PRODUCT INFORMATION
AERIUS® TABLETS AND SYRUP

NAME OF DRUG

Desloratadine

DESCRIPTION

AERIUS tablets contain desloratadine 5mg and the following inactive ingredients:

Tablet core: calcium hydrogen phosphate, microcrystalline cellulose, maize starch, talc
Coating: lactose, hypromellose, titanium dioxide, macrogol, indigo carmine CI73015, carnauba wax and white wax

AERIUS syrup contains desloratadine 0.5mg/mL. Inactive ingredients are propylene glycol, sorbitol, anhydrous citric acid, sodium citrate, disodium edetate, sucrose, bubble gum flavour, sunset yellow FCF CI15985, water and sodium benzoate as preservative.

PHARMACOLOGY

Pharmacodynamics

Desloratadine is a non-sedating long-acting histamine antagonist with potent, selective peripheral H_1-receptor antagonist activity. Desloratadine has demonstrated antiallergic and antihistaminic activities. After oral administration, desloratadine selectively blocks peripheral histamine H_1-receptors because the drug does not readily penetrate the central nervous system.

In addition to antihistaminic activity, desloratadine has demonstrated antiallergic activities from numerous *in vitro (*mainly conducted on cells of human origin) and *in viv*o studies. These studies have shown that desloratadine inhibits the following activities:

- the release of proinflammatory cytokines including IL-4, IL-6, IL-8, IL-13
- 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 in animal models

In a multiple dose clinical trial, in which up to 20mg of desloratadine was administered daily for 14 days, no statistically or clinically relevant cardiovascular effect was observed. In a clinical pharmacological trial, in which desloratadine was administered at a dose of 45mg daily (nine times the adult clinical dose) for ten days, no prolongation of the QTc interval was seen.

Desloratadine does not readily penetrate the central nervous system. At the recommended adult dose of 5mg daily, there was no excess incidence of somnolence as compared to placebo. AERIUS at a dose of 7.5mg daily did not affect psychomotor performance in clinical trials.

In clinical pharmacological trials, co-administration of alcohol did not increase the alcohol-induced impairment in performance or increase in sleepiness. No significant differences were found in the psychomotor test results between desloratadine and placebo groups, whether administered alone or with alcohol.

In addition to the established classifications of seasonal and perennial, allergic rhinitis can alternatively be classified as intermittent and persistent allergic rhinitis according to the duration of symptoms. Intermittent allergic rhinitis is defined as the presence of symptoms for less than 4

days per week or for less than 4 weeks. Persistent allergic rhinitis is defined as the presence of symptoms for 4 days or more per week and for more than 4 weeks.

Pharmacokinetics

Desloratadine plasma concentrations can be detected within 30 minutes of desloratadine administration. Desloratadine is well absorbed with maximum concentration achieved after approximately 3 hours; the terminal phase half-life is approximately 27 hours. The degree of accumulation of desloratadine was consistent with its half-life (approximately 27 hours) and a once daily dosing frequency. The bioavailability of desloratadine was dose proportional over the range of 5mg to 20mg.

Approximately 8% of subjects are slow metabolisers of desloratadine and have substantially higher plasma concentrations and a longer half-life. The slow metaboliser occurrence rate may vary according to ethnic background. To date this appears not to be clinically important.

Desloratadine is moderately bound (83% - 87%) to plasma proteins. There is no evidence of clinically relevant drug accumulation following once daily dosing of desloratadine (5mg to 20mg) for 14 days.

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

In a single dose trial using a 7.5mg dose of desloratadine, there was no effect of food (high-fat, high caloric breakfast) on the disposition of desloratadine. Similarly, there was no effect of grapefruit juice on the disposition of desloratadine.

In a single dose, crossover trial of desloratadine, the tablet and syrup formulations were bioequivalent and not affected by the presence of food (high fat, high caloric breakfast).
In separate single dose studies, at the recommended doses, paediatric patients had comparable AUC and C_{max} values of desloratadine to those in adults who received a 5mg dose of desloratadine syrup.

No clinically relevant changes in desloratadine plasma concentrations were observed in multiple-dose azithromycin, fluoxetine, cimetidine, ketoconazole and erythromycin interaction trials.

Preclinical Safety

Desloratadine is the primary active metabolite of loratadine. Preclinical studies conducted with desloratadine and loratadine demonstrated that there are no qualitative or quantitative differences in the toxicity profile of desloratadine and loratadine at comparable levels of exposure to desloratadine.

Clinical Studies

Efficacy in Seasonal Allergic Rhinitis

The clinical efficacy of AERIUS (desloratadine) in the treatment of seasonal allergic rhinitis (SAR) was demonstrated in four, multiple-dose, placebo-controlled clinical trials. A total of 2,499 subjects with SAR were randomized to treatment with either AERIUS or placebo. Of these, 1,838 patients received active treatment and 1316 were evaluable for efficacy at the two-week endpoint after having received either 5 mg or 7.5 mg of AERIUS.

Efficacy endpoints in the clinical trials included Total Symptom Score, Total Nasal Symptom Score, Total Non-Nasal Symptom Score, and Quality of Life analysis. AERIUS 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). AERIUS 5 mg was significantly more effective than placebo in reducing Total Nasal Symptoms (sum of scores for rhinorrhoea, sneezing, congestion, and nasal itching) and

Total Non-Nasal Symptoms (sum of scores for itchy burning eyes, tearing, ocular redness, and itchy ears/palate). Instantaneous assessments of efficacy at the end of the dosing interval demonstrated that reductions in symptoms which were observed following the first dose of AERIUS 5 mg were maintained for the full 24 hour dosing interval.

Quality of Life Assessments

Exploratory assessments of quality of life in the clinical trials indicated that SAR produced a mild but consistent burden of disease. Therapeutic response to desloratadine 5mg was correlated to improvements in tow quality of life domains – vitality and social functioning.

Efficacy in Chronic Idiopathic Urticaria
The clinical efficacy of AERIUS (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.

AERIUS 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 AERIUS and were sustained for the full 24 hour dosing interval.

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

Efficacy in Perennial Allergic Rhinitis
The clinical efficacy and safety of Aerius Tablets 5mg were evaluated in over 3000 patients 12 to 80 years of age with perennial allergic rhinitis. A total of 1515 patients received 5mg/day of Aerius in 3 double-blind, randomised, placebo-controlled clinical trials of 4 weeks' duration. In two of these studies, Aerius Tablets 5mg once daily was shown to significantly reduce symptoms of perennial allergic rhinitis.

TOTAL SYMPTOM SCORE (TSS) in a 4 Week Clinical Trial in Patients with Perennial Allergic Rhinitis
Protocol No P00218
Change from baseline in TSS - status at approx. 12 and 24 hours after dosing

Treatment group (n)	Mean baseline (sem)*	Change from baseline (sem)**	Placebo comparison (p-value)
Aerius 5mg (337)	12.37 (0.24)	-4.06 (0.29)	P=0.010
Placebo (337)	12.30 (0.23)	-3.27 (0.28)	

*At baseline, average of total symptom score of at least 10 was required for trial eligibility. TSS ranges from 0=no symptoms to 24=maximum symptoms. TSS was sum of 5 individual nasal symptoms (rhinorrhoea, nasal stuffiness/congestion, postnasal drip/drainage, nasal itching, sneezing) and 3 non-nasal symptoms (itching/burning eyes, tearing/watering eyes, itching of ears or palate). Each symptom scored 0 to 3 where 0=no symptom and 3=severe symptoms.
** Mean reduction in TSS averaged over the 4-week treatment period.

TOTAL SYMPTOM SCORE (TSS) in a 4 Week Clinical Trial in Patients with Perennial Allergic Rhinitis
Protocol No P02772
Change from Baseline in TSS – status over previous 12 hours measured at 12 and 24 hours after dosing

Treatment group (n)	Mean baseline (SEM)*	Change from baseline (SEM)**	Placebo comparison (p-value)
Aerius 5mg (587)	14.34 (0.13)	-3.90 (0.17)	P=0.001
Placebo (583)	14.20 (0.13)	-3.20 (0.17)	

*At baseline average of total symptom score of at least 9 was required for trial eligibility. TSS range from 0=no symptoms to 21=maximum symptoms. TSS was sum of 4 individual nasal symptoms (nasal congestion, rhinorrhoea, nasal itching, sneezing) and 3 non-nasal symptoms (eye tearing/watering, itching/burning eyes, ear itching). Each symptom was scored 0 to 3 where 0=no symptom and 3=severe symptoms.
**Mean reduction in TSS averaged over the 4-week treatment period.

A further study was conducted to compare Aerius 5mg to placebo in patients with perennial allergic rhinitis (Protocol No P00219). 346 patients received Aerius 5mg and 349 received placebo once daily over a 4-week period. No significant difference in efficacy was found between Aerius 5mg and placebo.

Safety Evaluation

A total of 2,762 subjects who received AERIUS in clinical programs for the SAR and CIU indications were evaluable for safety. Of these, 2,049 were treated with AERIUS in multiple-dose trials, with 1,876 receiving doses of 5 mg or higher. The overall incidence of treatment-related adverse events (AEs) in patients treated with AERIUS 5 mg was comparable to the incidence in patients treated with placebo (18% with AERIUS 5 mg vs 13% with placebo).

The most common adverse event, thought to be at least possibly related to treatment, was headache. Treatment-related headache was reported in 5.8% of subjects treated with AERIUS 5 mg compared with 3.9% of placebo subjects. 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 AERIUS an acceptable safety profile.

Paediatric Population

Safety of AERIUS Syrup was demonstrated in three paediatric trials. Children aged 6 months -11 years who were candidates for antihistamine therapy received a daily dose of AERIUS 1 mg (6 months to 11 months of age) AERIUS 1.25mg (1 to 5 years of age) or AERIUS 2.5mg (6 to 11 years of age). Treatment when given over two weeks was well tolerated as documented by clinical laboratory tests, vital signs and ECG interval data, including QTc. When given as a single dose in the recommended dosing regime, the plasma concentration of desloratadine was comparable in the paediatric and adult populations. Thus, since the course of the diseases (seasonal allergic rhinitis, perennial allergic rhinitis and chronic idiopathic urticaria) and the profile of desloratadine are similar in adults and paediatric patients, desloratadine efficacy data in adults can be extrapolated to the paediatric population.

Long-term safety or efficacy studies have not been conducted in children.

INDICATIONS

AERIUS is indicated for the relief of symptoms associated with seasonal and perennial allergic rhinitis, such as sneezing, nasal discharge and itching, as well as ocular itching, tearing and redness and itching of palate.

AERIUS is also indicated for the symptomatic relief itching and reduction in the size and number of hives associated with chronic idiopathic urticaria.

CONTRAINDICATIONS

AERIUS tablets and syrup are contraindicated in patients who have shown hypersensitivity or idiosyncrasy to desloratadine, to any of the excipients or to loratadine.

PRECAUTIONS

Efficacy and safety of AERIUS in children under 6 months of age have not been established.
In the case of severe renal insufficiency, AERIUS should be used with caution.

Use in Pregnancy (Category B1)
No teratogenic or mutagenic effects were observed in animal trials with desloratadine. Since no clinical data on exposed pregnancies are available with desloratadine, the safe use of AERIUS during pregnancy has not been established. AERIUS is not to be used during pregnancy unless the potential benefits outweigh the risks.

Use in Lactation
Desloratadine is excreted into breast milk, therefore the use of AERIUS is not recommended in breast-feeding women.

Carcinogenicity and Mutagenicity
The carcinogenic risk associated with desloratadine would appear to be minimal since an increased incidence of benign hepatic tumours was the only adverse finding in mice treated with high doses of loratadine. Desloratadine showed no mutagenic effects in *in vitro* and *in vivo* mutagenicity studies.

Drug Interactions
In a clinical pharmacology trial AERIUS taken concomitantly with alcohol did not potentiate the performance impairing effects of alcohol.

No clinically relevant interactions with AERIUS were observed in clinical trials in which azithromycin, cimetidine, fluoxetine, erythromycin or ketoconazole were co-administered. However, the enzyme responsible for the metabolism of desloratadine has not been identified yet, and therefore, some interactions with other drugs can not be fully excluded.

There was no effect of food or grapefruit juice on the disposition of desloratadine.

Laboratory Interactions
AERIUS should be discontinued approximately 48 hours prior to skin testing procedures since antihistamines may prevent or diminish otherwise positive reactions to dermal reactivity indicators.

ADVERSE REACTIONS
At the recommended adult dose of 5 mg daily, undesirable effects with Aerius were reported in 5% of patients in excess of those treated with placebo.

The type and frequency of adverse effects reported in the Aerius clinical trials were generally comparable to those reported with placebo.

Incidence of Treatment-Related Adverse Events Reported by ≥ 1.5% of Subjects Treated with Aerius 5 mg in Multiple-Dose Allergic Rhinitis and Chronic Idiopathic Urticaria Studies.

	Number[a] (%) of Subjects	
	Desloratadine 5.0 mg (n=2457)	**Placebo** (n=2445)
No. of Subjects (%) with Any Related Adverse Event[b]	**337 (13.7)**	**281 (11.5)**

Nervous System Disorders Somnolence	42 (1.7)	41 (1.7)
Gastrointestinal Disorders Dry Mouth	59 (2.4)	42 (1.7)
Body As a Whole-General Disorders Headache Fatigue	 92 (3.7) 37(1.5)	 81 (3.3) 16 (0.7)

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.

No effects on the ability to drive and use machines have been observed with the use of desloratadine

During the marketing of Aerius tablets, hypersensitivity reactions, including anaphylaxis and rash, have been reported very rarely.

In addition, cases of tachycardia, palpitations, psychomotor hyperactivity, seizures, elevations of liver enzymes, hepatitis, and increases in bilirubin have been reported very rarely.

In clinical trials in a paediatric population, AERIUS Syrup was administered to a total of 246 children aged 6 months to 11 years.. The overall incidence and type of adverse events in children 2 to 11 years of age was similar for the AERIUS Syrup and the placebo groups. In infants and toddlers aged 6 to 23 months, the most frequent adverse events reported in excess of placebo were diarrhoea (3.7%), fever (2.3%) and insomnia (2.3%).

Desloratadine does not readily penetrate the central nervous system. At the recommended adult dose of 5mg daily, there was no excess incidence of somnolence as compared to placebo. AERIUS given at a single daily dose of 7.5 mg did not affect psychomotor performance in clinical trails.

DOSAGE AND ADMINISTRATION

AERIUS can be taken regardless of mealtime.

AERIUS is not recommended for use in children under 12 months of age for allergic rhinitis and under 6 months of age for chronic idiopathic urticaria.

Allergic Rhinitis (including intermittent and persistent allergic rhinitis):

Adults and Adolescents 12 years and over:	One AERIUS Tablet or 10mL (5 mg) AERIUS Syrup once daily
Children 6 to 11 years of age:	5mL (2.5 mg) AERIUS Syrup once daily
Children 1 to 5 years of age:	2.5mL (1.25 mg) AERIUS Syrup once daily

Intermittent allergic rhinitis (presence of symptoms for less than 4 days per week or for less than 4 weeks) should be managed in accordance with the evaluation of patient's disease history and the treatment could be discontinued after symptoms are resolved and reinitiated upon their reappearance. In persistent allergic rhinitis (presence of symptoms for 4 days or more per week and for more than for weeks), continued treatment may be proposed to the patients during allergen exposure periods.

Chronic Idiopathic Urticaria

Adults and Adolescents 12 years and over:	One AERIUS Tablet or 10mL (5 mg) AERIUS Syrup once daily
Children 6 to 11 years of age:	5mL (2.5 mg) AERIUS Syrup once daily
Children 1 to 5 years of age:	2.5mL (1.25 mg) AERIUS Syrup once daily
Children 6 months to 11 months of age:	2 mL (1 mg) AERIUS Syrup once daily.

OVERDOSAGE

No cases of overdosage had been reported. Based on a multiple dose clinical trial, in which up to 45 mg of desloratadine was administered (9 times the adult clinical dose), no clinically relevant effects were observed.

In the event of overdose, contact the Poisons Information Centre (tel: 13 11 26) for the latest advice regarding treatment.

PRESENTATION

Tablets 5mg, light blue round embossed film coated tablets: 7's, 28's and a sample pack of 1's

Syrup 0.5mg/mL, clear orange coloured solution: 100mL and 200mL

STORAGE CONDITIONS

Tablets: Store below 25^{o}C. Protect from moisture.

Syrup: Store below 25°C. Store in original container.

POISON SCHEDULE

S2 (Pharmacy Medicine)

SPONSOR

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AUSTRALIA

This Product Information was approved by the Therapeutic Goods Administration on 16 April 2008.