

<b>PRODUCT</b>	<b>ACTILOR SYRUP 2.5 mg/ 5 ml</b>
REGISTRATION FILE – MODULE 1	

### 1.6.1 SUMMARY OF PRODUCT CHARACTERISTICS

#### 1. Name of the Medicinal Product:

Actilor Syrup 2.5 mg/ 5 ml

#### 2. Qualitative & Quantitative Composition:

Each 5 ml of syrup contains 2.5 mg Desloratadine.

#### 3. Pharmaceutical Form:

Syrup

#### 4. Clinical Particulars:

##### 4.1 Therapeutic indications

Actilor is indicated in adults, adolescents and children over the age of 1 year for the relief of symptoms associated with:

- allergic rhinitis
- urticaria

##### 4.2 Posology and method of administration

###### Posology

*Adults and adolescents 12 years of age and over*

The recommended dose of Desloratadine 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 and there are no data supporting the treatment of infectious rhinitis with Desloratadine.

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

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

The safety and efficacy of Desloratadine 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.

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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, or to loratadine.

**4.4 Special warning & 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. The safety of desloratadine in children 2 to 11 years of age who are poor metabolisers is the same as 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 should be used with caution.

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 & other forms of interaction**

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

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#### 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.

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 Pregnancy & 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. As a precautionary measure, it is preferable to avoid the use of desloratadine 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 therapy taking into account the benefit of breast feeding 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 & 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

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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.

#### Adults and adolescents

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 ( $\geq 1/10$ ), common ( $\geq 1/100$  to  $< 1/10$ ), uncommon ( $\geq 1/1,000$  to  $< 1/100$ ), rare ( $\geq 1/10,000$  to  $< 1/1,000$ ), very rare ( $< 1/10,000$ ) and not known (cannot be estimated from the available data).

<b>System Organ Class</b>	<b>Frequency</b>	<b>Adverse reactions seen with Desloratadine</b>
<b>Metabolism and nutrition disorders</b>	Not Known	Increased appetite
<b>Psychiatric disorders</b>	Very rare Not known	Hallucinations Abnormal behavior, aggression
<b>Nervous system disorders</b>	Common  Common (children less than 2 years)  Very rare	Headache  Insomnia,  Dizziness, somnolence, insomnia, psychomotor hyperactivity, seizures
<b>Cardiac disorders</b>	Very rare Not known	Tachycardia, palpitations QT prolongation

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<b>System Organ Class</b>	<b>Frequency</b>	<b>Adverse reactions seen with Desloratadine</b>
<b>Gastrointestinal disorders</b>	Common	Dry mouth
	Common (children less than 2 years)	Diarrhoea
	Very rare	Abdominal pain, nausea, vomiting, dyspepsia, diarrhoea
<b>Hepatobiliary disorders</b>	Very rare	Elevations of liver enzymes, increased bilirubin, hepatitis
	Not known	Jaundice
<b>Skin and subcutaneous tissue disorders</b>	Not known	Photosensitivity
<b>Musculoskeletal and connective tissue disorders</b>	Very rare	Myalgia
<b>General disorders and administration site conditions</b>	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
<b>Investigations</b>	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.

#### **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.

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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.

### **5.0 Pharmacological Properties**

#### **5.1 Pharmacodynamics**

Pharmacotherapeutic group: antihistamines – H<sub>1</sub> antagonist, ATC code: R06A X27

#### Mechanism of action

Desloratadine is a non-sedating, long-acting histamine antagonist with selective peripheral H<sub>1</sub>-receptor antagonist activity. After oral administration, desloratadine selectively blocks peripheral histamine H<sub>1</sub>-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, 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.

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When given at the recommended doses, the plasma concentrations of desloratadine 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.

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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 Pharmacokinetics**

### 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.

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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 metabolizers < 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 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. 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 can not 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.

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#### 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  $C_{max}$ ) 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 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 desloratadine and loratadine.

## **6. Pharmaceutical Particulars:**

### **6.1. List of excipients:**

<b>S.No.</b>	<b>Material</b>	<b>Function</b>
1.	Propylene Glycol BP	Solubilizing Agent
2.	Anhydrous Citric Acid BP	Buffering Agent
3.	Sodium Citrate BP	Buffering Agent
4.	Sodium Benzoate BP	Preservative Agent
5.	Disodium Edetate BP	Chelating Agent
6.	Liquid Sorbitol (Non-crystallizing 70%) BP	Sweetening Agent
7.	Saccharin Sodium BP	Sweetening Agent
8.	Raspberry Flavour	Flavoring Agent
9.	Purified Water USP/BP	Vehicle

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**6.2. Incompatibilities:**

Not Applicable

**6.3. Shelf life:**

36 months

**6.4. Special precautions for storage:**

Store below 30°C

**6.5. Nature & contents of container:**

150 ml amber glass bottle labeled and fitted with child resistant cap and plastic measuring cup, packed in a printed carton along with the pack insert.

**6.6 Manufacturer:**

Neopharma, Abu Dhabi, UAE  
Plot No. A1 89-95,  
Industrial City of Abu Dhabi (ICAD),  
Mussafah, Abu Dhabi, UAE

**6.7 Marketing Authorization Holder:**

Neopharma, Abu Dhabi, UAE  
Plot No. A1 89-95,  
Industrial City of Abu Dhabi (ICAD),  
Mussafah, Abu Dhabi, UAE

**6.8 Date of Revision of Text:**

08 Dec 2017.