S-CCDS-MK4117-MTL-112017

AERIUS® Syrup and Oral Solution

Brand of desloratadine

DESCRIPTION for AERIUS® Syrup: Each 1 ml of AERIUS® Syrup contains 0.5 mg of desloratadine. AERIUS® Syrup is a clear, orange solution. Inactive Ingredients: propylene glycol, sorbitol liquid, citric acid anhydrous, sodium citrate dihydrate, sodium benzoate, disodium edetate, sucrose, natural and artificial flavor, FD&C Yellow Dye No. 6 and purified water. Preservative: sodium benzoate 1.00 mg/ml.

DESCRIPTION for Oral Solution: Each 1 ml of AERIUS® Oral Solution contains 0.5 mg of desloratadine. AERIUS® Oral Solution is a clear solution. Inactive Ingredients: propylene glycol, sorbitol liquid, citric acid anhydrous, sodium citrate dihydrate, disodium edetate, hypromellose, sucralose, natural and artificial flavor, and purified water.

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 that there are no qualitative or quantitative

differences in the toxicity profile of desloratadine and loratadine at comparable levels of exposure to desloratadine.

Non-clinical data with desloratadine reveal no special hazard for humans based on conventional studies of safety pharmacology, repeated dose toxicity, genotoxicity, and toxicity to reproduction. The lack of carcinogenic potential was demonstrated in studies conducted with loratadine.

CLINICAL PHARMACOLOGY

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

Efficacy of AERIUS® Syrup had not been investigated in separate paediatric trials. Safety of AERIUS® Syrup was demonstrated in three pediatric trials. Children, 1-11 years of age, who were candidates for antihistamine therapy received a daily desloratadine dose of 1.25 mg (1 through 5 years of age) or 2.5 mg (6 through 11 years of age). Treatment was well tolerated as documented by clinical laboratory tests, vital signs, and ECG interval data, including QTc. When given at the recommended doses, the plasma concentration of desloratadine (see CLINICAL PHARMACOLOGY) was comparable in the pediatric and adult populations. Thus, since the course of SAR/CIU and the profile of desloratadine are similar in adults and pediatric patients, desloratadine efficacy data in adults can be extrapolated to the pediatric population.

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.

Desloratadine does not readily penetrate the central nervous system. At the recommended dose of 5 mg daily, there was no excess incidence of somnolence as compared to placebo. AERIUS® tablets even at a dose of 7.5 mg daily 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.

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

In clinical pharmacologic 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 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. Efficacy has not been clearly demonstrated in patients 12-17 years of age.

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 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 as early as 1 day after initiation of treatment. In each trial, the effects were sustained over the 24-hour dosing interval. Treatment with AERIUS® tablets also improved sleep and daytime function, as measured by reduced interference with sleep and routine daily activities.

AERIUS® Syrup 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.

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, the bioavailability of desloratadine was dose proportional over the range of 5 mg to 20 mg.

In a series of pharmacokinetic and clinical trials, 6% of the subjects reached a higher concentration of desloratadine. The prevalence of this poor metaboliser phenotype was comparable for adult (6%) and paediatric subjects 2- to 11-year-old (6%), and greater among Blacks (18% adult, 16% paediatric) than Caucasians (2% adult, 3% paediatric) in both populations.

In a multiple-dose pharmacokinetic study conducted with the tablet formulation in healthy adult subjects, four subjects were found to be poor metabolisers of desloratadine. These subjects had a C_{max} concentration about 3-fold higher at approximately 7 hours with a terminal phase half-life of approximately 89 hours.

Similar pharmacokinetic parameters were observed in a multiple-dose pharmacokinetic study conducted with the syrup formulation in paediatric poor metaboliser subjects 2- to 11-year-old diagnosed with allergic rhinitis. The exposure (AUC) to desloratadine was about 6-fold higher and the C_{max} was about 3 to 4-fold higher at 3-6 hours with a terminal half-life of approximately 120 hours. Exposure was the same in adult and paediatric poor metabolisers when treated with age-appropriate doses. The overall safety profile of these subjects was not different from that of the general population. The effects of AERIUS® syrup in poor metabolizers < 2 years of age have not been studied.

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) 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.

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, pediatric patients had comparable AUC and C_{max} values of desloratadine to those in adults who received a 5 mg dose of desloratadine Syrup.

INDICATIONS AND USAGE: AERIUS® Syrup and Oral Solution 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® Syrup and Oral Solution 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:
The prescriber should be aware that most cases of rhinitis below 2 years of age are of infectious origin and there are no data supporting the treatment of infectious rhinitis with AERIUS®.

Children 6 through 11 years of age: 5 ml (2.5 mg) AERIUS® Syrup and Oral Solution once a day, with or without a meal.

Children 2 through 5 years of age: 2.5 ml (1.25 mg) AERIUS® Syrup and Oral Solution once a day, with or without a meal.

Children 1 through 2 years of age (urticaria): 2.5 ml (1.25 mg) AERIUS® Syrup and Oral Solution once a day, with or without a meal.

In adults and adolescents (12 years of age and over): 10 ml (5 mg) AERIUS® Syrup and Oral Solution once a day, with or without a meal. 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: No clinically relevant interactions with AERIUS® tablets were observed in clinical trials (see section on Pharmacodynamic properties). There was no effect of food or grapefruit juice on the disposition of desloratadine.

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

ADVERSE EFFECTS: In clinical trials in a paediatric population, AERIUS® Syrup was administered to a total of 246 children aged 6 months through 11 years. The overall incidence of adverse events in children 2 through 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 diarrhea (3.7%), fever (2.3%) and insomnia (2.3%).

In clinical trials in a range of indications including SAR and CIU, at the recommended dose of 5 mg daily, undesirable effects with AERIUS® tablets were reported in 3% of patients in excess of those treated with placebo. The most frequent adverse events reported in excess of placebo were fatigue (1.2%), dry mouth (0.8%), and headache (0.6%).

Very rare cases of hypersensitivity reactions, including anaphylaxis and rash have been reported during the marketing of desloratadine. In addition, cases of dizziness, somnolence, insomnia, abdominal pain, nausea, vomiting, dyspepsia, diarrhea, myalgia, 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 are hallucinations, psychomotor hyperactivity, seizures.

CONTRAINDICATIONS: Hypersensitivity to the active substance 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® Syrup and Oral Solution in children under 1 year of age have not been established.

Effects on ability to drive and use machines: No effects on the ability to drive and use machines have been observed (see Pharmacodynamic properties). 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 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 PRECLINICAL TOXICOLOGY). Since no clinical data on exposed pregnancies are available with desloratadine, the safe use of AERIUS® Syrup and Oral Solution during pregnancy has not been established. AERIUS® Syrup and Oral Solution is not to be used during pregnancy unless the potential benefits outweigh the risks.

Desloratadine is excreted into breast milk, therefore the use of AERIUS® Syrup and Oral Solution is not recommended in breast-feeding women.

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® Syrup and Oral Solution in glass bottles of 50 ml, 60 ml, 100 ml, 120 ml, and 150 ml. Not all presentations may be available locally.

STORAGE: Store below 30°C. Store in the original container.

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.

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