1. NAME OF THE FINISHED PHARMACEUTICAL PRODUCT

LORATOL® Tablets

1.1 ***Strength***
10 mg Loratadine.

1.2 ***Pharmaceutical form***
Tablets.

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

2.1 ***Qualitative declaration***
Loratadine.

2.2 ***Quantitative declaration***
Each tablet contains 10 mg loratadine.

Excipient with known effect:
Each tablet contains 71.3 mg lactose monohydrate.

For the full list of excipients, see section 6.1.

2.3 ***Salts and hydrates***
Not applicable.

2.4 ***Esters and pro-drugs***
Not applicable.

2.5 ***Oral powders for solution or suspension***
Not applicable.

2.6 ***Parenterals excluding powders for reconstitution***
Not applicable.

2.7 ***Powders for reconstitution prior to parenteral administration***
Not applicable.

2.8 ***Concentrates***
Not applicable

2.9 ***Transdermal patches***
Not applicable.

2.10 ***Multidose solid or semi-solid products***
Not applicable.

2.11 ***Biological medicinal products***
Not applicable.

3. PHARMACEUTICAL FORM

Tablets, presented in a blister with 10 tablets.

4. CLINICAL PARTICULARS

4.1 *Therapeutic indications*

Loratol® Tablets is indicated for the symptomatic treatment of allergic rhinitis and chronic idiopathic urticaria.

4.2 *Posology and method of administration*

Adult and children (>12 years):	10mg once daily.
Children (2 – 12 years):	Body weight >30 kg: 10mg once daily.
	Body weight <30 kg: these tablets are not suitable for these children.

Paediatric population
Safety and effectiveness in children below the age of 2 is not established.

Geriatric population
No dosage adjustments are required in the elderly.

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 10 mg every other day is recommended for adults and children weighing more than 30 kg.

Patients with renal impairment
No dosage adjustments are required in patients with renal insufficiency.

4.3 *Method of administration*

Oral use.
The tablet may be taken without regard to mealtime.

4.4 *Contraindications*

Loratol® Tablets is contraindicated in patients who are hypersensitive to this medication or to any of its ingredients, listed in section 6.1.

4.5 *Special warnings and precautions for use*

Loratol® Tablets should be administered with caution in patients with severe liver and renal impairment (see section 4.2).

This medicine contains lactose: patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicine.

4.6 *Paediatric population*

Safety and effectiveness in children below the age of 2 years have not been established.
Keep the product out of reach and sight of children.

4.7 ***Interaction with other medicinal products and other forms of interaction***

When administered concurrently with alcohol, loratadine 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, which may cause an increase in adverse events (see sections 4.8 and 5.2).

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).
Antihistaminics should be discontinued about four days prior to skin testing procedures, since these drugs may prevent or diminish otherwise positive reactions to dermal reactivity indicators.

4.8 ***Additional information on special populations***

None.

4.9 ***Paediatric population***

Interaction studies have only been performed in adults.

4.10 ***Fertility, pregnancy and lactation***

Loratadine should not be administered during pregnancy. There is no experience of the use of loratadine in human pregnancy. In animal studies loratadine was not teratogenic, at high doses some embryotoxic effects were observed. Since loratadine is excreted in breast milk it should not be administered to lactating women. There are no data available on male and female fertility.

4.11 ***Effects on ability to drive and use machines***

In clinical trials that assessed driving ability, no impairment occurred in patients receiving loratadine. However, patients should be informed that very rarely some people experience drowsiness, which may affect their ability to drive or use machines.

4.12 ***Undesirable effects***

During controlled clinical studies the incidence of adverse events, including sedation and anticholinergic effect, observed with 10 mg loratadine was comparable to that observed with placebo. Fatigue, nausea and headache were reported rarely.

Tabulated list of undesirable effects and undesirable effect resulting from paediatric trials as reported in the SmPC of the reference product (Clarityn Allergy 10mg Tablets) are:

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***	***Averse 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%).

4.13 *Overdose*

Somnolence, tachycardia, and headache have been reported with overdoses greater than 10 mg (40 to 180 mg). In the event of overdosage, general symptomatic and supportive measures should be instituted promptly and maintained for as long as necessary.

Treatment of overdosage would reasonably consist of emesis (ipecac syrup), except in patients with impaired consciousness, followed by the administration of activated charcoal to absorb any remaining drug. If vomiting is unsuccessful, or contraindicated, gastric lavage should be performed with normal saline. Saline cathartics may also be of value for rapid dilution of bowel contents. Loratadine is not eliminated by haemodialysis. It is not known if loratadine is eliminated by peritoneal dialysis.

5. PHARMACOLOGICAL PROPERTIES

5.1 *Pharmacodynamic properties*

Pharmacotherapeutic group and ATC code: R06A X13 (Antihistamines – H_1 antagonist).

Loratadine is a long acting tricyclic antihistaminic with selective peripheral H_1 receptor antagonistic activity and no central sedative or anticholinergic effects. Loratadine shows more affinity to peripheral nervous system than central nervous system. Loratadine does not readily cross the blood – brain barrier.

Mechanism of action

Loratadine, the active ingredient in Loratol® Tablets, 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

After oral administration, loratadine is rapidly and well absorbed and undergoes an extensive first pass metabolism, mainly by CYP3A4 and CYP2D6. Loratadine and DL achieve maximum plasma concentrations (T_{max}) between 1-1.5 hours and 1.5- 3.7 hours after administration, respectively.

Increase in plasma concentrations of loratadine has been reported after concomitant use with ketoconazole, erythromycin, and cimetidine in electrocardiographic). Concomitant ingestion of food can delay slightly the absorption of loratadine but without influencing the clinical effect.

Distribution

Loratadine is highly bound (97% to 99%) and its active metabolite moderately bound (73% to 76%) to plasma proteins.

Biotransformation:

The major metabolite-desloratadine (DL) is pharmacologically active and responsible for a large part of the clinical effect. In healthy subjects, plasma distribution half-lives of loratadine and its active metabolite are approximately 1 and 2 hours, respectively. 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).

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.

Linearity

The bioavailability parameters of Loratadine and of the active metabolite are dose proportional.

Geriatric population
The pharmacokinetic profile of loratadine and its metabolites is comparable in healthy adult volunteers and in healthy geriatric volunteers.

Liver 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 metabolite were 24 hours and 37 hours, respectively, and increased with increasing severity of liver disease.

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 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.

5.3 *Preclinical safety data*
Preclinical data reveal no special hazard based on conventional studies of safety, pharmacology, repeated dose toxicity, genotoxicity and carcinogenic potential.

6. PHARMACEUTICAL PARTICULARS

6.1 *List of excipients*
Lactose monohydrate, maize starch, magnesium stearate.

6.2 *Incompatibilities*
None known

6.3 *Shelf life*
Proposed shelf-life: 36 Months.

6.4 *Special precautions for storage*
Store the tablets in the original package at a temperature below 30ºC.
Keep out of the reach and sight of children.
Do not use this medicine if the expiry date printed on the pack or bottle (Exp.) has passed.

6.5 *Nature and contents of container*

Transparent blister in PVC, covered with aluminium foil.
Each box contains a blister with 10 tablets.

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. MARKETING AUTHORISATION HOLDER AND MANUFACTURING SITE ADDRESSES

Marketing Authorisation Holder
Dafra Pharma GmbH,
Mühlenberg 7, 4052 Basel, Switzerland

Manufacturing site
Nobel Ilaç, San. Ve. Tic. A.S. Sancaklar 81100 Düzce, Turkey.