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Desloratadine

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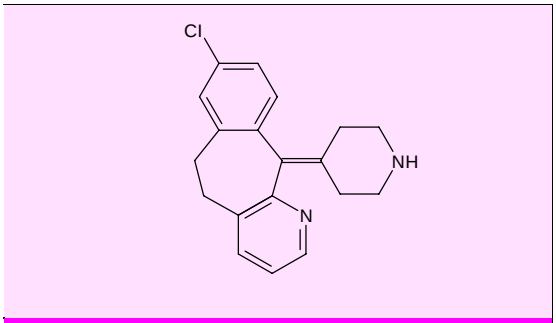
Contents

Abstract

▲ Desloratadine is the orally active major metabolite of the nonsedating H_1-antihistamine loratadine.
▲ The drug had no adverse cardiovascular effects in various animal models or when administered at 9 times the recommended adult dosage for 10 days in volunteers. Therapeutic dosages had no effects on wakefulness or psychomotor performance in healthy volunteers.
▲ No clinically significant interactions have been reported between desloratadine and drugs that inhibit the cytochrome P450 system, nor does the drug potentiate the adverse psychomotor effects of alcohol.
▲ Oral desloratadine 5mg once daily for up to 4 weeks in patients with seasonal allergic rhinitis (SAR) significantly reduced nasal (including congestion) and non-nasal symptoms and improved health-related quality of life compared with placebo. Similar beneficial effects were observed in patients with SAR and coexisting asthma (in whom asthma symptoms and use of β_2-agonists were reduced).
▲ Desloratadine 5mg once daily for 6 weeks significantly improved pruritus and reduced the number of hives compared with placebo in patients with chronic idiopathic urticaria (CIU). Sleep and daytime performance also improved.
▲ Desloratadine was well tolerated in clinical trials and had an adverse event profile similar to that of placebo in patients with SAR (with or without asthma) or CIU.

Features and properties of desloratadine	
Indications	
Seasonal allergic rhinitis (approved in Europe; pending in US)	
Chronic idiopathic urticaria (under review)	
Mechanism of action	
Histamine H_1-receptor antagonist	
Dosage and administration	
Usual dosage in clinical trials	5mg
Route of administration	Oral
Frequency of administration	Once daily
Pharmacokinetic profile (single dose)	
Peak plasma concentration	3.3 μg/L (5mg)
Area under the plasma concentration-time curve	77.5 μg/L • h (5mg)
Apparent total clearance	114-201 L/h (5-20mg)
Elimination half-life	19-34.6h (5-20mg)
Accumulation ratio	1.1-1.6 (5-20mg)
Clinically significant drug interactions	
With drugs that inhibit the cytochrome P450 system?	No
With alcohol?	No
Tolerability	
Not significantly different from placebo	



Desloratadine

Histamine plays a major role in the pathogenesis of allergic rhinitis and urticaria, primarily via the H_1-histamine receptor in target tissues. H_1-antihistamines have therefore been the main focus of drug development for the treatment of these disorders. First generation H_1-antihistamines such as chlorphenamine (chlorpheniramine) and diphenhydramine provide symptomatic relief of allergic rhinitis and urticaria but are associated with undesirable CNS effects such as sedation and impaired psychomotor activity at therapeutic dosages, and adverse anticholinergic effects.[1,2] Second generation agents such as loratadine, cetirizine, astemizole and terfenadine exhibit fewer sedative and anticholinergic effects, but use of the latter 2 agents has been associated with adverse cardiovascular effects.[1-4] The third generation[1] H_1-antihistamine desloratadine is the orally active major metabolite of loratadine. This review presents data on its use in treatment of seasonal allergic rhinitis (SAR) and chronic idiopathic urticaria (CIU).

1. Pharmacodynamic Profile

Receptor-Binding Studies

- When tested in >100 receptor and enzyme systems *in vitro*, desloratadine showed high specificity for H_1-histamine receptors, with 15- to 50-fold higher affinity for H_1-histamine than H_2-histamine or M_1, M_2, M_4, and M_5 muscarinic receptors.[5]

- The drug was 15 times more potent than loratadine, and 10 to 20 times more potent than terfenadine, in displacing radiolabelled mepyramine from H_1-receptors in membrane preparations from guinea-pig brain and lung tissue.[5] In isolated rat brain, desloratadine displaced ^{3}H-pyrilamine binding to the H_1-receptor with a dissociation constant (K_i) similar to that of chlorphenamine but 18-fold lower than that of loratadine.[5]

Antihistaminic and Antiallergic Activity

- Desloratadine inhibited intercellular adhesion molecule-1 (ICAM-1) expression by nasal epithelial cells[6] and the release of interleukin (IL)-8, RANTES and soluble ICAM-1 from human bronchial epithelial cells *in vitro*.[7] In addition, the drug inhibited the release of histamine, tryptase, leukotriene C_4 and prostaglandin D_2 from various human target cells (including lung mast cells, basophils and tissue mast cells) after immunological challenge.[8,9] TNF-α, IL-3, IL-6 IL-8 and GM-CSF secretion from human leukaemic mast cell and basophil lines was also reduced in the presence of desloratadine.[10]

- Orally administered desloratadine was ≈4-fold more potent than loratadine in blocking histamine-induced mouse paw oedema ($p < 0.05$) and ≈10-fold more potent than loratadine in reducing guinea-pig nasal responses to histamine challenge.[5] In guinea-pigs, the drug provided greater protection against lethal doses of histamine than loratadine (calculated oral dose which protected 50% of the animals for ≥30 min was 0.15 *vs* 0.37 mg/kg).[5]

- Oral desloratadine 5 mg/kg significantly reduced acute bronchospasm in allergic cynomolgus monkeys exposed to an antigen challenge ($p < 0.0025$ *vs* placebo).[5] In addition, single oral doses of desloratadine 0.3 and 1 mg/kg significantly reduced the number of allergic coughs induced by aerosolised ovalbumin in ovalbumin-sensitised guinea-pigs ($p < 0.05$ *vs* placebo).[5]

- The onset of action of oral desloratadine 5mg was rapid (≈28 minutes) in patients with SAR who were exposed to controlled pollen challenges in a small, short-term study.[11] Efficacy was based on reductions in patient-reported nasal and non-nasal total symptom severity scores (TSS) and the onset

of action was defined as the time taken from drug administration until TSS was reduced by ≈25%. Importantly, the drug continued to protect against allergen challenge for up to 24 hours after administration.

Cardiovascular Effects

• Unlike a number of other H_1-antihistamines,[4] desloratadine has not demonstrated any adverse cardiovascular or electrocardiographic (ECG) effects. Studies in rats, guinea-pigs and monkeys showed that oral or intravenous administration of the drug had no adverse effects on blood pressure, heart rate or ECG parameters.[12]

• At a dosage of 45 mg/day (9 times the recommended dose), desloratadine had no significant effects on the QTc, PR and QRS intervals compared with placebo when administered orally for 10 days in 24 healthy volunteers.[13,14]

CNS Effects

• Desloratadine 6 mg/kg did not cross the blood-brain barrier of guinea-pigs after intraperitoneal administration.[12] Consistent with this finding, oral desloratadine 1 to 12 mg/kg caused no behavioural, neurological or autonomic changes in rats.[12]

• The effects of a single oral dose of desloratadine 7.5mg on wakefulness and psychomotor performance did not differ significantly from those of placebo in 2 randomised, crossover studies (presented in 1 report)[15] involving a total of 44 volunteers. In contrast, diphenhydramine 50mg reduced wakefulness and impaired psychomotor performance ($p < 0.01$ *vs* desloratadine and placebo).

• Desloratadine, unlike diphenhydramine, did not impair driving performance compared with placebo in a randomised crossover study in 18 healthy volunteers.[16] Each volunteer received single oral doses of desloratadine 5mg, diphenhydramine 50mg and placebo at ≥5-day intervals and performed standard driving tests 2 and 3 hours after drug administration. Brake reaction time, the ability to maintain both a steady lateral position and a 40m distance between cars at 100 km/h, and the standard deviation of speed, were generally similar in desloratadine and placebo recipients. However, diphenhydramine significantly impaired brake reaction time ($p = 0.001$ *vs* desloratadine) and the ability to maintain a steady lateral position ($p < 0.0001$ *vs* desloratadine and placebo).

2. Pharmacokinetic Profile

• The pharmacokinetic profile of oral desloratadine was linear over the dosage range 5 to 20mg in a nonblind, randomised, crossover study in 20 fasting male volunteers who received each dose separated by a ≥14-day washout period.[17] Dose-normalised (to 5mg) maximum plasma concentrations (C_{max}) and the area under the concentration-time curve (AUC) of desloratadine were 3.3 μg/L and 77.5 μg/L · h, respectively. The absorption of desloratadine was not altered by coadministration with food.[17,18]

• The apparent total body clearance of single oral doses of desloratadine 5 to 20mg in healthy volunteers ($n = 10$ per dose) ranged from 114 to 201 L/h and the terminal elimination half-life ($t_{½}$) ranged from 19 to 34.6 hours.[19] These (as well as C_{max} and AUC) values were similar after once daily administration for 14 days in the same individuals, and the accumulation ratio ranged from 1.1 to 1.6 (in line with the dosing interval and $t_{½}$).[19]

• Absorption and elimination ($t_{½}$) of desloratadine 7.5mg was shown to be independent of race and gender in a study involving 12 Black male, 12 White male, 12 Black female and 12 White female volunteers who received the drug once daily for 14 days.[20]

Potential for Drug-Drug Interactions

• Clinical studies have shown that desloratadine does not have any clinically significant pharmacokinetic or pharmacodynamic interactions with drugs that inhibit the cytochrome P450 (CYP) system such as ketoconazole (CYP3A4),[21,22] erythromy-

cin (CYP3A4),[22,23] fluoxetine (CYP2D6)[24] or cimetidine (CYP2D6 and CYP3A4).[22]

• Desloratadine was a 4-fold weaker inhibitor of the intestinal wall p-glycoprotein (pGp) transport system *in vitro* than loratadine and therefore has a lower potential for intestinal pGp-mediated drug interactions.[25] In a parallel-group study involving 90 healthy volunteers, desloratadine 5mg once daily for 7 days (unlike fexofenadine 60mg twice daily) had no clinically relevant pharmacokinetic interactions with azithromycin (250mg once daily from days 3 to 7), a drug which may affect gut transport systems.[26] A second study in volunteers (n = 24)[27] showed that the bioavailability of a single dose of desloratadine 5mg was not affected by grapefruit juice (a substance which affects the pGp transport system) whereas that of fexofenadine 60mg was reduced.

• A randomised, 4-way crossover study in 25 healthy volunteers showed that desloratadine does not potentiate the effects of alcohol.[28] Psychomotor function was evaluated before and after administration of a single dose of desloratadine 7.5mg or placebo (each administered with or without an alcohol dose adjusted to achieve a mean blood level of 10 mg/L). Alcohol ingestion was associated with impaired psychomotor performance but neither desloratadine nor placebo potentiated its effects.

3. Therapeutic Trials

A number of randomised, double-blind trials have investigated the efficacy of desloratadine in patients with SAR (with or without coexisting asthma) or CIU. To date, only 2 of these studies (1 in patients with SAR in the absence of asthma[29] and 1 in patients with CIU)[30] have been published in full.

Seasonal Allergic Rhinitis (SAR) Without Coexisting Asthma

• Oral desloratadine 5mg once daily for 2 weeks was significantly more effective than placebo in the treatment of SAR symptoms in 2 studies (1 conducted in spring and 1 in autumn) published in a single report.[29] Overall, 674 patients aged ≥12 years with a ≥2-year history of SAR and a positive skin test were included in the trials. Significant improvements (i.e. reductions) in total nasal and non-nasal symptom severity scores were reported in desloratadine compared with placebo recipients in both seasons. In the study performed in spring, between-group differences were apparent from the first dose of desloratadine and were significant thereafter ($p < 0.01$ *vs* placebo for all time-points).

• Desloratadine 5mg demonstrated 24-hour efficacy in patients with SAR when administered once daily for 4 weeks.[31] In desloratadine recipients, the morning evaluation of nasal and non-nasal symptoms (an assessment of 24-hour efficacy) decreased by a mean of 16.5% after the first dose and 28.1% from days 1 to 29 (corresponding reductions with placebo were 6.7 and 20.9%; both $p < 0.05$).

• Unlike most other antihistamines, desloratadine appears to have a decongestant effect in patients with SAR. A study which pooled data from a number of randomised, double-blind trials involving >1300 patients aged ≥12 years who received desloratadine (5 or 7.5mg once daily) or placebo for 2 weeks showed that active treatment significantly reduced nasal congestion/stuffiness compared with placebo ($p = 0.02$ and 0.01 for desloratadine 5 and 7.5mg, respectively).[32] Patients in each treatment group had moderate to severe nasal congestion at baseline.

• The nasal decongestant effect is also apparent in a pooled analysis of 2 multicentre, randomised, double-blind 4-week studies in which patients received desloratadine 5mg or placebo (n = 613).[33] A significant reduction in nasal congestion was apparent after 1 dose of desloratadine ($p \leq 0.021$ *vs* placebo) and, consistent with its long elimination half-life (section 2), was maintained throughout the 24-hour dosing interval and 4 weeks of treatment (fig. 1a and fig. 1b).[33]

• Two weeks' treatment with desloratadine (dosage not stated) improved health-related quality of life (HRQoL) [evaluated by the Short-Form 36 (SF-36) Health Survey and the Rhinoconjunctivitis

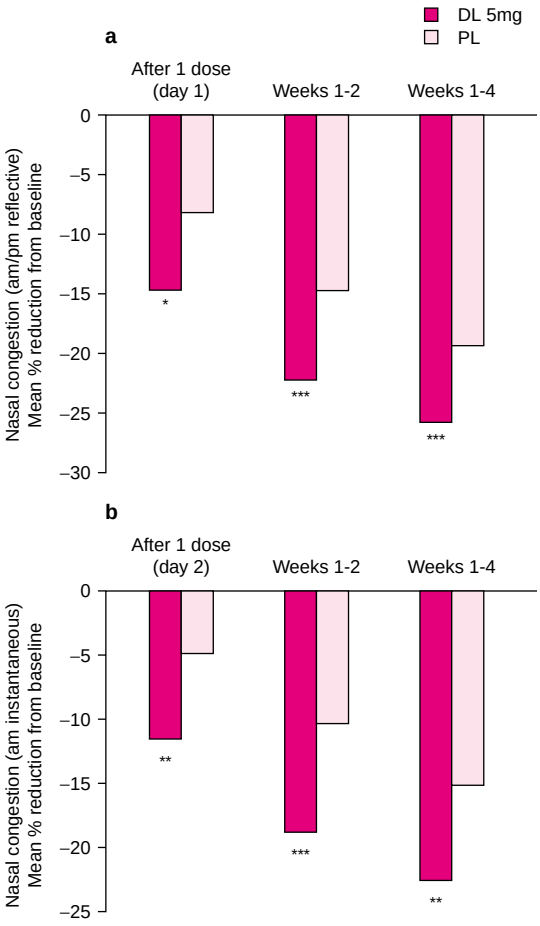


Fig. 1. Effects of desloratadine (DL) on nasal congestion in patients with seasonal allergic rhinitis (SAR) and asthma. In 2 randomised, multicentre double-blind studies 613 patients with SAR were randomised to receive DL 5mg or placebo (PL) once daily for 4 weeks.[33] Patients assessed the severity of nasal congestion over the previous 12 hours [am/pm reflective; (**a**)] and at the time of assessment [am instantaneous; (**b**)] using a 4-point scale (ranging from 0 to 3). * p = 0.021, ** p ≤ 0.01, *** p ≤ 0.001.

quality of life Questionnaire (RQLQ)] compared with placebo in a study involving 496 evaluable patients with SAR.[34] At baseline, patients had lower (i.e. worse) scores than the US general population for 4 out of 8 SF-36 domains (role limitations, bodily pain, social functioning and vitality) as well as a moderate disease burden according to RQLQ scores. Compared with baseline, active treatment significantly improved social functioning and vitality on the SF-36 and 5 out of 8 domains on the RQLQ (practical problems, nasal symptoms, eye symptoms, activities and overall).[34] Improvements in HRQoL correlated with symptomatic improvement.

- In 421 patients with moderate to severe SAR participating in a randomised, double-blind trial,[35] desloratadine 5 and 7.5mg once daily for 2 weeks significantly improved HRQoL compared with placebo. Vitality improved with the 7.5mg dosage and social functioning improved with both dosages ($p < 0.05$). Improvements in 4 RQLQ domains (practical problems, activities, other symptoms and overall) were also reported with both dosages.

SAR With Coexisting Asthma

Patients included in the trials reported in this section were aged ≥15 years, had documented histories of SAR, mild to moderate asthma symptoms at enrolment and were using inhaled bronchodilators. All studies were randomised, double-blind and placebo-controlled and were reported as abstracts.

- Desloratadine 5mg once daily for 2 weeks improved the total asthma symptom score (TASS; sum of individual scores for coughing, wheezing and breathing difficulties) from baseline ($p < 0.05$ *vs* placebo) and concomitantly reduced the use of inhaled β_2-agonists from baseline ($p = 0.002$ *vs* placebo) in a double-blind study involving 278 patients with SAR and coexisting mild asthma.[36] Patients were evaluated during allergy season.

- Significant relief of SAR symptoms was achieved with desloratadine 5mg once daily in a 2-week study[36] and three 4-week studies involving a total of >1000 patients with SAR and asthma.[37-39] The severity of SAR nasal (rhinorrhoea, itching, stuffiness and sneezing) and nonnasal (itching, tearing, eye redness, itching of ears and/or palate) symptoms was rated twice daily from 0 (none) to 3 (severe). Symptoms were summed for a TSS. In all 4-week studies, the morn-

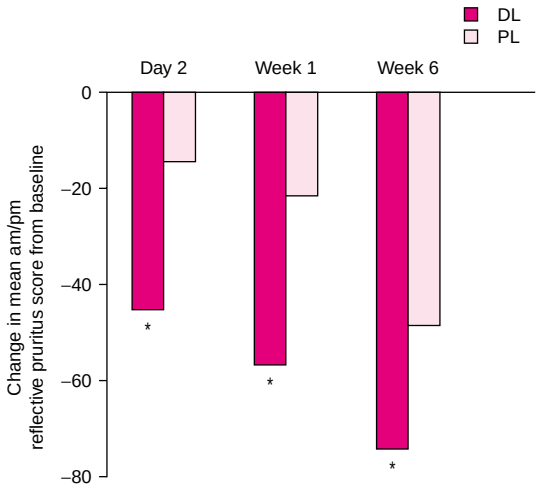


Fig. 2. Effects of desloratadine (DL) on pruritis in patients with chronic idiopathic urticaria (CIU). 190 patients (intent-to-treat population) with a current flare of CIU were randomised to receive DL 5mg or placebo (PL) once daily for 6 weeks. Pruritis was scored twice daily (mean am/pm reflective score) by the patient and changes were assessed versus baseline.[30] * $p < 0.001$ *vs* PL.

ing TSS was reduced significantly by desloratadine day 1 ($p < 0.006$ *vs* placebo) and was maintained for the duration of the study ($p < 0.05$).[37-39]

- A pooled analysis of 2 identical studies involving a total of 613 patients with SAR and asthma showed that desloratadine 5mg once daily for 4 weeks significantly reduced nasal congestion scores compared with placebo.[33] Significant reductions were evident after the first dose ($p < 0.025$ *vs* placebo) and were maintained throughout the study ($p < 0.001$).

Chronic Idiopathic Urticaria

The efficacy of desloratadine in the treatment of CIU has been evaluated in a randomised, double-blind, placebo-controlled trial involving 190 patients with a ≥6-week history of CIU and a current flare.[30] Patients received desloratadine 5mg or placebo once daily for 6 weeks; symptoms such as pruritus, number of hives and size of the largest hive were scored reflectively twice daily (am/pm) and interference with sleep and daily activities was recorded daily.

- Desloratadine had a rapid onset of action in patients with CIU, causing significant improvements in the mean am/pm reflective pruritus score (–45.2 *vs* –14.0% in placebo recipients; $p < 0.001$) within ≈36 hours of the first dose and the mean am/pm reflective TSS (sum of the scores for pruritus, number of hives and the size of the largest hive; –41.6 *vs* –10.6%, $p < 0.001$) after the first dose.[30] Morning instantaneous scores for pruritus indicated that the efficacy of the drug was maintained over the 24-hour dosage interval.

- Desloratadine reduced the reflective pruritus score significantly versus placebo ($p < 0.001$) during the first week of treatment and for the 6-week study duration in patients with CIU (fig. 2).[30] Similarly, the TSS was reduced from baseline to a greater extent by desloratadine than placebo over week 1 (–51.6 *vs* –19.3%; $p < 0.001$) and the reduction was maintained throughout the study ($p < 0.001$).[30]

- Desloratadine significantly improved sleep and daytime performance compared with placebo in patients with CIU.[30] Significant between-group differences ($p \leq 0.02$) in the reflective evaluation of these parameters were evident from the first dose, and were maintained for the entire study duration.[30] During the final week of treatment, improvements from baseline with desloratadine and placebo were ≈75 and 54% for sleep ($p \leq 0.03$) and ≈78 and 40% for daily performance ($p < 0.001$) [values estimated from a graph].

4. Tolerability

- Desloratadine 5mg once daily for 14 days was well tolerated in patients with SAR, with a tolerability profile similar to that of placebo in 2 studies (1 conducted in spring and 1 in autumn) involving 674 patients.[29] Headache was the most frequently reported event with both desloratadine and placebo; other events included pharyngitis, dry

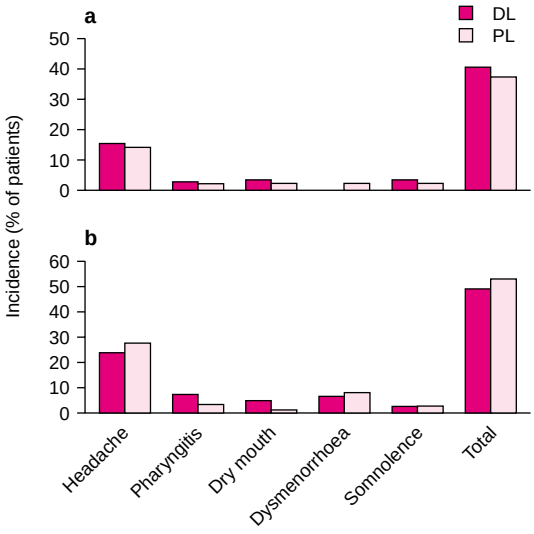


Fig. 3. Tolerability profile of desloratadine (DL) in patients with seasonal allergic rhinitis (SAR). 674 patients with SAR were randomised to receive DL 5mg or placebo (PL) once daily for 14 days during spring (**a**) or autumn (**b**) in 2 double-blind studies (presented in 1 report).[29] No significant between-group differences were reported in either study.

mouth, dysmenorrhoea and somnolence (fig. 3). No significant between-group differences were reported and all events were of mild to moderate severity. Withdrawal rates because of adverse events with desloratadine were similar to, or lower, than those with placebo.

- Desloratadine 5mg once daily was reported to be as well tolerated as placebo in patients with SAR and asthma treated for 4 weeks[38,39] but no further details were available from the abstract reports of this study.

- In a 6-week study[30] involving 190 patients with CIU, treatment-emergent adverse events were reported slightly but not significantly more frequently with desloratadine 5mg than with placebo (55.8 *vs* 43.2%). Headache (12.6 *vs* 16.8%) was the only event reported in >10% of patients in either group.

- The effects of desloratadine 5mg on ECG parameters were not significantly different from those of placebo in patients with SAR.[29] After 14 days' treatment, QT_c-intervals was reduced by ≤3% from baseline in all groups. Similarly, no clinically significant changes in ECG criteria from baseline were reported in patients with CIU treated for 6 weeks.[30]

5. Desloratadine: Current Status

Desloratadine is a nonsedating antihistamine that has received regulatory approval in the European Union and is commercially available in many European countries. It is effective in the treatment of SAR, including relief of nasal congestion. In addition, the drug has improved TASS and reduced β_2-agonist use in patients with SAR and asthma. Finally, desloratadine has shown clinical efficacy in the treatment of CIU.

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