randomized, multiple dose, parallel group studies investigated the effect of cimetidine (N=36) and fluoxetine (N=54) on the pharmacokinetics and cardiovascular pharmacodynamics of desloratadine.

Ketoconazole co-administered with desloratadine increased C_{max} and AUC values for desloratadine by 29% and 21%, respectively, and 3-hydroxy desloratadine C_{max} and AUC values by 77% and 110%, respectively. Erythromycin increased C_{max} and AUC values for desloratadine by 24% and 14%, respectively. The increases were 43% and 40%, respectively, for 3-hydroxy desloratadine. Azithromycin co-administered with desloratadine increased the C_{max} and AUC values for desloratadine by 15% and 5%, respectively. The increases were 15% and 4%, respectively, for 3-hydroxy desloratadine. Throughout these studies, there was no evidence of change in the safety profile of desloratadine, therefore the increases in plasma concentrations are not considered to be clinically relevant. Ketoconazole induced a small increase in the plasma desloratadine concentrations compared with those reported for loratadine. These data suggest that desloratadine has a reduced potential for interacting with inhibitors of CYP3A4. The similarity of the erythromycin concentrations from this study to previous studies suggests that desloratadine is unlikely to inhibit the metabolism of substrates of CYP3A4, which comprise at least 50% of drugs currently marketed. Fluoxetine co-administered with desloratadine resulted in no change in the AUC of desloratadine and an increase of 15% in the C_{max} of desloratadine. The C_{max} and AUC for 3-hydroxy desloratadine were increased by 17% and 13% respectively. Cimetidine co-administered with desloratadine increased C_{max} and AUC values by 12% and 19% respectively and the C_{max} and AUC of 3-hydroxy desloratadine were reduced by 11.2% and 2.8% respectively.

Serial ECG measurements showed no statistically significant or clinically relevant changes in QTc intervals. Mean changes in QTc were 5.4 msec and 2.3 msec for ketoconazole/desloratadine and desloratadine/placebo, respectively (p=0.14; LCI = -7.3; UCI= 11). Mean changes in QTc were 9.8 msec and 7.8 msec for erythromycin/desloratadine and desloratadine/placebo, respectively (p=0.53; LCI = -8.4; UCI = 4.5). Mean changes in QTc were -4.2 msec and -6.3 msec for desloratadine/Azithromycin and desloratadine/placebo, respectively (p = 0.61).
Reports of serious cardiac arrhythmias with the use of some antihistamines prompted a careful and extensive evaluation of the cardiovascular safety of desloratadine. Years of clinical experience with loratadine, and indirectly with desloratadine, indicates that desloratadine has not been associated with ventricular arrhythmias. Studies with desloratadine in rats, guinea pigs and monkeys, at multiples of the clinical dose, have confirmed there is no effect on important components of the ECG such as PR interval, QRS interval or QTc interval. Further studies on cardiac K^+ channels, including the important HERG channel, have shown no effect at 1 micromolar desloratadine concentration, which is well in excess of therapeutic plasma levels.

Asthmatics: In 2 four-week studies of 924 patients (aged 15 to 75 years) with seasonal allergic rhinitis and concomitant asthma, Desloratadine 5mg tablets improved rhinitis symptoms, with no decrease in pulmonary function. This supports the safety of administering desloratadine 5mg tablets to adult patients with seasonal allergic rhinitis with mild to moderate asthma.

10.3 Pharmacokinetics

In laboratory animals and humans, desloratadine was extensively absorbed (> 90%) following oral administration. In laboratory animals, accurate exposure estimates to desloratadine were only obtained at low doses since duration (0-24 hr) of plasma sampling did not allow for an accurate determination of AUC (0-∞). In rats and monkeys, CL/F values for desloratadine decreased with duration of dosing; however, in humans, single dose and multiple dose CL/F values were the same. The cause for the changes in CL/F in rats and monkeys is unknown. In all species, exposure to desloratadine was greater following desloratadine administration than following an equal dose (mg/kg or mg) of loratadine.

The low amounts of desloratadine recovered in urine and feces indicate that, in laboratory animals and humans (normal metabolizers), desloratadine is metabolically cleared from plasma.

In vivo and *in vitro* metabolic profiles for desloratadine, loratadine and their metabolites were obtained in laboratory animals and humans. The metabolic pathways for desloratadine were the same within each species following ^{14}C-desloratadine and ^{14}C-loratadine administration. The primary pathways for desloratadine metabolism involved hydroxylation at either the 3-, 5, or 6-positions. All desloratadine metabolites identified in human plasma and excreta following desloratadine and loratadine administration were also observed in profiles from at least one of the preclinical species.

The major (>5%) human metabolites of desloratadine were present in all species (mouse, rat, rabbit, monkey) after exposure to desloratadine and loratadine. In laboratory animals, hydroxylation was primarily at the 5- and 6-position while in humans hydroxylation occurred

primarily at the 3-position.

Human Pharmacokinetics

A multiple-dose pharmacokinetic study was conducted at the clinical dose of 5 mg in a large cohort of subjects (n=112) comprised of a 1:1 ratio of males to females and in which patient demographics were comparable to those of the general SAR population. Subjects received their treatment once daily for 10 days. Steady state for desloratadine and 3-hydroxy desloratadine (3-OH DL) was attained by Day 7. In this study, 4% of the subjects, defined as slow metabolizers, achieved a higher concentration of desloratadine. Maximum desloratadine concentration was about 3-fold higher at approximately 7 hours with a terminal phase half-life of approximately 89 hours. In these subjects, desloratadine is cleared from plasma by elimination of parent drug in urine and feces. The safety profile of these subjects was not different from that of the general population. The accumulation (R=1.11-1.64) after 14 days of once daily dosing was consistent with desloratadine half-life (~27 hours) and the once daily dosing frequency.

The influence of sex and race (Caucasian, Black) on the pharmacokinetic parameters (area under the curve [AUC], maximum concentration [C_{max}]) for desloratadine and 3-OH desloratadine was examined in a second multiple dose study. The mean AUC and C_{max} were higher in females (desloratadine: 3 and 10%, respectively, and 3-OH desloratadine: 48% and 45%, respectively) compared to males. With regards to race, AUC and C_{max} were higher (18% and 32%, respectively) in Blacks than Caucasians. In contrast, the 3-OH desloratadine parameters were lower (10%). Considering the magnitude of the changes and safety demonstrated following administration of a dose of 45 mg desloratadine, the increases are not clinically relevant, therefore, no dosage adjustment is required for race or gender.

Protein Binding: The *in vitro* protein binding of desloratadine to human plasma protein was determined by ultrafiltration and ranges between 82.8% to 87.2% over the concentration range of 5 to 400 ng/mL. For this degree of protein binding (free fraction 13%), interactions involving displacement are not known to be clinically important.

Effect of Food: Results from a single dose food effect study using a 7.5 mg dose of desloratadine demonstrated that there was no effect of food (high-fat, high caloric breakfast) on the disposition of desloratadine. In another study, grapefruit juice had no effect on the disposition of desloratadine.

Absorption:

Desloratadine plasma concentrations can be detected within 30 minutes of desloratadine administration. Desloratadine is well absorbed with maximum concentrations achieved after approximately 3 hours; the mean elimination half-life is approximately 27 hours. The bioavailability of desloratadine is dose proportional over the range of 5 mg to 20 mg.

Equivalent exposure (AUC) to desloratadine, 3-hydroxy desloratadine, and 3-hydroxy desloratadine glucuronide was achieved after desloratadine 5mg and loratadine 10 mg.

Distribution:
No information available.

Metabolism:
Desloratadine is extensively metabolized. The results of metabolic profiling indicated that hydroxylation of desloratadine to 3-hydroxy desloratadine (3-OH desloratadine) followed by its subsequent glucuronidation was the major pathway of metabolism of desloratadine. The enzyme responsible for the metabolism of desloratadine has not been identified yet, and therefore some interactions with other drugs cannot be fully excluded. In-vivo studies with specific inhibitors of CYP3A4 and CYP2D6 have shown that these enzymes are not important in the metabolism of desloratadine. Desloratadine does not inhibit CYP3A4 and CYP2D6 and is neither a substrate nor an inhibitor of p-glycoprotein.

Data from clinical pharmacology studies indicate that a subset of the general adult and pediatric patient population has a decreased ability to form 3-hydroxydesloratadine. Ninety pediatric and 440 adult subjects were phenotyped for the polymorphism in clinical pharmacology studies. The incidence of the trait was approximately 8.6% in adults and 15.6% in pediatric subjects. In both pediatric and adult studies the slow metabolizer trait is more frequent in subjects of African descent than Caucasians. The desloratadine exposure (AUC) associated with the slow metabolizer phenotype has been well characterized (~4 times that of normal metabolizers) in single dose studies and is similar in pediatric and adult subjects at various doses. Median (range) AUC in pediatric normal and slow metabolizers was 31.9 (14-74) ng.hr/mL and 116 (72-210) ng.hr/mL, respectively. The corresponding values for adult normal and slow metabolizers were 33.5 (8.7-99) ng.hr/mL and 139 (82-393) ng.hr/mL, respectively. In adults characterized as slow metabolizers, desloratadine exposure (AUC) after multiple dose s has been demonstrated to be about six fold higher than that of normal metabolizers. The desloratadine exposure after multiple doses has not been documented for children. The safety profile of adult and pediatric slow metabolizers of desloratadine was not different from that of the general population.

Desloratadine is moderately bound (83% to 87%) to plasma proteins.

Following administration of desloratadine 5mg for 28 days, the approximate two-fold degree of accumulation of desloratadine and 3-OH desloratadine is consistent with the half-life of DL and its active metabolite and a once daily dosing frequency. This accumulation is not clinically meaningful. The pharmacokinetics of desloratadine and 3-OH desloratadine do not change after daily dosing for 7 consecutive days.

There is no evidence of clinically relevant drug accumulation following once daily dosing of desloratadine (5 mg to 20 mg) for 14 days.

Results from a single dose trial of 7.5 mg desloratadine demonstrate that there was no effect of food (high-fat, high caloric breakfast) on the disposition of desloratadine. In another study, grapefruit juice had no effect on the disposition of desloratadine.

Elimination:
A human mass balance study documented a recovery of approximately 87% of the ^{14}C-desloratadine dose, which was equally distributed in urine and feces as metabolic products.

Special Populations and Conditions

Hepatic Dysfunction: In a single-dose (7.5 mg) study, the pharmacokinetics of subjects with mild, moderate and severe hepatic dysfunction (n=4/group), as defined by the Child -Pugh Classification (A, B or C), were compared with data from healthy subjects (n=8) without any evidence of hepatic dysfunction. Within the various subgroups of hepatic dysfunction, there were no significant differences in pharmacokinetics. Subjects with hepatic dysfunction had mean AUC and C_{max} values up to 2.4 times greater than healthy subjects. The pharmacokinetics of desloratadine was evaluated in subjects with normal hepatic function (n=9) or moderate dysfunction (n=11) following once daily administration of desloratadine 5mg for 10 days.

Subjects with hepatic dysfunction could experience a 3-fold increase in exposure (AUC) to desloratadine. The exposure to 3-OH DL in subjects with hepatic dysfunction was similar to that in normal subjects. The adverse event profile and electrocardiograms showed no consistent changes of clinical relevance in any subject with hepatic dysfunction. Since the increased concentrations are not considered clinically relevant, no dosage adjustment is recommended for subjects with hepatic dysfunction.

Renal Dysfunction: The pharmacokinetics of desloratadine following a single dose of 7.5 mg was evaluated in patients with mild (n=7), moderate (n=6), and severe (n=6) renal impairment or hemodialysis dependent (n=6) patients. There was little difference between the C_{max} and AUC values for subjects with mild and moderate insufficiency. Patients with varying degrees of renal dysfunction including dialysis dependent subjects experienced a 1.7- to 2.5-fold increase in desloratadine median AUC with minimal change in 3-hydroxy desloratadine concentrations.

Desloratadine and 3-hydroxy desloratadine were not removed by hemodialysis. Plasma protein binding of desloratadine and 3-hydroxy desloratadine was unaltered by renal disease. The results show that patients with varying degrees of renal dysfunction, including those with severe renal impairment or on dialysis, demonstrated no clinically relevant changes from baseline in pharmacokinetic parameters. In the case of severe renal insufficiency, DESLORATADINE ALLERGY CONTROL (desloratadine) should be used with caution.

Elderly: The pharmacokinetics of desloratadine was evaluated in a subset (n= 17) of subjects >65 years of age who participated in a multiple dose (5 mg once daily x 10 days) study. The mean AUC and C_{max} were 20% greater than in subjects <65 years old. The apparent total body clearance adjusted for body weight was similar between the two age groups. The mean plasma elimination half-life was prolonged by approximately 30% (33.7 hours) in subjects > 65 years old. There was no difference in the adverse event reporting frequency in this group. These age related changes are not clinically relevant, therefore, no dosage adjustment is warranted in subjects >65 years of age.

11 STORAGE, STABILITY AND DISPOSAL

Temperature and Moisture

Store between 15°C and 30°C. Protect from excessive moisture.

Keep out of the reach and sight of children.

12 SPECIAL HANDLING INSTRUCTIONS

None.

PART II: SCIENTIFIC INFORMATION

13 PHARMACEUTICAL INFORMATION

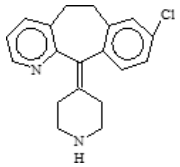
Drug Substance

Proper name: Desloratadine

Chemical name: 8-chloro-6,11-dihydro-11-(4-piperidinylidene)-5H-benzo-[5,6]cyclohepta[1,2-b]pyridine

Molecular formula and molecular mass: $C_{19}H_{19}ClN_2$ / 310.8 g/ mol

Structural formula:



Physicochemical properties:

Physical Form:	White to off-white powder	
Solubility:	ethanol	>100 mg/mL (freely soluble)
	methylene chloride	>100 mg/mL (freely soluble)
	methanol	>100 mg/mL (freely soluble)
	octanol	>100 mg/mL (freely soluble)
	0.1N HCl	39.7 mg/mL (soluble)
	DMSO	24.5 mg/mL (soluble)
	water	0.1mg/mL (very slightly soluble)
	pH 7.4 phosphate buffer	1.5 mg/mL (slightly soluble)
	0.1N NaOH	<0.1 mg/mL (practically insoluble)
pKa Values:	pyridine functional group	4.2
	piperidine functional group	9.7
Partition Coefficient:		log KO/W
	n-octanol/0.1N HCl	-2.27
	n-octanol/pH 3 buffer	-1.44
	n-octanol/pH 6 buffer	0.342
	n-octanol/pH 7 buffer	1.02
	n-octanol/pH 8 buffer	0.944
Melting Point:	Form I	156.0 to 157.5°C

14 CLINICAL TRIALS

14.1 Trial Design and Study Demographics

Efficacy in Seasonal Allergic Rhinitis

The clinical efficacy of desloratadine in the treatment of seasonal allergic rhinitis (SAR) was demonstrated in four multiple-dose, placebo-controlled clinical trials (C98-001, C98-223, C98-224, and C98-225). A total of 2499 subjects with SAR were randomized to treatment with either desloratadine or placebo. Of these, 1838 patients received active treatment. Efficacy endpoints in the clinical trials included Total Symptom Score, Total Nasal Symptom Score, Total Non-Nasal Symptom Score, and Quality of Life analysis. Desloratadine 5 mg once daily significantly reduced the Total Symptom Scores (the sum of individual scores for rhinorrhea, sneezing, congestion/stuffiness, nasal itching, itchy/burning eyes, tearing, ocular redness, and itchy ears/palate).

Efficacy in Perennial Allergic Rhinitis

The clinical efficacy of desloratadine in the treatment of perennial allergic rhinitis (PAR) was evaluated in two multiple-dose, placebo-controlled clinical trials (P00218 and P00219). A total of 1374 subjects with PAR were randomized to treatment with either desloratadine or placebo. Of these, 685 patients received active treatment.

Efficacy in Seasonal Allergic Rhinitis: Patients With SAR and Concomitant Mild to Moderate Asthma

Berger *et al* (2002) published results from a study evaluating safety and efficacy of (5 mg desloratadine) in patients with SAR and mild seasonal allergic asthma. The four week multi - center, double-blind, placebo-controlled study included 331 patients (ages 15 or older) with a two year history of SAR and increased asthma signs or symptoms in conjunction with fall/winter allergy season. Patients were clinically symptomatic at screening and were assigned to take either 5 mg desloratadine or placebo once daily for 4 weeks. The following symptoms were evaluated in the study: rhinorrhea, nasal stuffiness/congestion, nasal itching, sneezing, itching/burning eyes, tearing/watering eyes, redness of eyes, and itching of ears/palate. Patients evaluated symptoms twice daily (morning/evening) and the primary efficacy parameter was difference from baseline in AM/PM reflective total symptom scores.

Efficacy in Chronic Idiopathic Urticaria

The clinical efficacy of desloratadine in the treatment of chronic idiopathic urticaria (CIU) was documented in over 400 chronic idiopathic urticaria patients 12 to 84 years of age in 2 double-blind, placebo-controlled, randomized clinical trials of 6 weeks duration as demonstrated by reduction of associated itching and hives.

Safety Evaluation

A total of 3758 subjects who received desloratadine in clinical programs for the allergic rhinitis and CIU indications were evaluable for safety. Of these, 3045 were treated with desloratadine in multiple - dose trials, with 2872 receiving doses of 5 mg or higher.

14.2 Study Results

Efficacy in Seasonal Allergic Rhinitis

Desloratadine 5 mg was significantly more effective than placebo in reducing Total Nasal Symptoms including congestion and Total Non-Nasal Symptoms. Instantaneous assessments of efficacy at the end of the dosing interval demonstrated that reductions in symptoms which were observed following the first dose of desloratadine 5 mg were maintained for the full 24 hour dosing interval.

There was no significant difference in the effectiveness of desloratadine 5 mg across subgroups of patients defined by gender, age, or race.

Onset of Action Studies: Results from onset of action studies utilizing controlled-exposure chambers indicated that subjects first became aware of significant improvements in their SAR symptoms as early as 1 hour and 15 minutes following a 5.0 mg dose of desloratadine.

Quality of Life (QOL) Assessments: Exploratory assessments of quality of life in clinical trials indicated that SAR produced a consistent burden of disease. Improvements in therapeutic responses with desloratadine 5 mg were also associated with improvements in various QOL domains including but not limited to: activity limitations, sleep problems, general problems, practical problems, nasal symptoms, ocular problems, emotional function, vitality and social functioning (see Table 4).

Table 4 - Desloratadine (5 mg desloratadine) effectiveness in alleviating the burden of SAR: improvement in QOL domains.

Study	Study Description	Results
Pradalier A. *et al.* (2007)	*Methods:* A multicenter, double-blind, randomized, placebo-controlled, parallel-group study of desloratadine 5 mg vs placebo in patients with symptomatic SAR. *Objective:* To compare the effects of desloratadine and placebo on QOL in seasonal AR *Study duration:* Two weeks. *Population:* ITT population consisted of 483 subjects (234 patients in the desloratadine 5 mg arm vs 249 patients in the placebo arm). *Validated QOL measurement tool:* French-language version of RQLQ. The questionnaire includes 28 items in seven domains (activity limitations, sleep problems, general problems, practical problems, nasal symptoms, ocular symptoms, and emotional function). Patients rated experiences over the previous week using a 7-point scale: 0 (not bothered at all) to 6 (extremely bothered); the total score was the mean of the domain scores. *Secondary efficacy variables:* The change from baseline to D14 in TNSS. *Primary efficacy variable:* QOL assessment, and change from baseline in TNSS, TNNSS, TSS and individual symptom score and diary symptom score.	▪Mean total RQLQ score at D14: desloratadine was associated with a significantly larger improvement from baseline vs placebo (*P*=0.0003). ▪Compared to placebo, desloratadine demonstrated significant improvement (decrease in symptoms) in all RQLQ sub-domains (activity limitations, sleep problems, general problems, practical problems, nasal symptoms, ocular problems, and emotional function) vs placebo ($P \leq 0.043$). ▪The desloratadine group demonstrated significant decrease in TNSS (*P*=0.0003), TNNSS (*P*=0.001) and TSS (*P*=0.0001) at D14 compared to D0 vs placebo. ▪The desloratadine group demonstrated a significant decrease in morning and evening AR symptoms after just 1 day of treatment ($P \leq 0.02$).

*QOL: Quality of Life ITT: Intent-To-Treat D0: day 0;
D14: day 14;
RQLQ: French-language version of Rhinoconjunctivitis Quality of Life Questionnaire. TNSS: Total Nasal Symptoms Score;
TNNSS: Total Non-Nasal Symptoms Score; TSS: Total Symptoms Score.

Efficacy in Perennial Allergic Rhinitis

One of the two perennial allergic rhinitis trials supported efficacy of desloratadine, compared with placebo, for the primary efficacy endpoint (average am/pm instantaneous total symptom score excluding nasal stuffiness/congestion expressed as change from baseline). In that study, the majority of the secondary efficacy endpoints supported treatment efficacy. The second pivotal trial did not achieve statistical significance for the primary efficacy endpoint "average am/pm instantaneous total symptom score excluding nasal stuffiness/congestion, expressed as change from baseline". A statistically significant difference between desloratadine and placebo was shown in this trial for one of the secondary efficacy variables “joint investigator-subject evaluation of therapeutic response”.

Efficacy in Seasonal Allergic Rhinitis: Patients With SAR and Concomitant Mild to Moderate Asthma

The results showed that compared to placebo, desloratadine significantly reduced SAR total symptom scores with first dose, which continued throughout the study duration ($p < 0.001$). Desloratadine was safe and well tolerated in patients with SAR and mild seasonal allergic asthma. The number and type of treatment-related adverse events were similar between the desloratadine and placebo groups.

Table 5 - Published clinical trial evaluating safety and efficacy of 5 mg desloratadine in treating SAR in patients with SAR and concomitant mild to moderate asthma.

Study	Study Description	Results
Berger WE. *et al.* (2002)	*Methods:* A multicenter, parallel-group, double-blind, placebo-controlled, study of desloratadine 5 mg vs placebo in patients with SAR and mild seasonal allergic asthma. *Objective:* To evaluate the safety and efficacy of desloratadine 5 mg in patients experiencing moderate SAR, nasal congestion, and symptoms of seasonal allergic asthma. *Study duration:* Four weeks. *Population:* ITT population consisted of 331 subjects (168 patients in the desloratadine 5 mg arm vs 163 patients in the placebo arm). *Primary efficacy variable:* The mean AM/PM reflective TSS, expressed as the change from baseline for the averages of days 1 to 15, with additional analyses at days 1 to 29.	▪ Desloratadine significantly reduced mean AM/PM reflective TSS for SAR, beginning with the first dose ($P<0.001$) and continuing throughout days 1 to 15 (-4.90 vs -2.98; $P<0.001$) and days 1 to 29 (-5.47 vs -3.73; $P<0.001$).

SAR: Seasonal allergic rhinitis; ITT: Intent-To-Treat;
TSS: Total Symptoms Score

Efficacy in Chronic Idiopathic Urticaria

Desloratadine Tablets significantly reduced the severity of pruritus, number of hives, size of largest hive, and total symptom score when compared to placebo. Symptoms were effectively reduced as early as one day after initiation of treatment with desloratadine and were sustained for the full 24- hour dosing interval.

Treatment with desloratadine also improved sleep and daytime functions as measured by reduced interference with sleep and routine daily activities.

There was no significant difference in the effectiveness of desloratadine 5 mg across subgroups of patients defined by gender, age, or race.

Quality of Life (QOL) Assessment

A number of published clinical trials, evaluating the impact of 5 mg desloratadine on chronic idiopathic urticaria on QOL have demonstrated that desloratadine 5 mg significantly improves a variety of QOL domains. A summary is provided in Table 6.

Table 6 - Clinical trials demonstrating 5 mg; desloratadine effectiveness in alleviating the burden of chronic idiopathic urticaria: improvement in QOL domains.

Study	Study Description	Results
Grob JJ *et al* (2008)	*Methods:* A multicentered, double-blinded, randomized, placebo-controlled study of desloratadine 5 mg vs placebo in patient with a history of CIU. *Objective:* To evaluate the effect of desloratadine 5 mg on QOL scores in patients with CIU. *Study duration:* Six weeks. *Population:* ITT population consisted of 137 subjects (65 patients in the desloratadine arm vs 72 patients in the placebo arm). *Validated QOL measurement tool:* DLQI comprises 10 equally weighted items that evaluate the effect of skin problems on patients' lives: itchiness/soreness/ pain; embarrassment; interference with shopping; clothes purchases; social leisure; difficulty playing sports; difficulty with work or study; problems with partner; sexual difficulties; and problems at home caused by treatment. Each item is scored on a continuum from 0 (least impairment) to 3 (worst impairment), with total DLQI scores ranging from 0 to 30) and VQ-Dermato questionnaire comprises 28 items in seven domains (self-perception, daily living activity, mood state, social functioning, leisure activity, treatment induced restriction and physical discomfort), with each item scored on a scale of 0 to 4. Total VQ-Dermato scores range from 0 (least serious effect) to 112 (worst effect).	▪ A significantly greater improvement from D0 to D24 was associated with desloratadine treatment compared to placebo in DLQI overall score (18.5 *vs.* 29.1 points; *P*=0.009). ▪ Desloratadine treated patients had a significantly lower mean VQ-Dermato scores vs the placebo group in daily activities (18.1 vs. 32.6; *P*=0.001), mood (7.5 vs. 14.7; *P*=0.027), social life (10 vs. 21; *P*=0.005) and physical pain (42.3 vs. 58.2; *P*=0.006) from D1 to end of study. ▪ Desloratadine demonstrated trend toward significance in a fifth domain, self-image (21.5 vs. 30; *P*=0.075).

Study	Study Description	Results
Monroe E. *et al.* (2003)	*Methods:* A multicentered, double-blinded, randomized, placebo-controlled, parallel-group study of desloratadine 5 mg vs placebo in patient with moderate to severe CIU. *Objective:* To determine the efficacy (including secondary efficacy QOL sleep and daily activities parameters) and safety of desloratadine 5 mg in patients with moderate to severe CIU. *Study duration:* Six weeks. *Population:* ITT population consisted of 226 subjects (116 patients in the desloratadine arm vs 110 patients in the placebo arm). *Primary efficacy measure:* The change in average reflective AM/PM pruritus scores from baseline. *Secondary efficacy outcomes:* The reflective average AM/PM scores for number of hives, size of largest hive, and total symptom score (sum of pruritus, number of hives, and size of largest hive scores) as well as, QOL measurements, interference with sleep (AM reflective), and interference with daily activities (PM reflective).	▪There was a significant improvement with desloratadine for pruritus (58.4% vs 40.4% placebo; *P*=0.004), the number of hives (40.8% vs 19.9% placebo; *P*<0.001), and the size of the largest hive (39% vs 19.3% placebo; *P*<0.001); ▪Desloratadine significantly reduced interference of CIU on sleep. Days 1 to 8 resulted in a 44.0% improvement in sleep from baseline compared to a 14.4% improvement in the placebo group (*P*=0.007). As early as 24 hours after the first dose, interference with sleep was improved by 30.6% vs 2.8% for placebo (*P*=0.044). ▪Desloratadine significantly reduced interference of CIU on daily activity performance as early as D2 (40.9% improvement vs 5.6% for placebo group; *P*=0.002). The effect was also sustained for the entire treatment duration (46.9%for desloratadine vs 17.2% for placebo group; *P*=0.001).
Lachapelle JM *et al.* 2006	*Methods:* A multicentered, open label study of desloratadine 5 mg in patient with CIU. *Objective:* To assess the effect of once daily desloratadine 5 mg on the QOL of patients suffering from CIU. *Study duration:* Six weeks. *Population:* ITT population consisted of 121 patients. *Validated QOL measurement tool:* DLQI comprises 10 equally weighted items that evaluate the effect of skin problems on patients' lives: itchiness/soreness/ pain; embarrassment; interference with	▪Desloratadine demonstrated a statistically significant decrease in the Mean DLQI at baseline, D7, and D42 (13.4, 9.1, and 6.6 respectively). The mean proportional scores observed with desloratadine-treatment at D0, D7 and D42 (44.5%, 30.3%, and 21.9% respectively). The relative proportional changes from baseline were observed with desloratadine on both D7 and D42 (-31.6% and -50.9% respectively). All these changes were statistically significant (*P*<0.0001). ▪A clinically significant change (i.e. a decrease of at least 2 points) from baseline was observed with desloratadine for 66%

Study	Study Description	Results
	shopping; clothes purchases; social leisure; difficulty playing sports; difficulty with work or study; problems with partner; sexual difficulties; and problems at home caused by treatment. Each item is scored on a continuum from 0 (least impairment) to 3 (worst impairment), with total DLQI scores ranging from 0 to 30); pruritus, number and maximum size of hives, sleep quality and activity impairment were also assessed.	of patients at D7 and 77% of patient at D42. (*P*<0.0001) ▪There was complete relief by D2 in 33.3% of patients, marked relief by D2 in 35.1% of patients and approximately 9.6% who experienced no relief. ▪Pruritus and size of the hives significantly improved with desloratadine-treatment (*P*<0.005).
Grob JJ and Lachapelle JM (2008)	*Methods:* A structured search of the MEDLINE database was conducted to identify papers published between 1 January 1991 and 30 September 2007 on the treatment of CIU with the second-generation antihistamines cetirizine, desloratadine, fexofenadine, and levocetirizine, and their effects on patient-reported QOL. The Following search terms were used alone or in combination: 'chronic idiopathic urticaria'; 'pruritus'; 'wheals'; 'hives'; 'second-generation antihistamines'; 'cetirizine'; 'desloratadine'; 'fexofenadine'; 'levocetirizine'; and 'quality of life'. *Validated QOL measurement tool:* DLQI and VQ-Dermato validated instruments.: DLQI comprises 10 equally weighted items that evaluate the effect of skin problems on patients' lives: itchiness/soreness/ pain; embarrassment; interference with shopping; clothes purchases; social leisure; difficulty playing sports; difficulty with work or study; problems with partner; sexual difficulties; and problems at home caused by treatment. Each item is scored on a continuum from 0 (least impairment) to	▪Desloratadine 5 mg significantly lowered QOL scores in three studies (n=364) (*P*<0.05). ▪Three 6-week double-blind, placebo-controlled trials (n=553) establish that desloratadine significantly improved patient-reported pruritus, sleep disruption, and interference with daily activities (*P*<0.05). ▪Significant improvements were observed in QOL domains such as but not limited to self-consciousness regarding skin, problems with partner, and interference of CIU on outdoor activity, sport, leisure, work/study, and sexual activity (*P*<0.0001).

Study	Study Description	Results
	3 (worst impairment), with total DLQI scores ranging from 0 to 30) and VQ-Dermato questionnaire comprises 28 items in seven domains (self-perception, daily living activity, mood state, social functioning, leisure activity, treatment induced restriction and physical discomfort), with each item scored on a scale of 0 to 4. Total VQ-Dermato scores range from 0 (least serious effect) to 112 (worst effect).	

CIU: chronic idiopathic urticaria; QOL:
Quality of Life;
ITT: Intent-To-Treat;
DLQI: Dermatology Life Quality Index;
VQ-Dermato: Questionnaire; reproducible dermatology instrument designed to assess QOL outcomes in French speakers;
RQLQ: French-language version of Rhinoconjunctivitis Quality of Life Questionnaire; D0: day 0;
D7: day 7;
D42: day 42.

Safety Evaluation

The overall incidence of treatment-related adverse events (AEs) in patients treated with desloratadine 5 mg was comparable to the incidence in patients treated with placebo (15.1% with desloratadine 5 mg vs. 12.5% with placebo).

The most common adverse event thought to be at least possibly related to treatment was headache. Treatment-related headache was reported in 4.5% of subjects treated with desloratadine 5 mg compared with 3.9% of placebo subjects. There is no significant difference in the safety of desloratadine among subgroups defined by gender, age or race. There were no indications of any particular cardiovascular safety concerns during the clinical trials based on adverse events, vital signs and ECG assessments. No particular safety concerns relevant to the hepatic system were demonstrated. Overall, the incidence of AEs observed in this program was comparable to placebo, giving desloratadine an acceptable safety profile.

Very rare cases of hypersensitivity reactions, including anaphylaxis and rash have been reported during the marketing of desloratadine.

14.3 Comparative bioavailability Studies

Single center, randomized, single dose, blinded, 2-period, 2-sequence, crossover comparative bioavailability study of two formulations of Desloratadine 5 mg tablets in 22 healthy male volunteers in fasting conditions.

SUMMARY TABLE OF THE COMPARATIVE BIOAVAILABILITY DATA

Desloratadine (1 x 5 mg tablet of Desloratadine) From measured data **uncorrected for potency** Geometric Mean Arithmetic Mean (CV %)				
Parameter	**Test[1]**	**Reference[2]**	**% Ratio of Geometric Means**	**90% Confidence Interval**
AUC_{0-72} (pg•h/mL)	31151.4 33318.3 (39.6)	31807.1 34358.6 (43.3)	97.94	91.11 – 105.28
AUC_I (pg•h/mL)	33853.0 36525.3 (44.4)	34952.7 38504.9 (51.4)	96.85	89.10 – 105.28
C_{max} (pg/mL)	1596.3 1686.1 (33.1)	1650.6 1750.2 (36.0)	96.71	89.97 – 103.95
T_{max}[3] (h)	5.00 (1.00 – 12.00)	5.00 (1.50 – 6.03)		
$T_{½}$[4] (h)	19.17 (25.6)	20.04 (35.3)		

[1] DESLORATADINE ALLERGY CONTROL (desloratadine) tablets, 5 mg (Pharmascience Inc.)
[2] AERIUS®, (desloratadine) tablets, 5 mg (Bayer Inc., Consumer Care, previously Schering Canada Inc.)
[3] Expressed as the median (range) only
[4] Expressed as the arithmetic mean (CV %)

15 MICROBIOLOGY

Not applicable.

16 NON-CLINICAL TOXICOLOGY

General Toxicology:

Acute Toxicity

The acute oral (gavage) and intraperitoneal toxicity of desloratadine was evaluated in six week old Sprague-Dawley rats and CD-1 mice. Estimated oral and intraperitoneal LD_{50} values in both rats and mice were significant multiples of a human dose of 5.0 mg desloratadine/day. Oral LD_{50} values were 3530 and $\geq$ 5490 times the daily human dose in mice and rats respectively. Intraperitoneal LD_{50} values were $\geq$ 460 and $\geq$ 680 times a daily human dose in mice and rats, respectively (Table 7)

Table 7 – Desloratadine LD50 Values

Species	Sex	Route	LD_{50} Value (mg/kg) (Clin. Dose Multiple)[a]
Mouse	Male	PO	353 (3530X)
	Female	PO	353 (3530X)
Mouse	Male	IP	49 (490X)
	Female	IP	46 (460X)
Rat	Male	PO	616 (6160X)
	Female	PO	549 (5490X)
Rat	Male	IP	178 (1780X)
	Female	IP	68 (680X)

PO = Oral (gavage); IP = Intraperitoneal
a: Based upon a projected desloratadine clinical dose of 5.0 mg/day (0.10 mg/kg presuming a 50 kg patient).

In an oral (gavage) rising-dose tolerance study in young adult cynomolgus monkeys, emesis was observed at doses $\geq$ 23.5 and $\geq$ 93.75 mg/kg in males and females, respectively. Emesis occurred approximately 15 minutes after and/or up to three hours post dose. The maximum dose that did not produce emesis in male monkeys (11.75 mg/kg) still represents an 118-fold multiple of the human dose (0.10 mg desloratadine/kg/day), and an 92-fold monkey-to-human systemic exposure multiple compared to an arithmetic mean C_{max} value of 4.0 ng/mL in humans following a 5.0 mg/day dose of desloratadine.

Repeated-Dose Toxicity

Two-week, one-month and three-month desloratadine studies were conducted in rats at doses of up to 240 mg/kg for an initial pilot two-week study, up to 8 mg/kg for the second two-week study and up to 120 mg/kg for one- and three-months. Desloratadine systemic exposure at 60 mg/kg is similar to that achieved with a 120 mg/kg dose of loratadine. The no-effect level for the three-month study was ≥ 3 mg/kg (low-dose) but less than 30 mg/kg. Mortality was observed in the 30, 60 and 120 mg/kg dose groups and in the comparative control (120 mg loratadine/kg) dose group in the three-month study. Fecal changes were observed and were considered related to the anticholinergic effect of this class of compounds. Clinical pathology changes occurred at desloratadine doses ≥ 30 mg/kg (systemic exposure multiple of at least 458 times). The findings associated with target organs/tissues consisted mainly of vacuolation corresponding to phospholipidosis. Phospholipidosis is a common finding of amphiphilic compounds like desloratadine and loratadine. Centrilobular hepatocyte hypertrophy occurred at desloratadine doses of ≥ 30 mg/kg and at 120 mg/kg of loratadine. There was no evidence of phospholipidoses at the 3 mg/kg dose.

Renal tubular cell necrosis and/or renal tubular dilatation were observed at desloratadine doses ≥ 60 mg/kg (systemic exposure multiple of at least 605 times) or at a loratadine dose of 120 mg/kg (desloratadine systemic exposure multiple of at least 663 times).

Renal tubular casts were seen in males given either 60 mg/kg of desloratadine or 120 mg/kg of loratadine. Myofiber degeneration, muscle fibrosis and/or mononuclear infiltrates in muscle occurred at desloratadine doses of ≥ 60 mg/kg and at 120 mg/kg of loratadine. Luminal cellular debris was seen in the seminiferous tubules of the testes at a desloratadine dose of 60 mg/kg and at 120 mg/kg dose of loratadine.

Hypospermatogenesis occurred in the testes of one or more males given 120 mg loratadine/kg or desloratadine doses ≥ 30 mg/kg. Luminal cellular debris was present in the epididymides of the loratadine-dosed males and in the desloratadine-dosed males at doses ≥ 30 mg/kg. Oligospermia was also seen in the epididymides of one male given 30 mg/kg of desloratadine, in one male given 60 mg/kg of desloratadine, and in some males given 120 mg/kg of desloratadine or loratadine. However, there were no testicular changes observed in the one -month study at doses up to 120 mg/kg. Furthermore, these testicular-related changes were consistent with those previously observed with loratadine at doses as low as 2 mg loratadine/kg in rats but with a loratadine no effect dose of 1 mg loratadine/kg for similar findings after one year of dosing. This effect on rat testes has been reported with other antihistamines. With loratadine and desloratadine, this effect is only observed in rats. In the three -month study,

granulosa cell necrosis was seen in the ovaries of many females given 120 mg/kg of desloratadine and in some females given 120 mg/kg of loratadine. Uterine immaturity occurred in some females given 60 mg/kg of desloratadine and in many females given 120 mg/kg of desloratadine or loratadine.

A seven-day, a two-week, two one-month and a three-month study were conducted in monkeys with desloratadine. Desloratadine doses of up to 12 mg/kg (systemic exposure multiple of at least 182 times) were well tolerated for up to three-months of dosing and was

the no-effect dose in the one-month studies. Doses ≥ 36 mg/kg (systemic exposure multiple of at least 842 times) in the repeat one-month study caused emesis.

In the three-month study, the high dose of 18 mg/kg of desloratadine was increased to 24 mg/kg and the loratadine dose was increased from 22 mg/kg to 72 mg/kg on Day 36. Clinical signs, including few or no feces, extended abdomen, hunched posture and/or lethargy, at the 18/24 mg/kg of desloratadine (systemic exposure multiple of at least 953 times) and 22/72 mg/kg of loratadine (desloratadine systemic exposure multiple of at least 1147 times) doses were attributed to the anticholinergic effects of this class of compounds. Decreases in serum cholesterol and alkaline phosphatase were noted in the 18/24 mg/kg desloratadine group and in the 22/72 mg/kg loratadine group. Evaluation of histopathologic findings from the desloratadine 18/24 mg/kg dose group suggests that this dose produces phospholipidosis similar to that produced by the 22/72 mg/kg loratadine dose. There was no evidence of phospholipidosis following desloratadine doses of 6 mg/kg. There were no testicular changes observed in monkeys dosed for three months at doses up to 18/24 mg desloratadine/kg or 22/72 mg loratadine/kg. In this three-month study, the only effects observed at the 12 mg/kg dose of desloratadine were vacuolation in the salivary glands and lungs. A dose of 6 mg/kg (systemic exposure multiple 204 times) was the no-effect dose. The toxicity studies demonstrate adequate exposure multiples at the no-effect levels and ensure an acceptable safety profile for desloratadine (Table 8).

Table 8 - Systemic Exposure of Desloratadine in Animals Following PO Dose Repeated Administration of Desloratadine.

Species	Study	Dose Route/ No-Effect Dose (mg/kg)	Gender	AUC(0-24 hr) (ng•hr/mL)	Animal to Human Exposure Ratio (5.0 mg/day human dose)
Rat	3 Month Toxicity (Day 57)	Gavage 3	M F	1950 1890	34 33
Monkey	2-Week Toxicity (Day 14)	Gavage 6.5	M,F[a]	5115	90
Monkey	1-Month Toxicity (Day 15)	Gavage 12	M,F	10388	182

Species	Study	Dose Route/ No-Effect Dose (mg/kg)	Gender	AUC (0-24 hr) (ng•hr/mL)	Animal to Human Exposure Ratio (5.0 mg/day human dose)
Monkey	1-Month Toxicity Repeat (Day 15)	Gavage 12	M,F	16002	281
Monkey	3-Month Toxicity (Day 57)	Gavage 6	M,F	11623	204
a: M,F equals values for males and females combined.					

Carcinogenicity: Since animals and humans are exposed to desloratadine through metabolism of loratadine, carcinogenicity studies conducted with loratadine also assessed the carcinogenic risk of desloratadine.

In an 18-month carcinogenicity study in mice and a 2-year study in rats, loratadine was administered in the diet at doses up to 40 mg/kg/day (mice) and 25 mg/kg/day (rats). Pharmacokinetic assessments were carried out to determine the animal exposure to desloratadine as well as to loratadine in the carcinogenicity studies. Desloratadine AUC data demonstrated that the exposure of mice given 40 mg/kg/day loratadine was 33 times higher than in humans given the maximum recommended daily oral dose of desloratadine.

Desloratadine exposure of rats given 25 mg/kg/day of loratadine was 123 times higher than in humans given the highest recommended dose of desloratadine (5mg/day). Male mice given 40 mg/kg/day of loratadine had a significantly higher incidence of hepatocellular tumors (adenomas and carcinomas combined) than concurrent controls. In rats, a significantly higher incidence of hepatocellular tumors (adenomas and carcinomas combined) was observed in males given 10 mg/kg/day and in males and females given 25 mg/kg/day. The liver tumors observed in the loratadine carcinogenicity studies were considered to be due to nongenotoxic mechanism(s) that were observed only at high doses of loratadine; thus, these animal carcinogenicity findings were not considered relevant to humans taking recommended therapeutic doses of either loratadine or desloratadine.

Genotoxicity: In mutagenicity studies with desloratadine, there was no evidence of mutagenic potential in a reverse point mutation assay (Salmonella/E. coli mammalian microsome bacterial mutagenicity assay) or in two assays for chromosomal aberrations (human peripheral blood lymphocyte clastogenicity assay and mouse bone marrow micronucleus assay).

Reproductive and Developmental Toxicology: There was no effect on female fertility at doses up to 24 mg/kg/day which produced systemic exposure levels in female rats which were at least 506 times those in humans given the highest recommended clinical dose of desloratadine. In a separate study, decreased fertility in male rats was shown by lower female conception rates associated with decreases in sperm numbers and motility and histopathologic testicular changes, which occurred at an oral dose of desloratadine of 12 mg/kg (systemic exposure approximately 175 times higher than in humans given the maximum recommended dose of desloratadine). Although there was no overall effect on mean sperm motility or concentration, a few rats given desloratadine at a dose of 3 mg/kg/day appeared to have testicular findings consistent with those observed previously with loratadine, which had a no effe ct dose of 1 mg/kg/day for similar findings after one year of administration. There was no effect on fertility at 3 mg/kg/day, which produced plasma levels (AUC) in rats that were 34 times higher than in humans receiving the maximum clinical dose of desloratadine. This effect on rat testes has been reported with other antihistamines but as with desloratadine and loratadine, this effect is not observed in other laboratory animal species and appears to be unique to the rat.

17 SUPPORTING PRODUCT MONOGRAPHS

AERIUS® Tablets, 5 mg and AERIUS® KIDS Syrup, 0.5 mg/mL, submission control 263344, Product Monograph, Bayer Inc. (OCT 11, 2022)

PATIENT MEDICATION INFORMATION
READ THIS FOR SAFE AND EFFECTIVE USE OF YOUR MEDICINE

DESLORATADINE ALLERGY CONTROL
Desloratadine Tablets, 5 mg

Read this carefully before you start taking DESLORATADINE ALLERGY CONTROL. This leaflet is a summary and will not tell you everything about this drug. Talk to your healthcare professional about your medical condition and treatment and ask if there is any new information about DESLORATADINE ALLERGY CONTROL.

Serious Warnings and Precautions

- Tell your doctor if you have severe liver or kidney disease.

What is DESLORATADINE ALLERGY CONTROL used for?

DESLORATADINE ALLERGY CONTROL provides:

- fast 24 hour effective relief from seasonal allergies (trees, grass, pollen and ragweed) and year round allergies (dust mites, animal dander and moulds) resulting in symptoms including nasal congestion, sneezing, runny nose, itchy nose, stuffiness; itchy palate; itchy ears; itchy throat; allergic cough; as well as swollen, itchy, burning, watery and red eyes.
- fast and effective relief of allergic skin conditions, such as skin itch and hives.

How does DESLORATADINE ALLERGY CONTROL work?

DESLORATADINE ALLERGY CONTROL is a product proven to work in multiple ways. Its' anti-allergic action and anti- inflammatory properties provide a multi defense against allergy symptoms. DESLORATADINE ALLERGY CONTROL is a long- acting antihistamine that blocks the action of histamine.

DESLORATADINE ALLERGY CONTROL has anti-inflammatory properties that also help by reducing swelling and related symptoms such as nasal congestion, redness and hives.
Most people will feel relief of allergy symptoms within 75 minutes of taking DESLORATADINE ALLERGY CONTROL.

Symptom relief will be maintained for 24 hours.
DESLORATADINE ALLERGY CONTROL does not cause drowsiness.
DESLORATADINE ALLERGY CONTROL can be used by people with mild to moderate asthma.

What are the ingredients in DESLORATADINE ALLERGY CONTROL?

Medicinal ingredient: Desloratadine 5 mg
Non-medicinal ingredients: FD&C Blue No.2 aluminum lake, hypromellose, lactose, magnesium oxide, microcrystalline cellulose, polyethylene glycol, pregelatinized starch, titanium dioxide and zinc stearate.

DESLORATADINE ALLERGY CONTROL comes in the following dosage forms:

Tablets: 5 mg

Do not use DESLORATADINE ALLERGY CONTROL if:

you are

- allergic to desloratadine or to any of the other product ingredients
- pregnant or nursing

To help avoid side effects and ensure proper use, talk to your healthcare professional before you take DESLORATADINE ALLERGY CONTROL. Talk about any health conditions or problems you may have, including if you:

- have liver or kidney disease
- plan to become pregnant
- have medical or family history of seizures

Tell your healthcare professional about all the medicines you take, including any drugs, vitamins, minerals, natural supplements or alternative medicines.

The following may interact with DESLORATADINE ALLERGY CONTROL:

- DESLORATADINE ALLERGY CONTROL may affect the way other medicines work, and other medicines may affect how DESLORATADINE ALLERGY CONTROL works.
- If you are taking any medication, it is important to ask your doctor or pharmacist before taking DESLORATADINE ALLERGY CONTROL.

How to take DESLORATADINE ALLERGY CONTROL:

Usual dose:

Adults and children (12 years of age and older): Swallow one tablet with water, once daily, regardless of mealtime.

Overdose:

If you think you, or a person you are caring for, have taken too much DESLORATADINE ALLERGY CONTROL, contact a healthcare professional, hospital emergency department, or regional poison control centre immediately, even if there are no symptoms.

Missed Dose:

If you miss taking your dose on time, do not worry; take your dose when you remember. Do not exceed more than one dose in 24 hours.

What are possible side effects from using DESLORATADINE ALLERGY CONTROL?

These are not all the possible side effects you may have when taking DESLORATADINE ALLERGY

CONTROL. If you experience any side effects not listed here, tell your healthcare professional.

Side effects that may occur include, dry mouth, fatigue, increased appetite and headache.

At the recommended dose, this medicine is not expected to affect your ability to drive or use machines. Drowsiness has been reported very rarely. Although most people do not experience drowsiness, it is recommended not to engage in activities requiring mental alertness, such as driving a car or operating machinery until you have established your own response to the medicinal product.

Serious side effects and what to do about them			
Symptom / effect	**Talk to your healthcare professional**		**Stop taking drug and get immediate medical help**
	Only if severe	**In all cases**	
VERY RARE			
Allergic reaction (rash, itching, swelling of lips, tongue, face, throat and difficulty in breathing)			√
Fast heart rate or heart palpitations			√
Restlessness with increased body movement			√
Seizures			√
Liver dysfunction - i.e. inflammation of the liver (appearance of jaundice - yellowing of the skin)			√

If you have a troublesome symptom or side effect that is not listed here or becomes bad enough to interfere with your daily activities, tell your healthcare professional.

Reporting Side Effects

You can report any suspected side effects associated with the use of health products to Health Canada by:

- Visiting the Web page on Adverse Reaction Reporting (https://www.canada.ca/en/health-canada/services/drugs-health-products/medeffect-canada.html) for information on how to report online, by mail or by fax; or
- Calling toll-free at 1-866-234-2345.

NOTE: Contact your health professional if you need information about how to manage your side effects. The Canada Vigilance Program does not provide medical advice.

Storage:

Store between 15°C and 30°C. Protect tablets from excessive moisture. Keep out of the reach and sight of children.

If you want more information about DESLORATADINE ALLERGY CONTROL:

- Talk to your healthcare professional
- Find the full product monograph that is prepared for healthcare professionals and includes this Patient Medication Information by visiting the Health Canada website: (https://www.canada.ca/en/health-canada/services/drugs-health-products/drug-products/drug-product-database.html; the manufacturer's website www.pharmascience.com)

This leaflet was prepared by Pharmascience Inc.

Last Revised: September 12, 2023