1. NAME OF THE MEDICINAL PRODUCT
Avrotyn Syrup 5mg/5ml

2. QUALITATIVE AND QUANTITATIVE COMPOSITION
Each ml of 5ml syrup contains 5mg loratadine.
For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM
Syrup (Oral solution)
Clear, colourless to light yellow syrup.

4. CLINICAL PARTICULARS
4.1 Therapeutic indications
Avrotyn is indicated for the relief of symptoms associated with allergic rhinitis such as such as sneezing, runny or itchy nose and burning or itchy eyes in adults and children over the age of 2 years. It may also be used to help relieve symptoms of urticaria (itching and redness, which is often known as hives) and other allergic skin disorders.

4.2 Posology and method of administration
Adults and children over 12 years of age :
10ml (10mg) of the syrup once daily.
Paediatric population
Children 2 to 12 years of age ***are dosed by weight:***
Body weight more than 30kg: 10ml (10mg) of the syrup once daily.
Body weight 30kg or less: 5ml (5mg) of the syrup once daily.
The safety and efficacy of Avrotyn Syrup in children under 2 years of age has not been established. No data are available.
Patients with hepatic impairment
Patients with severe liver impairment should be administered a lower initial dose because they may have reduced clearance of loratadine. An initial dose of 10mg every other day is recommended for adults and children weighing more than 30kg and for children weighing 30kg or less, 5ml (5mg) every other day is recommended.
Patients with renal impairment
No dosage adjustments are required in patients with renal insufficiency.
Elderly
No dosage adjustments are required in the elderly.

Method of administration
Oral use. The syrup may be taken without regard to meal time.

4.3 Contraindications
Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.

4.4 Special warnings and precautions for use
Avrotyn Syrup should be administered with caution in patients with severe liver impairment (see section 4.2).
This medicinal product contains sucrose; thus patients with rare hereditary problems of fructose intolerance, glucose-galactose malabsorption or sucrose isomaltase insufficiency should not take this medicine.
The administration of Avrotyn Syrup should be discontinued at least 48 hours before skin tests since antihistamines may prevent or reduce otherwise positive reactions to dermal reactivity index.

4.5 Interaction with other medicinal products and other forms of interaction
When administered concomitantly with alcohol, Avrotyn Syrup has no potentiating effects as measured by psychomotor performance studies.
Potential interaction may occur with all known inhibitors of CYP3A4 or CYP2D6 resulting in elevated levels of loratadine (see Section 5.2), which may cause an increase in adverse events.
Increase in plasma concentrations of loratadine has been reported after concomitant use with ketoconazole, erythromycin, and cimetidine in controlled trials, but without clinically significant changes (including electrocardiographic).
Paediatric population
Interaction studies have only been performed in adults.

4.6 Fertility, pregnancy and lactation
Pregnancy
A large amount of data on pregnant women (more than 1000 exposed outcomes) indicate no malformative nor feto/ neonatal toxicity of loratadine 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 Avrotyn Syrup during pregnancy.
Breast-feeding
Loratadine is excreted in breast milk. Therefore, the use of Avrotyn Syrup is not recommended in breast-feeding women.
Fertility
There are no data available on male and female fertility.

4.7 Effects on ability to drive and use machines
In clinical trials that assessed driving ability, no impairment was observed in patients receiving loratadine. Avrotyn Syrup has no or negligible influence on the ability to drive and use machines. However, patients should be informed that very rarely some people experience drowsiness, which may affect their ability to drive or use machines.

4.8 Undesirable effects
Summary of the safety profile
In clinical trials involving adults and adolescents in a range of indications including allergic rhinitis (AR) and chronic idiopathic urticarial (CIU), at the recommended dose of 10mg daily, adverse reactions with loratadine were reported in 2% of patients in excess of those treated with placebo. The most frequent adverse reactions reported in excess of placebo were somnolence (1.2%), headache (0.6%), increased appetite (0.5%) and insomnia (0.1%).
Tabulated list of adverse reactions
The following adverse reactions reported during the post-marketing period are listed in the following table by System Organ Class. 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).
Within each frequency grouping, adverse reactions are presented in order of decreasing seriousness.

System Organ Class	**Frequency**	**Adverse Experience Term**
Immune System disorders	Very rare	Hypersensitivity reactions (including angioedema and anaphylaxis)
Nervous system disorders	Very rare	Dizziness, convulsion
Cardiac disorders	Very rare	Tachycardia, palpitation
Gastrointestinal disorders	Very rare	Nausea, dry mouth, gastritis
Hepatobiliary disorders	Very rare	Abnormal hepatic function
Skin and subcutaneous tissue disorders	Very rare	Rash, alopecia

General disorders and administration site conditions	Very rare	Fatigue

Paediatric population
In clinical trials in a paediatric population, children aged 2 through 12 years, common adverse reactions reported in excess of placebo were headache (2.7%), nervousness (2.3%), and fatigue (1%).
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.

4.9 Overdose
Overdosage with loratadine increased the occurrence of anticholinergic symptoms. Somnolence, tachycardia and headache have been reported with overdoses.
In the event of overdose, general symptomatic and supportive measures are to be instituted and maintained for as long as necessary. Administration of activated charcoal as a slurry with water may be attempted. Gastric lavage may be considered. Loratadine is not removed by haemodialysis and it is not known if loratadine is removed by peritoneal dialysis. Medical monitoring of the patient is to be continued after emergency treatment.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties
Pharmacotherapeutic group : antihistamines – H_1 antagonist, ATC code : R06A X13.

Mechanism of action
Loratadine, the active ingredient in Avrotyn Syrup, is a tricyclic antihistamine with selective, peripheral H_1-receptor activity.

Pharmacodynamic effects
Loratadine has no clinically significant sedative or anticholinergic properties in the majority of the population and when used at the recommended dosage.
During long-term treatment there were no clinically significant changes in vital signs, laboratory test values, physical examinations or electrocardiograms.
Loratadine has no significant H_2-receptor activity. It does not inhibit norepinephrine uptake and has practically no influence on cardiovascular function or on intrinsic cardiac pacemaker activity.
Human histamine skin wheal studies following a single 10 mg dose has shown that the antihistamine effects are seen within 1-3 hours reaching a peak at 8-12 hours and lasting in excess of 24 hours. There was no evidence of tolerance to this effect after 28 days of dosing with loratadine.

Clinical efficacy and safety
Over 10,000 subjects (12 years and older) have been treated with loratadine 10 mg tablets in controlled clinical trials. Loratadine 10 mg tablets once daily was superior to placebo and similar to clemastine in improving the effects on nasal and non-nasal symptoms of AR. In these studies somnolence occurred less frequently with loratadine than with clemastine and about the same frequency as terfenadine and placebo.
Among these subjects (12 years and older), 1000 subjects with CIU were enrolled in placebo controlled studies. A once daily 10 mg dose of loratadine was superior to placebo in the management of CIU as demonstrated by the reduction of associated itching, erythema and hives. In these studies the incidence of somnolence with loratadine was similar to placebo.

Paediatric population
Approximately 200 paediatric subjects (6 to 12 years of age) with seasonal allergic rhinitis received doses of loratadine syrup up to 10 mg once daily in controlled clinical trials. In another study, 60 paediatric

subjects (2 to 5 years of age) received 5 mg of loratadine syrup once daily. No unexpected adverse events were observed.
The paediatric efficacy was similar to the efficacy observed in adults.

5.2 Pharmacokinetic properties

Absorption

Loratadine is rapidly and well-absorbed. Concomitant ingestion of food can delay slightly the absorption of loratadine but without influencing the clinical effect. The bioavailability parameters of loratadine and of the active metabolite are dose proportional.

Distribution

Loratadine is highly bound (97% to 99%) and its active metabolite moderately bound (73% to 76%) to plasma proteins.
In healthy subjects, plasma distribution half-lives of loratadine and its active metabolite are approximately 1 and 2 hours, respectively.

Biotransformation

After oral administration, loratadine is rapidly and well absorbed and undergoes an extensive first pass metabolism, mainly by CYP3A4 and CYP2D6. The major metabolite-desloratadine (DL)- is pharmacologically active and responsible for a large part of the clinical effect. Loratadine and DL achieve maximum plasma concentrations (Tmax) between 1–1.5 hours and 1.5–3.7 hours after administration, respectively.

Elimination

Approximately 40% of the dose is excreted in the urine and 42% in the faeces over a 10 day period and mainly in the form of conjugated metabolites. Approximately 27% of the dose is eliminated in the urine during the first 24 hours. Less than 1% of the active substance is excreted unchanged in active form, as loratadine or DL.
The mean elimination half-lives in healthy adult subjects were 8.4 hours (range = 3 to 20 hours) for loratadine and 28 hours (range = 8.8 to 92 hours) for the major active metabolite.

Renal impairment

In patients with chronic renal impairment, both the AUC and peak plasma levels (C_{max}) increased for loratadine and its active metabolite as compared to the AUCs and peak plasma levels (C_{max}) of patients with normal renal function. The mean elimination half-lives of loratadine and its active metabolite were not significantly different from that observed in normal subjects. Haemodialysis does not have an effect on the pharmacokinetics of loratadine or its active metabolite in subjects with chronic renal impairment.

Hepatic impairment

In patients with chronic alcoholic liver disease, the AUC and peak plasma levels (C_{max}) of loratadine were double while the pharmacokinetic profile of the active metabolite was not significantly changed from that in patients with normal liver function. The elimination half-lives for loratadine and its active metabolite were 24 hours and 37 hours, respectively, and increased with increasing severity of liver disease.

Elderly

The pharmacokinetic profile of loratadine and its active metabolite is comparable in healthy adult volunteers and in healthy geriatric volunteers.

5.3 Preclinical safety data

Non-clinical data reveal no special hazard for humans based on conventional studies of safety, pharmacology, repeated dose toxicity, genotoxicity and carcinogenic potential.
In reproductive toxicity studies, no teratogenic effects were observed. However, prolonged parturition and reduced viability of offspring were observed in rats at plasma levels (AUC) 10 times higher than those achieved with clinical doses.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Sucrose
Propylene glycol (E1520)

Glycerol (E422)
Citric Acid Anhydrous
Sodium Benzoate (E211)
Purified water

6.2 Incompatibilities
Not applicable.

6.3 Shelf life
36 months; after first opening, the syrup is stable for 1 month.

6.4 Special precautions for storage
This medicinal product does not require any special storage conditions.
Do not freeze.
Keep the bottle in the outer carton in order to protect from light.

6.5 Nature and contents of container
Amber bottle of 100ml with ROPP cap. A 10ml plastic measuring cup is included.

6.6 Special precautions for disposal and other handling
Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7. APPLICANT/MANUFACTURER
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