SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Desloratadine Denk 0,5 mg/ml drank

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each ml of oral solution contains 0.5 mg desloratadine.

Excipient(s) with known effect:
This medicinal product contains 150 mg/ml of sorbitol and 150.51 mg/ml of propylene glycol.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Oral solution

4. CLINICAL PARTICULARS

4.1. Therapeutic indications

Desloratadine Denk is indicated in adults, adolescents and children over the age of 1 year for the relief of symptoms associated with:
- Allergic rhinitis (see section 5.1)
- Urticaria (see section 5.1)

4.2. Posology and method of administration

Posology
Adults and adolescents (12 years of age and over)
The recommended dose of Desloratadine Denk is 10 ml (5 mg) oral solution once a day.

Paediatric population
The prescriber should be aware that most cases of rhinitis below 2 years of age are of infectious origin (see section 4.4) and there are no data supporting the treatment of infectious rhinitis with Desloratadine Denk.

Children 1 through 5 years of age: 2.5 ml (1.25 mg) Desloratadine Denk oral solution once a day.

Children 6 through 11 years of age: 5 ml (2.5 mg) Desloratadine Denk oral solution once a day.

The safety and efficacy of Desloratadine Denk 0.5 mg/ml oral solution in children below the age of 1 year have not been established. No data are available.

There is limited clinical trial efficacy experience with the use of desloratadine in children 1 through 11 years of age and adolescents 12 through 17 years of age (see sections 4.8 and 5.1).

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 the allergen exposure periods.

Method of administration

Oral use.
The dose can be taken with or without food.

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

Desloratadine should be administered with caution in patients with medical or familial history of seizures, and mainly young children, being more susceptible to develop new seizures under desloratadine treatment. Healthcare providers may consider discontinuing desloratadine in patients who experience a seizure while on treatment.

Paediatric population
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 metabolisers of desloratadine and exhibit a higher exposure (see section 5.2). The safety of desloratadine in children 2- to 11- years of age who are poor metabolisers is the same in children who are normal metabolisers. The effects of desloratadine in poor metabolisers < 2 years of age have not been studied.

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

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

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

No clinically relevant interactions were observed in clinical trials with desloratadine tablets in which erythromycin or ketoconazole were co-administered (see section 5.1).

Paediatric population
Interaction studies have only been performed in adults.

In a clinical pharmacology trial, desloratadine tablets taken concomitantly with alcohol did not potentiate the performance impairing effects of alcohol (see section 5.1). However, cases of alcohol intolerance and intoxication have been reported during post-marketing use. Therefore, caution is recommended if alcohol is taken concomitantly.

4.6. Fertility, pregnancy and lactation

Pregnancy
A large amount of data on pregnant women (more than 1,000 pregnancy outcomes) indicate no malformative nor foeto/ neonatal toxicity of desloratadine. Animal studies do not indicate direct or indirect harmful effects with respect to reproductive toxicity (see section 5.3). As a precautionary measure, it is preferable to avoid the use of Desloratadine Denk during pregnancy.

Breast-feeding

Desloratadine has been identified in breastfed newborns/infants of treated women. The effect of desloratadine on newborns/infants is unknown. A decision must be made whether to discontinue breast-feeding or to discontinue/abstain from Desloratadine Denk therapy taking into account the benefit of breastfeeding for the child and the benefit of therapy for the woman.

Fertility
There are no data available on male and female fertility.

4.7. Effects on ability to drive and use machines

Desloratadine has no or negligible influence on the ability to drive and use machines based on clinical trials. Patients should be informed that most people do not experience drowsiness. Nevertheless, as there is individual variation in response to all medicinal products, it is recommended that patients are advised not to engage in activities requiring mental alertness, such as driving a car or using machines, until they have established their own response to the medicinal product.

4.8. Undesirable effects

Summary of the safety profile

Paediatric population
In clinical trials in a paediatric population, the desloratadine syrup formulation 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 and toddlers aged 6 to 23 months, the most frequent adverse reactions reported in excess of placebo were diarrhoea (3.7%), fever (2.3%) and insomnia (2.3%). In an additional study, no adverse events were seen in subjects between 6 and 11 years of age following a single 2.5 mg dose of desloratadine oral solution.

In a clinical trial with 578 adolescent patients, 12 through 17 years of age, the most common adverse event was headache; this occurred in 5.9 % of patients treated with desloratadine and 6.9 % of patients receiving placebo.

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 %).

Tabulated list of adverse reactions
The frequency of the clinical trial adverse reactions reported in excess of placebo and other undesirable effects reported during the post-marketing period are listed in the following table. Frequencies are defined as very common (≥ 1/10), common (≥ 1/100 to < 1/10), uncommon (≥ 1/1,000 to < 1/100), rare (≥ 1/10,000 to < 1/1,000), very rare (< 1/10,000) and not known (cannot be estimated from the available data).

System Organ Class	**Frequency**	**Adverse reactions seen with desloratadine**
Metabolism and nutrition disorders	Not known	Increased appetite
Psychiatric disorders	Very rare	Hallucinations
	Not known	Abnormal behaviour, aggression, depressed mood

Nervous system disorders	Common	Headache
	Common (children less than 2 years)	Insomnia
	Very rare	Dizziness, somnolence, insomnia, psychomotor hyperactivity, seizures
Eye disorders	Not known	Dry eyes
Cardiac disorders	Very rare	Tachycardia, palpitations
	Not known	QT prolongation
Gastrointestinal disorders	Common	Dry mouth
	Common (children less than 2 years)	Diarrhoea
	Very rare	Abdominal pain, nausea, vomiting, dyspepsia, diarrhoea
Hepatobiliary disorders	Very rare	Elevation of liver enzymes, increased bilirubin, hepatitis
	Not known	Jaundice
Skin and subcutaneous tissue disorders	Not known	Photosensitivity
Musculoskeletal and connective tissue disorders	Very rare	Myalgia
General disorders and administration site conditions	Common	Fatigue
	Common (children less than 2 years)	Fever
	Very rare	Hypersensitivity reactions (such as anaphylaxis, angioedema, dyspnoea, pruritus, rash and urticaria)
	Not known	Asthenia
Investigations	Not known	Weight increased

Paediatric population
Other undesirable effects reported during the post-marketing period in paediatric patients with an unknown frequency included QT prolongation, arrhythmia, bradycardia, abnormal behaviour, and aggression.

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation 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 Nederlands Bijwerkingen Centrum Lareb, website: www.lareb.nl.

4.9. Overdose

The adverse event profile associated with overdosage, as seen during post-marketing use, is similar to that seen with therapeutic doses, but the magnitude of the effects can be higher.

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

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

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

Paediatric population
The adverse event profile associated with overdosage, as seen during post-marketing use, is similar to that seen with therapeutic doses, but the magnitude of the effects can be higher.

5. PHARMACOLOGICAL PROPERTIES

5.1. Pharmacodynamic properties

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

Mechanism of action
Desloratadine is a non-sedating, long-acting histamine antagonist with selective peripheral H_1- receptor 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.

Clinical efficacy and safety

Paediatric population
Efficacy of desloratadine oral solution has not been investigated in separate paediatric trials. However, the safety of desloratadine syrup formulation, which contains the same concentration of desloratadine as desloratadine oral solution, was demonstrated in three paediatric 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 concentrations of desloratadine (see section 5.2) were comparable in the paediatric and adult populations. Thus, since the course of allergic rhinitis/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.

Efficacy of desloratadine syrup has not been investigated in paediatric trials in children less than 12 years of age.

Adults and adolescents
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. In controlled clinical trials, at the recommended dose of 5 mg daily for adults and adolescents, there was no excess incidence of somnolence as compared to placebo. Desloratadine 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 trials 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 allergic rhinitis, desloratadine 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. Desloratadine effectively controlled symptoms for 24 hours. The efficacy of desloratadine tablets has not been clearly demonstrated in trials with adolescent patients 12 through 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.

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 six 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 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 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

Absorption

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 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 desloratadine in poor metabolisers < 2 years of age have not been studied.

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.

Distribution
Desloratadine is moderately bound (83 % - 87 %) to plasma proteins. There is no evidence of clinically relevant active substance accumulation following once daily 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. As desloratadine oral solution contains the same concentration of desloratadine, no bioequivalence study was required and it is expected to be equivalent to the syrup and tablet.

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. Desloratadine does not inhibit CYP3A4 *in vivo*, and *in vitro* studies have shown that the medicinal product does not inhibit 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.

Renally impaired patients
The pharmacokinetics of desloratadine in patients with chronic renal insufficiency (CRI) was compared with that of healthy subjects in one single-dose study and one multiple dose study. In the single-dose study, the exposure to desloratadine was approximately 2 and 2.5-fold greater in subjects with mild to moderate and severe CRI, respectively, than in healthy subjects. In the multiple-dose study, steady state was reached after Day 11, and compared to healthy subjects the exposure to desloratadine was ~1.5-fold greater in subjects with mild to moderate CRI and ~2.5-fold greater in subjects with severe CRI. In both studies, changes in exposure (AUC and Cmax) of desloratadine and 3-hydroxydesloratadine were not clinically relevant.

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

6. PHARMACEUTICAL PARTICULARS

6.1. List of excipients

Excipients: hypromellose, sucralose, citric acid, sodium citrate, liquid (non-crystallising) sorbitol (E420), propylene glycol (E1520), liquid tutti frutti flavour, purified water

6.2. Incompatibilities

Not applicable

6.3. Shelf life

3 years

6.4. Special precautions for storage

This medicinal product does not require any special temperature storage conditions. Store in the original package in order to protect from light.

6.5. Nature and contents of container

Desloratadine Denk oral solution is packed in 30, 60, 100, 125, 150, 220, 250 and 300 ml amber type III glass bottles closed with a white plastic child-resistant screw cap.

Not all pack sized may be marketed.

All packages are supplied with a measuring syringe or a measuring spoon (with double pits of 2.5 and 5 ml capacities or with one pit marked for doses of 2.5 ml and 5 ml).

6.6. Special precautions for disposal

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7. MARKETING AUTHORISATION HOLDER

Denk Pharma GmbH & Co. KG
Prinzregentenstraße 79
81675 München
Duitsland

8. MARKETING AUTHORISATION NUMBER(S)

RVG 124513

9. DATE OF FIRST AUTHORISATION

Datum van eerste verlening van de vergunning: 10 februari 2020
Datum van laatste verlenging: 22 januari 2025

10. DATE OF REVISION OF THE TEXT

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