AERIUS® SYRUP

Desloratadine

DESCRIPTION: Each 1 ml of syrup contains 0.5 mg of desloratadine.

PHARMACOLOGICAL PROPERTIES

Pharmacodynamic properties

Pharmacotherapeutic group: antihistamines – H_1 antagonist, ATC code : R06A X27

Desloratadine is a non-sedating, long acting histamine antagonist with selective peripheral H_1-receptors antagonist activity. After oral administration desloratadine selectively blocks peripheral histamine H_1-receptors because the substance is excluded from entry to the central nervous system.

Desloratadine has demonstrated antiallergic properties from *in vitro* studies. These include inhibiting the release of proinflammatory cytokines such as IL-4, IL-6, IL-8, and IL-13 from human mast cells/basophils, as well as inhibition of the expression of the adhesion molecule P-selectin on endothelial cells. The clinical relevance of these observations remains to be confirmed.

Efficacy of Aerius syrup has not been investigated in separate paediatric trials. Safety of Aerius syrup was demonstrated in three-paediatric trials. Children ages 1 through 11 years of age who were candidates for antihistamine therapy received a daily dose of 1.25 mg (1-5 years of age) and 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 Pharmacokinetic properties) was comparable in the paediatric and adult populations. Thus, since the course of SAR/CIU and the profile of desloratadine are similar in adults and paediatric patients, desloratadine efficacy data in adults can be extrapolated to the paediatric population.

In a multiple dose clinical trial, in adults and adolescents, 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 pharmacology trial, in adults and adolescents, in which desloratadine was administered to adults at a dose of 45 mg daily (nine times the clinical dose) for ten days, no prolongation of QTc interval was seen.

Desloratadine does not readily penetrate the central nervous system. At the recommended dose of 5 mg daily for adults and adolescents, there was no excess incidence of somnolence as compared to placebo. Aerius tablets given at a single daily dose of 7.5 mg to adults and adolescents did not affect psychomotor performance in clinical trials. In a single dose study performed in adults, desloratadine 5 mg did not affect standard measures of flight performance including exacerbation of subjective sleepiness or tasks related to flying.

In clinical pharmacology trial in adults, co-administration with 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.

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

In adult and adolescent patients with seasonal allergic rhinitis, Aerius tablets were effective in relieving symptoms such as sneezing, nasal discharge and itching, as well as ocular itching, tearing and redness, and itching of palate. Aerius effectively controlled symptoms for 24 hours.

In two placebo-controlled six week trials in patients with CIU, Aerius was 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. An improvement in pruritus of more than 50% was observed in 55% of patients treated with desloratadine compared with 19% of patients treated with placebo. Treatment with Aerius also significantly reduced interference with sleep and daytime function, as measured by a four-point scale used to assess these variables.

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.

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.

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.

Pharmacokinetic properties

Desloratadine plasma concentrations can be detected within 30 minutes of desloratadine administration in adults and adolescents. 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 5 mg to 20 mg.

In a pharmacokinetic trial in which patient demographics were comparable to those of the general SAR population, 4% of the subjects achieved a higher concentration of desloratadine. This percentage may vary according to ethnic background. Maximum desloratadine concentration was about 3-fold higher at approximately 7 hours with a terminal phase half-life of approximately 89 hours. The safety profile of these subjects was not different from that of the general population.

Desloratadine is moderately bound (83% - 87%) to plasma proteins. There is no evidence of clinically relevant drug accumulation following once daily adult and adolescent dosing of desloratadine (5 mg to 20 mg) for 14 days.
In a single dose, crossover study of desloratadine, the tablet and the syrup formulations were found to be bioequivalent.

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 5 mg dose of desloratadine syrup.

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. Studies conducted show that desloratadine does not inhibit CYP3A4 and desloratadine is not a substrate or 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.

Preclinical safety data

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 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.

INDICATIONS AND USAGE:

AERIUS is indicated for the relief of symptoms associated with:

- allergic rhinitis (AR, including intermittent and persistent allergic rhinitis)
- urticaria

DOSAGE AND ADMINISTRATION:

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

Children 1 through 5 years of age: 2.5 ml (1.25 mg) AERIUS syrup once a day, with or without a meal.

In adults and adolescents (12 years of age and over): 10 ml (5 mg) AERIUS syrup once a day, with or without a meal.

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 in which erythromycin or ketoconazole were co-administered (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:

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 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 %).

In clinical trials in a range of indications including SAR and CIU and, 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 %). Other undesirable effects reported very rarely during the post-marketing period are listed in the following table:

Cardiac disorders	Tachycardia, palpitations, psychomotor hyperactivity, seizures
Gastrointestinal disorders	Abdominal pain, nausea, vomiting, dyspepsia, diarrhoea, increased appetite
Hepato-biliary disorders	Hepatitis, Elevations of liver enzymes, increased bilirubin
General disorders	Hypersensitivity reactions (such as anaphylaxis, angioedema, pruritus, rash and urticaria)
Nervous system disorders	Somnolence

CONTRAINDICATIONS:

Hypersensitivity to the active substance or to any of the excipients.

PRECAUTIONS:

Efficacy and safety of AERIUS syrup in children under 1 year of age have not been established. In the case of severe renal insufficiency, AERIUS syrup should be used with caution. This medicinal product contains sucrose and sorbitol; thus, patients with rare hereditary problems of fructose intolerance, glucose-galactose malabsorption or sucrose-isomaltase insufficiency should not take this medicine.

Effects on ability to drive and use machines: No effects on the ability to drive and use machines have been observed (see Pharmacodynamic properties).

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 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.

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

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 considers discontinuing desloratadine in patients who experience a seizure while on treatment.

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.

PRESENTATIONS:
AERIUS Syrup, box of 1 bottle of 60 ml. Reg. No.: DKI0487101137A1

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

HARUS DENGAN RESEP DOKTER

Manufactured by :
Schering-Plough Labo N.V.,
Heist, Belgium.
Registered by :
PT Organon Pharma Indonesia Tbk
Pasuruan, Jawa Timur

References:
PI 07/08 LRN 034117-DL-TB-PIPB.3
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