S-CCDS-MK4117-MTL-112017

AERIUS® Tablets

Brand of desloratadine

DESCRIPTION: Each AERIUS Tablet contains 5.0 mg of desloratadine. AERIUS Tablet is a light blue round tablet, embossed with elongated letters 'S' and 'P' on one side and plain on the other. Inactive Ingredients: dibasic calcium phosphate dihydrate, microcrystalline cellulose, corn starch, talc, film coat [containing lactose monohydrate, hypromellose, titanium dioxide, macrogol 400, indigotin (E132)], clear coat (containing hypromellose, macrogol 400), carnauba wax, and white wax.

ACTIONS: Desloratadine is a non-sedating long-acting histamine antagonist with potent, selective peripheral H_1-receptor antagonist activity. Desloratadine has demonstrated antiallergic, antihistaminic, and anti-inflammatory activity.

In addition to antihistaminic activity, desloratadine has demonstrated antiallergic and anti-inflammatory activity from numerous *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, 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 in animal models.

PRECLINICAL TOXICOLOGY: Desloratadine is the primary active metabolite of loratadine. Non-clinical studies conducted with desloratadine and loratadine demonstrated comparable qualitative and quantitative toxicity profile of desloratadine and loratadine at comparable levels of exposure to desloratadine.

Carcinogenesis, Mutagenesis, Impairment of Fertility: Carcinogenicity studies were not conducted for desloratadine. Desloratadine has no known carcinogenic potential to-date in man based on the available data with loratadine.

Desloratadine showed no mutagenic effects in *in vitro* and *in vivo* mutagenicity studies.

There was no effect on female fertility at doses up to 12 mg/kg (≈280x the clinical exposure at the recommended therapeutic dose). In a rat fertility study, increases in preimplantation losses resulting in lower numbers of implantation sites and fetuses, were observed at 24 mg/kg (≈500x the clinical exposure at the recommended therapeutic dose) of desloratadine in female rats. 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 ≥12 mg/kg (≥≈175x the clinical exposure at the recommended therapeutic dose). At a dose level of 3 mg/kg toxicity (≈34x the clinical exposure at the recommended therapeutic dose), there was no overall effect on male rat fertility. However, a few rats given desloratadine at a dose level of 3 mg/kg, showed decreases in sperm parameters and testicular and epididymal microscopic changes. These histopathological observations were specific to the rat, have been observed with other antihistamines, and were not observed in mice or monkeys. Extensive clinical experience with loratadine has not demonstrated any clinical effects on human male or female fertility.

There are no clinical data with desloratadine on human male reproduction despite the observation of similar rat testicular lesions with loratadine and some other antihistamines. Available data with loratadine showed no clinical effect on male fertility. There is also no available evidence suggesting that antihistamines affect either human male or female fertility.

Desloratadine was not teratogenic in rats or rabbits at exposures that were 228 and 864 times higher, respectively, than the exposure in humans at the recommended clinical dose.

CLINICAL PHARMACOLOGY

Pharmacodynamic Properties: After oral administration in animals, desloratadine selectively blocks peripheral histamine H_1-receptors because the drug is effectively excluded from entry to the central nervous system (CNS).

In a multiple dose clinical trial in which up to 20 mg of desloratadine was administered daily for 14 days, no statistically or clinically relevant cardiovascular effect was observed. In a clinical pharmacologic trial in which 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.

In clinical studies of patients with Seasonal Allergic Rhinitis treated with desloratadine for up to 4 weeks, limited data showed that the effect of desloratadine on QTc prolongation was similar to that of placebo. There are no clinical studies with desloratadine beyond 4 weeks of duration.

Non-clinical studies showed no significant activity in the CNS with oral administration of desloratadine. In clinical studies, at the recommended dose of 5 mg daily, there was no excess somnolence as compared to placebo. AERIUS Tablets at a dose of 7.5 mg did not affect psychomotor performance in

clinical trials. In a single dose study, desloratadine 5 mg did not affect standard measures of flight performance including exacerbation of subjective sleepiness or tasks related to flying.

In two separate studies desloratadine 7.5 mg was co-administered with ketoconazole 200 mg twice daily and erythromycin 500 mg every eight hours under steady state conditions to normal, healthy male (n=12) and female (n=12) volunteers. Concentrations of desloratadine decreased in 2 of 24 subjects during co-administration of ketoconazole. In the remainder of subjects, co-administration of ketoconazole and desloratadine resulted in a 45% and 39% increase in C_{max} and AUC, respectively, for desloratadine. In a similar study erythromycin increased C_{max} and AUC values for desloratadine by 24% and 14% respectively. No clinically relevant effects on ECG parameters during concomitant administration with ketoconazole or erythromycin were observed.

In single dose clinical pharmacologic trials, co-administration of alcohol with 7.5 mg of desloratadine 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 adult and adolescent patients with allergic rhinitis (AR), AERIUS Tablets were effective in relieving symptoms such as sneezing, nasal discharge and itching, congestion/stuffiness, as well as ocular itching, tearing and redness, and itching of palate. AERIUS Tablets effectively controlled symptoms for 24 hours.

AERIUS was effective in alleviating the burden of seasonal allergic rhinitis as shown by the total score of the rhino-conjunctivitis quality of life questionnaire. The greatest amelioration was seen in the domains of practical problems and daily activities limited by symptoms.

In addition to the established classifications of seasonal and perennial, allergic rhinitis can alternatively be classified as intermittent allergic rhinitis 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.

Chronic idiopathic urticaria was studied as a clinical model for urticarial conditions, since the underlying pathophysiology is similar, regardless of etiology, and because chronic patients can be more easily recruited prospectively. Since histamine release is a causal factor in all urticarial diseases, desloratadine is expected to be effective in providing symptomatic relief for other urticarial conditions, in addition to chronic idiopathic urticaria, as advised in clinical guidelines.

In two placebo-controlled six week trials conducted in adults and adolescents with chronic idiopathic urticaria (CIU), AERIUS Tablets were effective in relieving pruritus and decreasing the size and

number of hives by the end of the first dosing interval. In each trial, the effects were sustained over the 24 hour dosing interval. As with other antihistamine trials in CIU, the minority of patients who were identified as non-responsive to antihistamines was excluded. Treatment with AERIUS Tablets also improved sleep and daytime function, as measured by reduced interference with sleep and routine daily activities.

Pharmacokinetic Properties: 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. In adults and adolescents, bioavailability of desloratadine was dose proportional over the range of 5 mg to 20 mg.

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

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. *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 or CYP2D6 and is neither a substrate nor an inhibitor of P-glycoprotein.

In a single dose trial using a 7.5 mg dose of desloratadine, 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.

INDICATIONS AND USAGE: AERIUS Tablets are indicated for the rapid relief of symptoms associated with allergic rhinitis (including intermittent and persistent allergic rhinitis) such as sneezing, nasal discharge and itching, congestion/stuffiness, as well as ocular itching, tearing and redness, itching of palate and coughing.

AERIUS Tablets are also indicated for the relief of symptoms associated with urticaria such as the relief of itching and the size and number of hives.

DOSAGE AND ADMINISTRATION: Adults and Adolescents (12 years of age and older): For oral use. One AERIUS 5 mg film-coated tablet once a day, regardless of mealtimes, and as and when necessary, for the relief of symptoms associated with allergic rhinitis (including intermittent and persistent allergic rhinitis) and urticaria. Desloratadine is not recommended for long-term use.

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 4 weeks), continued treatment may be proposed to the patients during allergen exposure periods.

DRUG INTERACTIONS: AERIUS was shown to have no clinically relevant effects on ECG parameters with ketoconazole and erythromycin (see section on Pharmacodynamic properties). There was no effect of food or grapefruit juice on the disposition of desloratadine.

AERIUS taken concomitantly with alcohol did not potentiate the performance impairing effects of alcohol (see section on Pharmacodynamic properties).

ADVERSE EFFECTS: The type and frequency of undesirable effects reported throughout the AERIUS clinical trials were generally comparable to those reported with placebo.

In controlled and uncontrolled clinical trials, no clinically relevant drug-related adverse effects including cardiovascular effects were observed with AERIUS Tablets. At the recommended dose of 5 mg daily, undesirable effects were observed with AERIUS were reported in 4% of patients in excess of those treated with placebo. No excess incidence of somnolence was reported (2% in the desloratadine treated and 2% in the placebo groups).

Incidence of Treatment-Related Adverse Events Reported by ≥ 2% of Subjects in Placebo-Controlled Multiple-Dose Clinical Trials

Adverse Event	AERIUS (desloratadine 5.0 mg) (n=659)	Placebo (n=661)
	Numbers* (%) of Subjects	
Headache	38(6)	26(4)
Fatigue	17(3)	10(2)
Dry Mouth	21(3)	12(2)

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

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

Other adverse effects reported very rarely during the post-marketing period include hallucinations, dizziness, somnolence, insomnia, psychomotor hyperactivity, seizures, abdominal pain, nausea, vomiting, dyspepsia, diarrhoea, myalgia.

CONTRAINDICATIONS: Hypersensitivity to the desloratadine, loratadine or to any of the excipients.

SPECIAL POPULATIONS:

Age: In older subjects (≥ 65 years old; n=17) following multiple-dose administration of desloratadine, the mean C_{max} and AUC values were 20% greater than in younger subjects (<65 years old). The oral total body clearance (CL/F) when normalised for body weight was similar between the two age groups. The mean plasma elimination half-life was prolonged by approximately 30% (33.7hr) in subjects ≥ 65 years old. Currently available information suggests that dosage adjustment in elderly subjects may not be necessary. However, this has not yet been fully determined.

Gender: Results of the population pharmacokinetics analysis showed that the AUC and C_{max} were higher in 24 females (3% and 10% respectively) as compared to 24 males following administration of 7.5 mg desloratadine for 14 days. However, these apparent differences are not considered clinically relevant and therefore no dosage adjustment is recommended.

Race: Results of the population pharmacokinetics analysis including subjects of Caucasian (n=24) and Black (n=24) showed that the AUC and C_{max} for desloratadine were higher in Blacks (18% and 32% respectively) following administration of 7.5 mg desloratadine for 14 days. These differences are not considered to be clinically relevant and therefore no dose adjustment is recommended.

Hepatic: Desloratadine pharmacokinetics were characterised following a single oral dose in subjects with mild (n=4), moderate (n=4) and severe (n=4) hepatic dysfunction as defined by the Child-Pugh classification of hepatic dysfunction and 8 subjects with normal hepatic function. The pharmacokinetics were similar across the hepatic dysfunction groups. Subjects with hepatic dysfunction had approximately a 2.4-fold increase in AUC as compared with normal subjects. This level of exposure was not associated with any serious or unexpected adverse events in this or other studies. There were no statistically significant differences in the half-life among subjects with hepatic dysfunction and normal subjects. Currently available information on the use of desloratadine in subjects with hepatic dysfunction suggests that there may not be a need for dosage adjustment. However, this has not yet been fully determined.

Renal: C_{max} for desloratadine increased (≤2.5-fold) in subjects with renal dysfunction following a single oral dose of 7.5 mg desloratadine. No clinically relevant changes in pharmacokinetics of desloratadine were observed in subjects with renal dysfunction following single oral dosing. No dosage adjustment is recommended in subjects with renal impairment.

PRECAUTIONS: Efficacy and safety of AERIUS 5 mg Tablets in children under 12 years of age have not been established; therefore, use of AERIUS 5 mg Tablets in children is not recommended.

Effects on Ability to Drive and Use Machines: Based on assessments using the Standard Highway Driving Test, the Car Following Test, and a full battery of psychometric evaluations, no undesirable effects on the ability to drive and use machines have been observed. However, patients should be informed that very rarely some people experience drowsiness, which may affect their ability to drive or use machines.

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.

USAGE DURING PREGNANCY AND LACTATION: No teratogenic or mutagenic effects were observed in animal trials with desloratadine (see Preclinical TOXICOLOGY). Since no clinical data on exposed pregnancies are available with desloratadine, the use of AERIUS during pregnancy has not been established. Therefore use only if the potential benefit justifies the potential risk to the fetus.

Desloratadine is excreted into breast milk; therefore breast-feeding is not recommended in lactating women taking AERIUS Tablets.

OVERDOSAGE INFORMATION: In the event of overdose, consider standard measures to remove unabsorbed active substance. Symptomatic and supportive treatment is recommended.

Based on a multiple dose clinical trial in adults and adolescents, in which up to 45 mg of desloratadine was administered (9 times the clinical dose), no clinically relevant effects were observed.

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

HOW SUPPLIED: AERIUS Tablets: In blister packs of 10's, 10 X 10's and 50 X 10's.

STORAGE: Store below 30°C. Store in the original container. Tablets should be consumed immediately after removing from the foil-backed blister packs. Exposed tablets should be discarded.

Keep out of reach of children.
Shelf-life information can be found on the inner and outer labels of the products.
Further information can be obtained from the doctor or the pharmacist.

Product Registrant

Organon Singapore Pte. Ltd.
150 Beach Road
#36-01/08 Gateway West
Singapore 189720

Zuellig Pharma (B) Sdn Bhd
Unit 5, 1st floor,
Spg 607, Jalan Gadong,
Kg Beribi, BSB, BE1118
Brunei Darussalam

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