SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

DOXAFIN 2.5 mg/5 ml Syrup

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each 5 ml syrup contains
Active substance:
Deslorotadine……2.5 mg

Excipients:
FD&C Yellow 6, Eurocert sunset yellow…...0.23 mg
Sorbitol liquid, crystallized, 70%.....1.77 g
Liquid sucrose…….....…..1.49 g
For a full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Syrup
Clear, yellow-orange colored solution with characteristic odor (strawberry)

4. CLINICAL PARTICULARS

4.1. Therapeutic indications

DOXAFIN is indicated for the relief of symptoms associated with allergic rhinitis like sneezing, nasal discharge and itching, congestion/stuffiness, as well as ocular itching, tearing and redness, itching of palate and coughing.

DOXAFIN is also indicated for the relief of symptoms associated with urticaria including itching, skin blisters and redness.

4.2. Posology and method of administration

Posology/frequency and duration of administration
Intermittent allergic rhinitis with symptoms lasting less than 4 days per week or less than 4 weeks should be managed in accordance with the evaluation of patient's disease history and the treatment should be interrupted if symptoms resolve and recur.
In persistent allergic rhinitis with symptoms lasting 4 days or more per week and for more than 4 weeks, continued treatment should be proposed to the patients if allergy occurs.

Method of administration
Children 6 through 11 months of age: 2 ml DOXAFIN once daily (1 mg) with or without meals for the relief of symptoms associated with allergic rhinitis including intermittent and persistent allergic rhinitis and urticaria.
Use the measuring spoon up to 2 ml.

Children 1 through 5 years of age: 2.5 ml DOXAFIN once daily (1.25 mg) with or without meals for the relief of symptoms associated with allergic rhinitis including intermittent and persistent allergic rhinitis and urticaria.
Use the measuring spoon up to 2.5 ml.

Children aged 6 through 11 years: 5 ml DOXAFIN once daily (2.5 mg) with or without meals for the relief of symptoms associated with allergic rhinitis including intermittent and persistent allergic rhinitis and urticaria.
Use the measuring spoon up to 5 ml.

In adults and adolescents (12 years of age and older): 10 ml DOXAFIN once daily (5 mg) with or without meals for the relief of symptoms associated with allergic rhinitis including intermittent and persistent allergic rhinitis and urticaria.
Use the measuring spoon twice up to 5 ml.

Additional information for special populations
Renal impairment:
It should be used with caution in patients with severe renal impairment.

Hepatic impairment:
No data is available regarding the use in patients with hepatic impairment.

Pediatric population:
Method of administration in pediatric population is given above.

Geriatric population:
Efficacy and safety in geriatric population have not been established yet.

4.3. Contraindications

Hypersensitivity to the active substance, to any of the excipients listed in section 6.1, or to loratadine.

4.4. Special warnings and precautions for use

Efficacy and safety of desloratadine in children under 6 months of age has not been established (see section 5.1.)

In children below 2 years of age, the diagnosis of allergic rhinitis is particularly difficult to distinguish from other forms of rhinitis. The absence of upper respiratory tract infection or structural abnormalities, as well as patient history, physical examinations, and appropriate laboratory and skin tests should be considered.

Approximately 6% of adults and children 2- to 11-year old are phenotypic poor metabolizers of desloratadine and exhibit a higher exposure. The safety of desloratadine in children 2- to 11-years of age who are poor metabolizers is the same as in children who are normal metabolizers. The effect of desloratadine in poor metabolizers of desloratadine under 2 years of age has not been studied.

In the case of severe renal insufficiency, DOXAFIN should be used with caution (see section 5.2).

Sucrose and sorbitol:
This medicinal product contains sucrose and sorbitol; thus, patients with rare hereditary problems of fructose intolerance, glucose-galactose malabsorption or sucrase-isomaltase insufficiency should not take this medicine.

Sunset yellow:

This medicinal product contains sunset yellow as coloring agent which may induce allergic reactions.

4.5. Interactions with other medicinal products and other forms of interaction

No clinically relevant interactions were observed in clinical trials with desloratadine in which erythromycin or ketoconazole were co-administered.

In clinical pharmacology studies of desloratadine taken concomitantly with alcohol, desloratadine did not potentiate the performance-impairing effect of alcohol (see section 5.1).

DOXAFIN interacts with oral contraceptives. Therefore, an alternative, effective and safe contraceptive method should be used during treatment.

4.6. Fertility, pregnancy and lactation

General recommendation
Pregnancy category is C.

Women of childbearing potential/Contraception
DOXAFIN interacts with oral contraceptives. Therefore, an alternative, effective and safe contraceptive method should be used during treatment.

Pregnancy
There are no sufficient data from the use of desloratadine in pregnant women. Animal studies do not indicate reproductive toxicity.
Potential risk for humans is unknown (see Section 5.3). Its use during pregnancy is therefore not recommended.

Breast-feeding
If therapeutic doses of DOXAFIN are administered to breast-feeding women, desloratadine is excreted into breast milk to the extent which may have an effect on the infant. DOXAFIN should not be used during breast-feeding.

Reproductive ability / Fertility
Animal studies do not indicate reproductive toxicity.
Potential risk for humans is unknown.

4.7. Effects on ability to drive and use machines

No effect of desloratadine on the ability to drive and use machines has been observed. However, patients should be informed that although very rarely, drowsiness may occur in some patients and this may affect their ability to drive or use machines.

4.8. Undesirable effects

In clinical trials in a pediatric population, desloratadine 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 desloratadine and the placebo groups. In infants 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%).

At the recommended dose, in clinical trials involving adults and adolescents in a range of indications

including allergic rhinitis and chronic idiopathic urticaria, undesirable effects with desloratadine were reported in 3% of patients in excess of those treated with placebo. The most frequent of adverse events reported in excess of placebo were fatigue (1.2%), dry mouth (0.8%) and headache (0.6%).

Adverse events are listed below according to system organ class. The frequencies are defined as follows:

In different organ systems;
Very common (≥1/10), common (between ≥1/100 and < 1/10), uncommon (between ≥1/1,000 and <1/100), rare (between ≥1/10.000 and <1/1.000), very rare (<1/10.000), not known (cannot be estimated from the available data).

Nervous system disorders
Common: Fatigue
Uncommon: Headache

Gastrointestinal disorders
Uncommon: Dry mouth

Post-marketing experience:
The following are very rare side effects reported in post-marketing experience:

Psychiatric disorders
Very rare: Hallucinations

Nervous system disorders
Very rare: Dizziness, somnolence, insomnia, psychomotor hyperactivity, stroke

Cardiac disorders
Very rare: Tachycardia, palpitations

Gastrointestinal disorders
Very rare: Abdominal pain, nausea, vomiting, dyspepsia, diarrhea

Hepatobiliary disorders
Very rare: Elevations of liver enzymes, hepatitis and increased bilirubin

Musculoskeletal and connective tissue, bone disorders
Very rare: Myalgia

General disorders and administration site conditions
Very rare: Hypersensitivity reactions (anaphylaxis, angioedema, dyspnea, pruritus, rash, and urticaria)

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorization of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system.

4.9. Overdose

In the event of overdose, standard precautions should be taken to remove unabsorbed active substance.

Symptomatic and supportive treatment is recommended.

Based on a multiple dose clinical trial, 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.

5. PHARMACOLOGICAL PROPERTIES

5.1. Pharmacodynamic properties

Pharmacotherapeutic group: Other antihistamines for systemic use
ATC code: R06AX27

Mechanism of action:
Desloratadine is a non-sedating, long-acting, potent, selective peripheral histamine H1-receptor antagonist. 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 desloratadine syrup has not been investigated in separate pediatric trials. However, the safety of desloratadine syrup was demonstrated in three pediatric trials. Children, 6 months to 11 years of age, who were candidates for antihistamine therapy received a daily desloratadine dose of 1 mg (6 to 11 months), 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 (corrected QT). When given at the recommended doses, the pharmacokinetic activity of desloratadine was comparable in the pediatric and adult populations. Thus, since the course of seasonal allergic rhinitis/chronic idiopathic urticaria 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 pharmacology trial, in which desloratadine was administered at a dose of 45 mg daily (nine times the clinical dose) for ten days, no prolongation of QTc (time from the Q wave to the T wave in an ECG) interval was seen.

Desloratadine does not readily penetrate the central nervous system. In controlled clinical trials, at the recommended dose of 5 mg daily, there was no excess incidence of somnolence as compared to

placebo. Desloratadine tablets given at a single daily dose of 7.5 mg 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 trials, 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. In a clinical pharmacology trial desloratadine taken concomitantly with alcohol did not potentiate the performance impairing effects of 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 allergic rhinitis, desloratadine 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.

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.

Desloratadine tablets were 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.

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 6-week trials in patients with chronic idiopathic urticaria, desloratadine 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 chronic idiopathic urticaria, the minority of patients who were identified as nonresponsive 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 desloratadine also significantly reduced interference with sleep and daytime function, as measured by a four-point scale used to assess these variables.

5.2. Pharmacokinetic properties

General properties

Absorption:
Desloratadine plasma concentrations can be detected within 30 minutes of administration. Desloratadine is well absorbed with maximum concentration achieved after approximately 3 hours. The terminal phase half-life of desloratadine 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.

Distribution:
In a series of pharmacokinetic and clinical trials, 6% of the subjects reached a higher concentration of desloratadine. The prevalence of this poor metabolizer phenotype was comparable for adult (6%) and pediatric subjects 2- to 11-year old (6%), and greater among Blacks (18% adult, 16% pediatric) than Caucasians (2% adult, 3% pediatric) 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 metabolizers 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 pediatric poor metabolizer 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 pediatric poor metabolizers 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 desloratadine 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 active substance 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, pediatric patients had comparable AUC and C_{max} values of desloratadine to those in adults who received a 5 mg dose of desloratadine syrup.

Biotransformation:
The enzyme responsible for the metabolism of desloratadine has not been identified yet, and therefore, some interactions with other medicinal products cannot be fully excluded. *In vivo* studies with specific inhibitors of CYP3A4 and CYP2D6 have shown that these enzymes are not effective in metabolism of desloratadine and *in vitro* studies have shown that the medicinal product does not inhibit CYP3A4 or CYP2D6 and is neither a substrate nor an inhibitor of P-glycoprotein.

Elimination:
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.

5.3. 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 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.

6. PHARMACEUTICAL PARTICULARS

6.1. List of excipients

Propylene glycol
Sorbitol liquid, crystallized, 70%
Sodium citrate dihydrate
Sodium benzoate
Disodium edetate
Citric acid monohydrate
Liquid sucrose
Strawberry flavor 052311 A7
FD&C Yellow 6, Eurocert sunset yellow
Deionized water

6.2. Incompatibilities

Not applicable for this product.

6.3. Shelf life

48 months

6.4. Special precautions for storage

Store at room temperature below 25°C.

6.5. Nature and contents of container

Amber-colored glass bottle closed with a plastic cap.
Each box contains 1 bottle and a propylene measuring spoon of 5 ml marked for doses of 2 ml and 2.5 ml.

6.6. Special precautions for disposal and other handling

Any unused product or waste material should be disposed of in accordance with local disposal regulations.

7. MARKETING AUTHORIZATION HOLDER

DEVA Holding A.Ş.
Halkalı Merkez Mah. Basın Ekspres Cad. No: 1
34303 Küçükçekmece - ISTANBUL/TURKEY

8. MARKETING AUTHORIZATION NUMBER(S)

210/67

9. DATE OF FIRST AUTHORIZATION/RENEWAL OF THE AUTHORIZATION

Date of first authorization : 28.02.2007
Renewal of the authorization : 05.05.2014

10. DATE OF REVISION OF THE TEXT

22.06.2021