



1. Generic Name

Levocetirizine Hydrochloride 5 mg and Sustained Release Pseudoephedrine Hydrochloride 120 mg Tablets

2. Qualitative and Quantitative composition

Each uncoated bilayered tablet contains:

Levocetirizine Hydrochloride IP5 mg

(as immediate release form)

Pseudoephedrine Hydrochloride IP120 mg

(as sustained release form)

Colour: Approved colour used

3. Dosage form and strength

Dosage: Sinarest LP NEO Tablet is available in oral dosage form.

Strength: Sinarest LP NEO Tablet is an oral tablet containing Levocetirizine Hydrochloride 5 mg and Pseudoephedrine Hydrochloride 120 mg.

4. Clinical particulars

4.1 Therapeutic indication

Sinarest LP NEO Tablet is indicated in treatment of seasonal allergic rhinitis.

4.2 Posology and method of administration

Posology: In Adults and Children over 12 years, the usual recommended oral dose of Sinarest LP NEO Tablet for adult is one tablet once or twice daily.

Method of administration: Oral

4.3 Contraindication

The use of Sinarest LP NEO Tablet is contraindicated in patients with:

- Hypersensitivity to levocetirizine, to other piperazine derivatives or pseudoephedrine or to any ingredient in this product.

- Concomitant use of other sympathomimetic decongestants, beta-blockers (see section 4.5) or monoamine oxidase inhibitors (MAOIs), or within 14 days of stopping MAOI treatment (see section 4.5). The concomitant use of MAOIs may cause a rise in blood pressure and/or hypertensive crisis (see section 4.5).
- Cardiovascular disease including hypertension
- Diabetes mellitus
- Pheochromocytoma
- Hyperthyroidism
- Closed angle glaucoma
- Severe acute or chronic renal failure, with creatinine clearance less than 30 mL/min.
- Severe hepatic dysfunction

4.4 Special warnings and precautions for use

- The use of the Sinarest LP NEO tablet formulation is not recommended in children aged less than 6 years since this formulation does not allow for appropriate dose adaptation. It is recommended to use a paediatric formulation of levocetirizine.
- The administration of levocetirizine to infants and toddlers aged less than 2 years is not recommended.
- Precaution is recommended with intake of alcohol (see Interactions).
- Caution should be taken in patients with predisposing factors of urinary retention (e.g. spinal cord lesion, prostatic hyperplasia) as levocetirizine may increase the risk of urinary retention.
- Caution should be taken in patients with epilepsy and patients at risk of convulsion as levocetirizine may cause seizure aggravation.
- Response to allergy skin tests is inhibited by antihistamines and a wash-out period (of 3 days) is required before performing them.
- Pruritus may occur when levocetirizine is stopped even if those symptoms were not present before treatment initiation. The symptoms may resolve spontaneously. In some cases, the symptoms may be intense and may require treatment to be restarted. The symptoms should resolve when the treatment is restarted.
- Patients with difficulty in urination and/or enlargement of the prostate, or patients with thyroid disease who are receiving thyroid hormones should not take pseudoephedrine unless directed by a physician.
- Caution should be exercised when using the product in the presence of severe hepatic impairment or moderate renal impairment. Sinarest LP NEO is contraindicated in patients with severe renal impairment (see section 4.3) and caution should also be exercised in occlusive vascular disease.
- If any of the following occur, this product should be stopped
 - Hallucinations
 - Restlessness
 - Sleep disturbances
- Severe Skin reactions: Severe skin reactions such as acute generalized exanthematous pustulosis (AGEP) may occur with pseudoephedrine-containing products. This acute pustular eruption may occur within the first 2 days of treatment, with fever, and numerous, small, mostly non-follicular pustules arising on a widespread oedematous erythema and mainly localized on the skin folds, trunk, and upper extremities. Patients should be carefully

monitored. If signs and symptoms such as pyrexia, erythema, or many small pustules are observed, administration of this medicine should be discontinued, and appropriate measures taken if needed.

- Ischaemic colitis: Some cases of ischaemic colitis have been reported with pseudoephedrine. Pseudoephedrine-containing products should be discontinued, and medical advice sought if sudden abdominal pain, rectal bleeding or other symptoms of ischaemic colitis develop.
- Ischaemic optic neuropathy: Cases of ischaemic optic neuropathy have been reported with pseudoephedrine.
- Pseudoephedrine should be discontinued if sudden loss of vision or decreased visual acuity such as scotoma occurs.
- Posterior reversible encephalopathy syndrome (PRES) and reversible cerebral vasoconstriction syndrome (RCVS)
- Cases of PRES and RCVS have been reported with the use of pseudoephedrine-containing products (see section 4.8). The risk is increased in patients with severe or uncontrolled hypertension, or with severe acute or chronic kidney disease/renal failure (see section 4.3).
- Pseudoephedrine-containing products should be discontinued and immediate medical assistance sought if the following symptoms occur: sudden severe headache or thunderclap headache, nausea, vomiting, confusion, seizures and/or visual disturbances. Most reported cases of PRES and RCVS resolved following discontinuation and appropriate treatment.

4.5 Drug interactions

- No interaction studies have been performed with levocetirizine (including no studies with CYP3A4 inducers); studies with the racemate compound cetirizine demonstrated that there were no clinically relevant adverse interactions (with antipyrine, azithromycin, cimetidine, diazepam, erythromycin, glipizide, ketoconazole and pseudoephedrine). A small decrease in the clearance of cetirizine (16%) was observed in a multiple dose study with theophylline (400 mg once a day); while the disposition of theophylline was not altered by concomitant cetirizine administration.
- In a multiple dose study of ritonavir (600 mg twice daily) and cetirizine (10 mg daily), the extent of exposure to cetirizine was increased by about 40% while the disposition of ritonavir was slightly altered (-11%) further to concomitant cetirizine administration.
- The extent of absorption of levocetirizine is not reduced with food, although the rate of absorption is decreased.
- In sensitive patients, the concurrent administration of cetirizine or levocetirizine and alcohol or other CNS depressants may cause additional reductions in alertness and impairment of performance.
- MAOIs and/or RIMAs: Pseudoephedrine exerts its vasoconstricting properties by stimulating α -adrenergic receptors and displacing noradrenaline from neuronal storage sites. Since monoamine oxidase inhibitors (MAOIs) impede the metabolism of sympathomimetic amines and increase the store of releasable noradrenaline in adrenergic nerve endings, MAOIs may potentiate the pressor effect of pseudoephedrine. This product should not be used in patients taking monoamine inhibitors or within 14 days of stopping treatment as there is an increased risk of hypertensive crisis.
- Moclobemide: Risk of hypertensive crisis.

- Antihypertensives: Because of its pseudoephedrine content, this product may partially reverse the hypotensive action of antihypertensive drugs which interfere with sympathetic activity including bretylium, betanidine, guanethidine, debrisoquine, methyldopa, adrenergic neurone blockers and beta-blockers.
- Cardiac glycosides: Increased risk of dysrhythmias.
- Ergot alkaloids (ergotamine & methysergide): Increased risk of ergotism.
- Appetite suppressants and amphetamine-like psychostimulants: Risk of hypertension.
- Oxytocin: Risk of hypertension.
- Anticholinergic drugs: Enhances effects of anticholinergic drugs (such as Tricyclic antidepressants).
- Anaesthetic agents: Concurrent use with halogenated anaesthetic agents such as chloroform, cyclopropane, halothane, enflurane or isoflurane may provoke or worsen ventricular arrhythmias.

4.6 Use in special population

Paediatric: For children aged 2 to 6 years, no adjusted dosage is possible with this formulation. It is recommended to use a paediatric formulation of levocetirizine.

Geriatric: Normal adult dosage is appropriate for elderly patients with normal renal function. Adjustment of the dose is recommended in elderly patients with moderate to severe renal impairment (see Renal impairment below).

Renal failure: The dosing intervals must be individualised according to renal function (eGFR -estimated Glomerular Filtration Rate). Caution should be exercised when administering Sinarest LP NEO tablets to patients with moderate renal impairment (eGFR 30 to < 60 mL/min).

Refer to the following table and adjust the dose as indicated.

Dosing adjustments for patients with impaired renal function:

Group	eGFR (ml/min)	Dosage and frequency
Normal renal function	≥ 90	1 tablet once daily
Mildly decreased renal function	$60 - < 90$	1 tablet once daily
Moderately decreased renal function	$30 - < 60$	1 tablet once every 2 days
Severely decreased renal function	$15 - < 30$ (not requiring dialysis)	Contra-indicated
End stage renal disease (ESRD)	< 15 (requiring dialysis treatment)	Contra-indicated

In paediatric patients suffering from renal impairment, the dose will have to be adjusted on an individual basis considering the renal clearance of the patient and his body weight. There are no specific data for children with renal impairment.

Liver impairment: Caution should be exercised when administering Sinarest LP NEO tablets to patients with severe hepatic impairment. In patients with hepatic impairment and renal impairment, adjustment of the dose is recommended (see Renal impairment above).

Fertility, pregnancy and lactation:

Pregnancy

There are no or limited amount of data (less than 300 pregnancy outcomes) from the use of levocetirizine in pregnant women. However, for cetirizine, the racemate of levocetirizine, a large amount of data (more than 1000 pregnancy outcomes) on pregnant women indicates no malformities or feto/ neonatal toxicity. Animal studies do not indicate direct or indirect harmful effects with respect to pregnancy, embryo/foetal development, parturition or postnatal development (see section 5.3).

For pseudoephedrine, there are no adequate and well-controlled studies in pregnant women.

Systemic administration of pseudoephedrine, up to 50 times the human daily dosage in rats and up to 35 times the human daily dosage in rabbits, did not produce teratogenic effects.

Therefore, as clinical data are limited, the use of Sinarest LP NEO Tablets is not recommended during pregnancy.

Breastfeeding

Cetirizine, the racemate of levocetirizine, has been shown to be excreted in human. Therefore, the excretion of levocetirizine in human milk is likely. Adverse reactions associated with levocetirizine may be observed in breastfed infants. Therefore, caution should be exercised when prescribing levocetirizine to lactating women.

Pseudoephedrine is excreted in breast milk in small amounts, but the effect of this on breast-fed infants is not known. It has been estimated that approximately 0.4 to 0.7% of a single 60 mg dose of pseudoephedrine ingested by a nursing mother will be excreted in the breast milk over 24 hours. Data from a study of lactating mothers taking 60 mg pseudoephedrine every 6 hours suggests that from 2.2 to 6.7% of the maximum daily dose (240 mg) may be available to the infant from a breastfeeding mother.

Due to the potential for infant exposure to both active ingredients, Sinarest LP NEO is not recommended for use in breastfeeding women.

Fertility

For levocetirizine no clinical data are available.

4.7 Effects on ability to drive and use machine

Comparative clinical trials have revealed no evidence that levocetirizine at the recommended dose impairs mental alertness, reactivity or the ability to drive and use machines.

Nevertheless, some patients could experience somnolence, fatigue and asthenia under therapy with levocetirizine. Therefore, patients intending to drive, engage in potentially hazardous activities or operate machinery should take their response to the medicinal product into account.

4.8 Undesirable effects

Levocetirizine:

Clinical studies

Adults and adolescents above 12 years of age

In a therapeutic studies including women and men aged 12 to 71 years, 15.1% of the patients in the levocetirizine 5 mg group had at least one adverse drug reaction compared to 11.3% in the placebo group. 91.6 % of these adverse drug reactions were mild to moderate.

In therapeutic trials, the dropout rate due to adverse events was 1.0% (9/935) with levocetirizine 5 mg and 1.8% (14/771) with placebo.

In a clinical therapeutic trials with levocetirizine included 935 subjects exposed to the medicinal product at the recommended dose of 5 mg daily. From this pooling, following incidence of adverse drug reactions were reported at rates of 1% or greater (common: $\geq 1/100$ to $< 1/10$) under levocetirizine 5 mg or placebo:

Preferred Term (WHOART)	Placebo (n =771)	Levocetirizine 5 mg (n = 935)
Headache	25 (3.2%)	24 (2.6%)
Somnolence	11 (1.4%)	49 (5.2%)
Mouth dry	12 (1.6%)	24 (2.6%)
Fatigue	9 (1.2%)	23 (2.5%)

Further uncommon incidences of adverse reactions (uncommon $\geq 1/1,000$ to $< 1/100$) like asthenia or abdominal pain were observed.

The incidence of sedating adverse drug reactions such as somnolence, fatigue, and asthenia was altogether more common (8.1%) under levocetirizine 5 mg than under placebo (3.1%).

Paediatric population

In two placebo-controlled studies in paediatric patients aged 6-11 months and aged 1 year to less than 6 years, 159 subjects were exposed to levocetirizine at the dose of 1.25 mg daily for 2 weeks and 1.25 mg twice daily respectively.

The following incidence of adverse drug reactions was reported at rates of 1% or greater under levocetirizine or placebo.

System Organ Class and Preferred Term	Placebo (n=83)	Levocetirizine (n=159)
Gastrointestinal disorders		
Diarrhoea	0	3(1.9%)
Vomiting	1(1.2%)	1(0.6%)
Constipation	0	2(1.3%)
Nervous system disorders		
Somnolence	2(2.4%)	3(1.9%)
Psychiatric disorders		
Sleep disorder	0	2(1.3%)

In children aged 6-12 years, a double blind placebo-controlled studies were performed where 243 children were exposed to 5 mg levocetirizine daily for variable periods ranging from less than 1 week to 13 weeks. The following incidence of adverse drug reactions was reported at rates of 1% or greater under levocetirizine or placebo.

Preferred Term	Placebo (n=240)	Levocetirizine 5mg (n=243)
Headache	5(2.1%)	2(0.8%)
Somnolence	1(0.4%)	7(2.9%)

Post-marketing experience

Adverse reactions from post-marketing experience are per System Organ Class and per frequency. The frequency is defined as follows: 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 ($< 1/10,000$), not known (cannot be estimated from the available data).

- Immune system disorders:

Not known: hypersensitivity including anaphylaxis

- Metabolism and nutrition disorders:

Not known: increased appetite

- Psychiatric disorders:

Not known: aggression, agitation, hallucination, depression, insomnia, suicidal ideation, nightmare

- Nervous system disorders:

Not known: convulsion, paraesthesia, dizziness, syncope, tremor, dysgeusia

- Ear and labyrinth disorders:

Not known: vertigo

- Eyes disorders:

Not known: visual disturbances, blurred vision, oculogyration

- Cardiac disorders:

Not known: palpitations, tachycardia

- Respiratory, thoracic and mediastinal disorders:

Not known: dyspnoea

- Gastrointestinal disorders:

Not known: nausea, vomiting, diarrhoea

- Hepatobiliary disorders:

Not known: hepatitis

- Renal and urinary disorders:

Not known: dysuria, urinary retention

- Skin and subcutaneous tissue disorders:

Not known: angioneurotic oedema, fixed drug eruption, pruritus, rash, urticaria

- Musculoskeletal, connective tissues, and bone disorders:

Not known: myalgia, arthralgia

- General disorders and administration site conditions:

Not known: oedema

- Investigations:

Not known: weight increased, abnormal liver function tests

Description of selected adverse reactions

After levocetirizine discontinuation, pruritus has been reported.

Pseudoephedrine:

Clinical Trial Data

The safety of pseudoephedrine from clinical trial data is based on data from 6 randomised, placebo-controlled single dose clinical trials and 6 randomised, placebo-controlled multiple dose clinical trials for the treatment of nasal congestion with allergic rhinitis or common cold or prevention of sinus symptoms/infection after a natural cold.

Table 1 includes adverse events from a clinical trial and post-marketing experience. Adverse events included from clinical trials are those that occurred where greater than one event was reported, and the incidence was greater than placebo and in 1% of patients or more.

Post-marketing Data

Adverse drug reactions (ADRs) identified during post-marketing experience with pseudoephedrine are included in Table 1 below.

The adverse drug reactions are ranked by frequency, using the following convention.

Very common

Common

Uncommon

Rare

Very rare

Not known

$\geq 1/10$

$\geq 1/100$ and $< 1/10$

$\geq 1/1,000$ and $< 1/100$

$\geq 1/10,000$ and $< 1/1,000$

$< 1/10,000$

(cannot be estimated from the available data)

Table 1: Adverse Reactions Reported in Clinical Trials and Post-marketing Experience

System Organ Class	Adverse Reactions			
	Frequency Category			
	Very Common ($\geq 1/10$)	Common ($\geq 1/100$ to $< 1/10$)	Rare $\geq 1/10,000$ to $< 1/1,000$	Not known
Immune System Disorders				Hypersensitivity – cross-sensitivity may occur with other sympathomimetics
Psychiatric Disorders		Insomnia Nervousness		Anxiety Euphoric mood Excitability Hallucinations Irritability Paranoid delusions Restlessness Sleep disorder
Nervous System Disorders	Headache	Dizziness		Cerebrovascular accident Paraesthesia Posterior reversible encephalopathy syndrome(PRES) (see section 4.4) Reversible cerebral vasoconstriction syndrome(RCVS) (see section 4.4) Psychomotor hyperactivity Somnolence Tremor
Eye Disorders				Ischaemic optic neuropathy

Cardiac Disorders				Dysrhythmias Myocardial infarction/myocardial ischaemia Palpitations Tachycardia
Vascular Disorders				Hypertension
Gastrointestinal Disorders		Dry mouth Nausea		Ischaemic colitis Vomiting
Skin and Subcutaneous Tissue Disorders				Angioedema Pruritus Rash Severe skin reactions, including acute generalised exanthematous pustulosis(AGEP)
Renal and Urinary Disorders				Dysuria Urinary retention (in men in whom prostatic enlargement could have been an important predisposing factor)

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

Levocetirizine:

Symptoms of overdose may include drowsiness in adults. In children, agitation and restlessness may initially occur, followed by drowsiness.

Management of overdoses

There is no known specific antidote to levocetirizine.

Should overdose occur, symptomatic or supportive treatment is recommended. Gastric lavage may be considered shortly after ingestion of the drug. Levocetirizine is not effectively removed by haemodialysis.

Pseudoephedrine:

Overdose may result in:

Hyperglycaemia, hypokalaemia CNS stimulation, insomnia; irritability, restlessness, anxiety, agitation; confusion, delirium, hallucinations, psychoses, seizures, tremor, intracranial

haemorrhage including intracerebral haemorrhage, drowsiness in children, mydriasis, palpitations, tachycardia, reflex bradycardia, supraventricular and ventricular arrhythmias, dysrhythmias, myocardial infarction, hypertension, vomiting, ischaemic bowel infarction, acute renal failure, difficulty in micturition.

Management

Necessary measures should be taken to maintain and support respiration and control convulsions. Catheterisation of the bladder may be necessary. If desired, the elimination of pseudoephedrine can be accelerated by acid diuresis or by dialysis.

5. Pharmacological properties

5.1 Mechanism of action

Levocetirizine:

Pharmacotherapeutic group: antihistamine for systemic use, piperazine derivatives, ATC code: R06A E09.

Mechanism of action

Levocetirizine, the (R) enantiomer of cetirizine, is a potent and selective antagonist of peripheral H₁-receptors.

Binding studies revealed that levocetirizine has high affinity for human H₁-receptors ($K_i = 3.2$ nmol/l). Levocetirizine has an affinity 2-fold higher than that of cetirizine ($K_i = 6.3$ nmol/l). Levocetirizine dissociates from H₁-receptors with a half-life of 115 ± 38 min.

After single administration, levocetirizine shows a receptor occupancy of 90% at 4 hours and 57% at 24 hours.

Pharmacodynamic studies in healthy volunteers demonstrate that, at half the dose, levocetirizine has comparable activity to cetirizine, both in the skin and in the nose.

Pseudoephedrine:

Pseudoephedrine is a sympathomimetic with a mixed mechanism of action, direct and indirect. It indirectly stimulates alpha-adrenergic receptors, causing the release of endogenous norepinephrine (NE) from the granularity of neurons, while it directly stimulates beta-adrenergic receptors. It is an orally effective upper respiratory tract decongestant.

5.2 Pharmacodynamic properties

Levocetirizine:

The pharmacodynamic activity of levocetirizine has been studied in randomised, controlled trials:

In a study comparing the effects of levocetirizine 5 mg, desloratadine 5 mg, and placebo on histamine-induced wheal and flare, levocetirizine treatment resulted in significantly decreased wheal and flare formation which was highest in the first 12 hours and lasted for 24 hours, ($p < 0.001$) compared with placebo and desloratadine.

The onset of action of levocetirizine 5 mg in controlling pollen-induced symptoms has been observed at 1 hour post drug intake in placebo-controlled trials in the model of the allergen challenge chamber.

In vitro studies (Boyden chambers and cell layers techniques) showed that levocetirizine inhibits eotaxin-induced eosinophil trans endothelial migration through both dermal and lung cells. A pharmacodynamic experimental study in vivo (skin chamber technique) showed three main inhibitory effects of levocetirizine 5 mg in the first 6 hours of pollen-induced reaction, compared with placebo in 14 adult patients: inhibition of VCAM-1 release, modulation of vascular permeability and a decrease in eosinophil recruitment.

Clinical efficacy and safety

The efficacy and safety of levocetirizine have been demonstrated in several double-blind, placebo controlled, clinical trials performed in adult patients suffering from seasonal allergic rhinitis, perennial allergic rhinitis, or persistent allergic rhinitis. Levocetirizine has been shown to significantly improve symptoms of allergic rhinitis, including nasal obstruction in some studies.

A 6-month clinical study in 551 adult patients (including 276 levocetirizine-treated patients) suffering from persistent allergic rhinitis (symptoms present 4 days a week for at least 4 consecutive weeks) and sensitized to house dust mites and grass pollen demonstrated that levocetirizine 5 mg was clinically and statistically significantly more potent than placebo on the relief from the total symptom score of allergic rhinitis throughout the whole duration of the study, without any tachyphylaxis. During the whole duration of the study, levocetirizine significantly improved the quality of life of the patients.

In a placebo-controlled clinical trial including 166 patients suffering from chronic idiopathic urticaria, 85 patients were treated with placebo and 81 patients with levocetirizine 5 mg once daily over six weeks. Treatment with levocetirizine resulted in significant decrease in pruritus severity over the first week and over the total treatment period as compared to placebo. Levocetirizine also resulted in a larger improvement of health-related quality of life as assessed by the Dermatology Life Quality Index as compared to placebo.

Chronic idiopathic urticaria was studied as a model for urticarial conditions. Since histamine release is a causal factor in urticarial diseases, levocetirizine is expected to be effective in providing symptomatic relief for other urticarial conditions, in addition to chronic idiopathic urticaria.

ECGs did not show relevant effects of levocetirizine on QT interval.

Paediatric population

The paediatric safety and efficacy of levocetirizine tablets have been studied in two placebo controlled clinical trials including patients aged 6 to 12 years and suffering from seasonal and perennial allergic rhinitis, respectively. In both trials, levocetirizine significantly improved symptoms and increased health-related quality of life.

In children below the age of 6 years, clinical safety has been established from several short- or long-term therapeutic studies:

- one clinical trial in which 29 children 2 to 6 years of age with allergic rhinitis were treated with levocetirizine 1.25 mg twice daily for 4 weeks
- one clinical trial in which 114 children 1 to 5 years of age with allergic rhinitis or chronic idiopathic urticaria were treated with levocetirizine 1.25 mg twice daily for 2 weeks
- one clinical trial in which 45 children 6 to 11 months of age with allergic rhinitis or chronic idiopathic urticaria were treated with levocetirizine 1.25 mg once daily for 2 weeks
- one long-term (18 months) clinical trial in 255 levocetirizine - treated atopic subjects aged 12 to 24 months at inclusion.

The safety profile was like that seen in the short-term studies conducted in children 1 to 5 years of age.

Pseudoephedrine:

Sympathomimetics. R01BA02.

Pseudoephedrine has direct and indirect sympathomimetic activity and is an orally effective upper respiratory tract decongestant.

Pseudoephedrine is substantially less potent than ephedrine in producing both tachycardia and elevation in systolic blood pressure and considerably less potent in causing stimulation of the central nervous system.

5.3 Pharmacokinetic properties

Levocetirizine:

The pharmacokinetics of levocetirizine are linear with dose- and time-independent with low inter-subject variability. The pharmacokinetic profile is the same when given as the single enantiomer or when given as cetirizine. No chiral inversion occurs during the process of absorption and elimination.

Absorption

Levocetirizine is rapidly and extensively absorbed following oral administration. In adults, peak plasma concentrations are achieved 0.9 h after dosing. Steady state is achieved after two days. Peak concentrations are typically 270 ng/ml and 308 ng/ml following a single and a repeated 5 mg o.d. dose, respectively. The extent of absorption is dose-independent and is not altered by food, but the peak concentration is reduced and delayed.

Distribution

No tissue distribution data are available in humans, neither concerning the passage of levocetirizine through the blood-brain-barrier. In rats and dogs, the highest tissue levels are found in liver and kidneys, the lowest in the CNS compartment.

In humans, levocetirizine is 90% bound to plasma proteins. The distribution of levocetirizine is restrictive, as the volume of distribution is 0.4 l/kg.

Biotransformation

The extent of metabolism of levocetirizine in humans is less than 14% of the dose and therefore differences resulting from genetic polymorphism or concomitant intake of enzyme inhibitors are expected to be negligible. Metabolic pathways include aromatic oxidation, N- and O-dealkylation and taurine conjugation. Dealkylation pathways are primarily mediated by CYP 3A4 while aromatic oxidation involved multiple and/or unidentified CYP isoforms.

Levocetirizine had no effect on the activities of CYP isoenzymes 1A2, 2C9, 2C19, 2D6, 2E1 and 3A4 at concentrations well above peak concentrations achieved following a 5 mg oral dose.

Due to its low metabolism and absence of metabolic inhibition potential, the interaction of levocetirizine with other substances, or vice-versa, is unlikely.

Elimination

The plasma half-life in adults is 7.9 ± 1.9 hours. The half-life is shorter in small children.

The mean apparent total body clearance in adults is 0.63 ml/min/kg. The major route of excretion of levocetirizine and metabolites is via urine, accounting for a mean of 85.4% of the dose. Excretion via faeces accounts for only 12.9% of the dose. Levocetirizine is excreted both by glomerular filtration and active tubular secretion.

Special population

Renal impairment

The apparent body clearance of levocetirizine is correlated to the creatinine clearance. It is therefore recommended to adjust the dosing intervals of levocetirizine in patients with moderate and severe renal impairment (see section 4.2). In normal subjects. The amount of levocetirizine removed during a standard 4-hour haemodialysis procedure was < 10%.

Paediatric population

Data from a paediatric pharmacokinetic study with oral administration of a single dose of 5 mg levocetirizine in 14 children age 6 to 11 years with body weight ranging between 20 and 40 kg show that C_{max} and AUC values are about 2-fold greater than that reported in healthy adult subjects in a cross-study comparison. The mean C_{max} was 450 ng/ml, occurring at a mean time of 1.2 hours, weight-normalized, total body clearance was 30% greater, and the elimination half-life 24% shorter in this paediatric population than in adults. Dedicated pharmacokinetic studies have not been conducted in paediatric patients younger than 6 years of age. A retrospective population pharmacokinetic analysis was conducted in 323 subjects (181 children 1 to 5 years of age, 18 children 6 to 11 years of age, and 124 adults 18 to 55 years of age) who received single or multiple doses of levocetirizine ranging from 1.25 mg to 30 mg. Data generated from this analysis indicated that administration of 1.25 mg once daily to children 6 months to 5 years of age is expected to result in plasma concentrations similar to those of adults receiving 5 mg once daily.

Elderly

Limited pharmacokinetic data are available in elderly subjects. Following once daily repeat oral administration of 30 mg levocetirizine for 6 days in 9 elderly subjects (65–74 years of age), the total body clearance was approximately 33% lower compared to that in younger adults. The disposition of racemic cetirizine has been shown to be dependent on renal function

rather than on age. This finding would also be applicable for levocetirizine, as levocetirizine and cetirizine are both predominantly excreted in urine. Therefore, the levocetirizine dose should be adjusted in accordance with renal function in elderly patients.

Gender

Pharmacokinetic results for 77 patients (40 men, 37 women) were evaluated for potential effect of gender. The half-life was slightly shorter in women (7.08 ± 1.72 hr) than in men (8.62 ± 1.84 hr); however, the body weight-adjusted oral clearance in women (0.67 ± 0.16 ml/min/kg) appears to be comparable to that in men (0.59 ± 0.12 ml/min/kg). The same daily doses and dosing intervals are applicable for men and women with normal renal function.

Race

The effect of race on levocetirizine has not been studied. As levocetirizine is primarily renally excreted, and there are no important racial differences in creatinine clearance, pharmacokinetic characteristics of levocetirizine are not expected to be different across races. No race-related differences in the kinetics of racemic cetirizine have been observed.

Hepatic impairment

The pharmacokinetics of levocetirizine in hepatically impaired subjects have not been tested. Patients with chronic liver diseases (hepatocellular, cholestatic, and biliary cirrhosis) given 10 or 20 mg of the racemic compound cetirizine as a single dose had a 50% increase in half life along with a 40% decrease in clearance compared to healthy subjects.

Pharmacokinetic / pharmacodynamic relationship

The action on histamine-induced skin reactions is out of phase with the plasma concentrations.

Pseudoephedrine:

Pseudoephedrine is rapidly and completely absorbed after oral administration. After an oral dose of 180 mg to man, peak plasma concentrations of 500-900 ng/ml were obtained about 2 hours post dose. The plasma half-life was about 5.5 hours and was increased in subjects with alkaline urine and decreased in subjects with acid urine. The only metabolism was N-demethylation which occurred to a small extent. Excretion was mainly via the urine.

6. Nonclinical properties

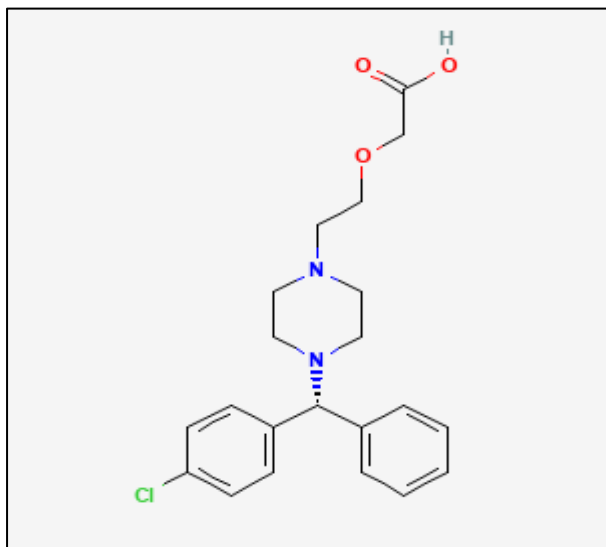
6.1 Animal Toxicology or Pharmacology

Non-clinical data for levocetirizine 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 active ingredient-Pseudoephedrine is a well-known constituent of medicinal products, and its safety is well documented. The results of pre-clinical studies do not add anything of relevance for therapeutic purposes.

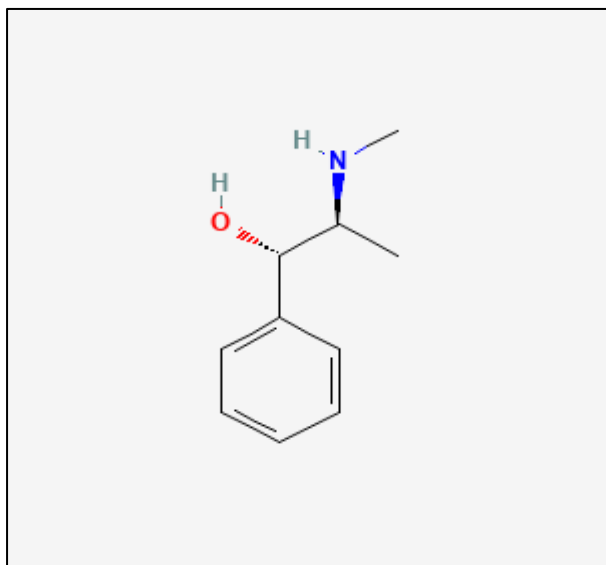
7. Description

Levocetirizine is in a class of medications called antihistamines. Its chemical name is 2-(2-{4-[(R)-(4-chlorophenyl) (phenyl)methyl] piperazin-1-yl} ethoxy) acetic acid dihydrochloride and its structural formula is:



Its empirical formula is $C_{21}H_{25}ClN_2O_3$, and its molecular weight is 388.8878 g/mol.

Pseudoephedrine is an alpha-Adrenergic Agonist. Its chemical name is (1*S*,2*S*)-2-(methylamino)-1-phenylpropan-1-ol and its structural formula is:



Its empirical formula is $C_{10}H_{15}NO$, and its molecular weight is 165.23 g/mol.

8. Pharmaceutical particulars

8.1 Incompatibilities

There are no known incompatibilities.

8.2 Shelf-life

24 months

8.3 Packaging Information

Sales: 10's

8.4 Storage and handling instructions

Store in a dry, well-ventilated place at a temperature not exceeding 30°C.

Keep out of reach of children.

9. Patient Counselling Information

9.1 Adverse Reactions

Refer part 4.8

9.2 Drug Interactions

Refer part 4.5

9.3 Dosage

Refer part 4.2

9.4 Storage

Refer part 8.4

9.5 Risk Factors

Refer part 4.4

9.6 Self-monitoring information

NA

9.7 Information on when to contact a health care provider or seek emergency help

Patient is advised to be alert for the emergence or worsening of the adverse reactions and contact the prescribing physician.

9.8 Contraindications

Refer part 4.3

10. Manufactured by

The Madras Pharmaceuticals
137 B, Old Mahabalipuram Road, Karapakkam,
Chennai-600096, Tamil Nadu, India.

11. Details of permission or license number with date

Mfg.Lic.No.- 247; Dated: 28/10/2024

12. Date of revision

June 2026.