Montelukast + Levocetirizine dihydrochloride

STELIX™ 10 mg/5 mg Film-Coated Tablet

Leukotriene Receptor Antagonist/Antihistamine

℞

NAME OF THE MEDICINAL PRODUCT
Montelukast sodium/Levocetirizine dihydrochloride 10 mg/5 mg film-coated tablet

FORMULATION
Each film-coated tablet contains:
Montelukast sodium equivalent to
Montelukast (as sodium) ..... 10 mg
Levocetirizine dihydrochloride .... 5 mg

PRODUCT DESCRIPTION:
White coloured, circular, biconvex film-coated tablets plain on both sides.

INDICATIONS:
Montelukast Levocetirizine dihydrochloride film-coated tablets are indicated for chronic allergic conditions like seasonal allergic rhinitis, perennial allergic rhinitis, rhinitis associated with asthma.

DOSING AND ADMINISTRATION:
Adults
One tablet containing Montelukast 10 mg levocetirizine 5 mg once daily. Or as prescribed by the physician.

Elderly
One tablet containing Montelukast 10 mg levocetirizine 5 mg once daily. Or as prescribed by the physician.
Patients with Renal Impairment
In adults and children 12 years of age and older with:
Mild renal impairment (ClCr 50-80 mL/min): one tablet containing Montelukast 10mg plus Levocetirizine 2.5mg once daily.
Moderate renal impairment (ClCr 30-50 mL/min): one tablet containing Montelukast 10mg plus Levocetirizine 2.5mg once daily, every other day.
Patients with hepatic disease
No dosage adjustment is needed in patients solely with mild to moderate hepatic impairment. Usage is not recommended in patients with severe hepatic impairment.

Children and Adolescents
Children aged 2 – 6 : one fast melt tablet containing 4mg Montelukast and 2.5mg Levocetirizine once daily.
Children aged 6 –14: one chewable tablet containing 5mg Montelukast and 5mg Levocetirizine once daily.
Children aged 15 + : one tablet containing 10mg Montelukast and Levocetirizine 5mg once daily.
Or as prescribed by the physician.

PHARMACOLOGY
Montelukast
The cysteinyl leukotrienes (LTC4, LTD4, and LTE4) are potent inflammatory eicosanoids released from various cells including mast cells and eosinophils. These important mediators bind to cysteinyl leukotriene receptors. Cysteinyl leukotrienes have been correlated with the pathophysiology of asthma and allergic rhinitis. In asthma, leukotriene-mediated effects include bronchoconstriction, mucous secretion, vascular permeability, and eosinophil recruitment. In allergic rhinitis, cysteinyl leukotrienes are released from the nasal mucosa after allergen exposure during both early- and late-phase reactions and are associated with symptoms of allergic rhinitis. Intranasal challenge with cysteinyl leukotrienes has been shown to increase nasal airway resistance and symptoms of nasal obstruction. Montelukast is an orally active compound which binds with high affnity and selectivity to the cysteinyl leukotriene type 1 receptor thereby preventing cysteinyl leukotrienes from exerting their effects.
Levocetirizine
Levocetirizine, the active enantiomer of cetirizine, is anti-histamine. Its principal effects are mediated via selective inhibition of H1 receptors. The antihistamine activity of Levocetirizine has been documented in a variety of animal and human models.
PHARMACOKINETICS
Montelukast
Absorption
Montelukast is rapidly absorbed following oral administration. Mean peak plasma concentration (Cmax) is achieved 3 hours (Tmax) after administration of a 10mg dose in adults in the fasted state. The mean oral bioavailability is 64%. The oral bioavailability and Cmax are not influenced by a standard meal. Safety and efficacy were demonstrated in clinical trials where the 10-mg film-coated tablet was administered without regard to the timing of food ingestion. Cmax is achieved in 2 hours after administration of the 5mg chewable tablet in adults in the fasted state. The mean oral bioavailability is 73% and is decreased to 63% by a standard meal.
Distribution
Montelukast is more than 99% bound to plasma proteins. Steady-state volume of distribution of Montelukast averages 8 -11 liters. Studies in rats with radio labeled Montelukast indicate minimal distribution across the blood-brain barrier. In addition, concentrations of radio labeled material at 24 hours post dose were minimal in all other tissues.
Metabolism
Montelukast is extensively metabolized. In studies with therapeutic doses, plasma concentrations of metabolites of Montelukast are undetectable at steady state in adults and children. In vitro studies using human liver microsomes indicate that cytochrome P450 3A4, 2A6 and 2C9 are involved in the metabolism of Montelukast. Based on further in vitro results in human liver microsomes, therapeutic plasma concentrations of Montelukast do not inhibit cytochromes P450 3A4, 2C9, 1A2, 2A6, 2C19, or 2D6. The contribution of metabolites to the therapeutic effect of Montelukast is minimal.

Elimination
The plasma clearance of Montelukast averages 45 ml/min in healthy adults. Following an oral dose of radio labeled Montelukast, 86% of the radioactivity was recovered in 5-day fecal collections and <0.2% was recovered in urine. Coupled with estimates of Montelukast oral bioavailability, this indicates that Montelukast and its metabolites are excreted almost exclusively via the bile.
Elderly
The pharmacokinetic profile and the oral bioavailability of a single 10-mg oral dose of Montelukast are similar in elderly and younger adults. The plasma half-life of Montelukast is slightly longer in the elderly. Due to the Levocetirizine component of Montelukast plus Levocetirizine however, dosage adjustment may be required in elderly patients **(See Dosage and Administration – Elderly)**.
Patients with Renal Impairment
Since Montelukast and its metabolites are not excreted in the urine, the pharmacokinetics of Montelukast was not evaluated in patients with renal insufficiency. Due to the Levocetirizine component of MONTELUKAST PLUS LEVOCETIRIZINE however, dosage adjustment is required in patients with renal impairment **(See Dosage and Administration – Patients with Renal Impairment)**.
Patients with Hepatic Impairment
Patients with mild-to-moderate hepatic insufficiency and clinical evidence of cirrhosis had evidence of decreased metabolism of Montelukast resulting in 41% (90% CI=7%, 85%) higher mean Montelukast area under the plasma concentration curve (AUC) following a single 10-mg dose. The elimination of Montelukast was slightly prolonged compared with that in healthy subjects (mean half-life, 7.4 hours). No dosage adjustment is required in patients with mild-to-moderate hepatic insufficiency.

Levocetirizine dihydrochloride
Absorption
Levocetirizine is rapidly and extensively absorbed following oral administration. Peak plasma concentrations are achieved 0.9 h after dosing. Steady state is achieved after two days. Peak concentrations are 270 ng/ml and 308 ng/ml following a single and a repeated 5 mg dose once daily, 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. Levocetirizine is 90% bound to plasma proteins. The distribution of Levocetirizine is restrictive, as the volume of distribution is 0.4 l/kg.
Metabolism
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 mean apparent total body clearance 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 feces accounts for only 12.9% of the dose. Levocetirizine is excreted both by glomerular filtration and active tubular secretion. Elderly
Limited pharmacokinetic data is available in elderly subjects. Following once daily repeated oral administration of 30mg Levocetirizine for 6 days in 9 elderly subjects (74-75 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 age. Therefore, the dosage of Levocetirizine should be adjusted in accordance with renal function in elderly patients.
Patients with Renal Impairment
The apparent body clearance of Levocetirizine is correlated to the creatinine clearance. It is therefore recommended to adjust the dosage and frequency of dosage of Levocetirizine, based on creatinine clearance in patients with moderate and severe renal impairment (see Dosage and Administration).
Patients with Hepatic Impairment
Levocetirizine has not been studied in patients with hepatic impairment. The non-renal clearance (indicative of hepatic contribution) was found to constitute about 28% of the total body clearance in healthy adult subjects after oral administration. As Levocetirizine is mainly excreted unchanged by the kidney, it is unlikely that the clearance of Levocetirizine is significantly decreased in patients solely with hepatic impairment.
Children
In children 6-11 years of age, Cmax and AUC values are about 2-fold greater than normal healthy adults when given the same dose (5mg once daily). Cmax occurred 1.2 hours post dose in children, total body clearance was 30% greater and the elimination half-life 24% shorter than adults.

CONTRAINDICATIONS:
MONTELUKAST + LEVOCETIRIZINE is contraindicated in patients with a known hypersensitivity to Montelukast or Levocetirizine, patients with severe renal (creatinine clearance less than 10 ml/min) or hepatic impairment, in children 6-11 years of age with renal impairment, and during women who are pregnant or breastfeeding.

WARNINGS AND PRECAUTIONS:
Montelukast:

Acute Asthma
Montelukast is not indicated for use in the reversal of bronchospasm in acute asthma attacks, including status asthmaticus. Patients should be advised to have appropriate rescue medication available. Therapy with montelukast can be continued during acute exacerbations of asthma.
Patients who have exacerbations of asthma after exercise should have available for rescue a short-acting inhaled beta2-agonist.

Concomitant Corticosteroid Use
While the dose of inhaled corticosteroid may be reduced gradually under medical supervision, montelukast should not be abruptly substituted for inhaled or oral corticosteroids.

Aspirin Sensitivity
Patients with known aspirin sensitivity should continue avoidance of aspirin or non-steroidal anti-inflammatory agents while taking montelukast. Although montelukast is effective in improving airway function in asthmatics with documented aspirin sensitivity, it has not been shown to truncate bronchoconstrictor response to aspirin and other non-steroidal anti-inflammatory drugs in aspirin-sensitive asthmatic patients.

Eosinophilic Conditions
Patients on therapy with montelukast may present with systemic eosinophilia sometimes presenting with clinical features of vasculitis consistent with Churg-Strauss syndrome, a condition, which is often treated with systemic corticosteroid therapy. These events usually, but not always, have been associated with the reduction of oral corticosteroid therapy. Physicians should be alert to eosinophilia, vasculitic rash, worsening pulmonary symptoms, cardiac complications, and/or neuropathy presenting in their patients. A causal association between, montelukast and these underlying conditions has not been established.

Neuropsychiatric Events
Neuropsychiatric events have been reported in adult, adolescent, and pediatric patients taking montelukast. Post-marketing reports with montelukast use include agitation, aggressive behavior or hostility, anxiousness, depression, disorientation, dream abnormalities, hallucinations, insomnia, irritability, memory impairment, restlessness, somnambulism, suicidal thinking, and behavior (including suicide), and tremor. The clinical details of some post-marketing reports involving montelukast appear consistent with a drug-induced effect.
Patients and prescribers should be alert for neuropsychiatric events. Patients should be instructed to notify their prescriber if these changes occur. Prescribers should carefully evaluate the risks and benefits of continuing treatment with montelukast if such events occur.

Phenylketonuria
Phenylketonuric patients should be informed about the presence of phenylalanine (a component of aspartame) in this product.

Levocetirizine:
Somnolence
In clinical trials the occurrence of somnolence, fatigue, and asthenia has been reported in some patients under therapy with levocetirizine. Patients should be cautioned against engaging in hazardous occupations requiring complete mental alertness and motor co-ordination such as operating machinery or driving a motor vehicle after ingestion of levocetirizine. Concurrent use of levocetirizine with alcohol or other central nervous system depressants should be avoided because additional reductions in alertness and additional impairment of central nervous system performance may occur.

Urinary Retention
Urinary retention has been reported post-marketing with levocetirizine. Levocetirizine should be used with caution in patients with predisposing factors of urinary retention (e.g. spinal cord lesion, prostatic hyperplasClinical studies
Adults and adolescents above 12 years of age: ia) as levocetirizine may increase the risk of urinary retention. Discontinue, if urinary retention occurs.

OVERDOSAGE:
There is no data reported on the overdosage of this combination. However, overdosage has been reported with individual molecules.
Montelukast:
No specific information is available on the treatment of overdosage with montelukast.
There have been reports of acute overdosage in post-marketing experience and clinical studies of up to at least 150 mg/day with montelukast. These include reports in adults and children with a dose as high as 1000 mg. The clinical and laboratory findings observed were consistent with the safety profile in adults and pediatric patients. There were no adverse experiences in the majority of overdosage reports. The most frequently occurring adverse experiences were consistent with the safety profile of montelukast and included abdominal pain, somnolence, thirst, headache, vomiting and psychomotor hyperactivity.
In the event of overdose, it is reasonable to employ the usual supportive measures; e.g., remove unabsorbed material from the gastrointestinal tract, employ clinical monitoring, and institute supportive therapy, if required.
It is not known whether montelukast is removed by peritoneal dialysis or hemodialysis.
Levocetirizine:
Symptoms of overdose may include drowsiness in adults, and in children, initially agitation and restlessness occur, followed by drowsiness. There is no known specific antidote to levocetirizine. Should overdose occur, symptomatic or supportive treatment is recommended. Gastric lavage should be considered following short-term ingestion. Levocetirizine is not effectively removed by dialysis, and dialysis will be ineffective unless a dialyzable agent has been concomitantly ingested.

ADVERSE REACTION:
Levocetirizine

Clinical studies

Adults and adolescents above 12 years of age:
In therapeutic studies in 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.

Length(139 mm) x Height(270mm)

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

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: 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 %)
Fatique	9 (1.2 %)	23 (2.5 %)

Further uncommon incidences of adverse reactions (uncommon :1/1000, <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%).

Pediatric population
In two placebo-controlled studies in pediatric patients aged 6–11 months and aged 1 year to less than 6 years, 159 subjects were exposed to levocetirizine at the dose of 1.25mg daily for 2 weeks and 1.25mg 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 disorder		
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 disorders	0	2(1.3%)

In children aged 6–12 years double blind placebo-controlled studies were performed where 243 children were exposed to 5mg 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 5 mg (n=243)
Headache	5 (2.1 %)	2(0.5 %)
Somnolence	1 (0.4 %)	7(2.9 %)

Post-marketing experience
Adverse reactions from post-marketing experience are per MedDRA, System Organ Class and per frequency.
The frequency is de-ned as follows:

· 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)
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, ·xed 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.

Levocetirizine:

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 malformative or foeto/ neonatal toxicity.
Animal studies do not indicate direct or indirect harmful effects with respect to pregnancy, embryonal/foetal development, parturition, or postnatal development (see section 5.3).

The use of Levocetirizine may be considered during pregnancy, if necessary

Breast-feeding
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.

Fertility
For levocetirizine no clinical data are available

DRUG INTERACTIONS

Montelukast

In drug-interactions studies, the recommended clinical dose of Montelukast did not have clinically important effects on the pharmacokinetics of the following drugs: theophylline, prednisone, prednisolone, oral contraceptives (ethinyl estradiol/ norethindrone 35/1), terfenadine, digoxin and warfarin. The area under the plasma concentration curve (AUC) for Montelukast was decreased approximately 40% in subjects with co-administration of phenobarbital. Since Montelukast is metabolized by CYP 3A4, caution should be exercised, particularly in children, when Montelukast is coadministered with inducers of CYP 3A4, such as phenytoin, phenobarbital and rifampicin. In vitro studies have shown that Montelukast is a potent inhibitor of CYP 2C8. However, data from a clinical drug-drug interaction study involving Montelukast and rosiglitazone (a probe substrate representative of drugs primarily metabolized by CYP 2C8) demonstrated that Montelukast does not inhibit CYP 2C8 in vivo. Therefore, Montelukast is not anticipated to markedly alter the metabolism of drugs metabolized by this enzyme (e.g., paclitaxel, rosiglitazone, and repaglinide.)

Levocetirizine

In vitro data indicate that levocetirizine is unlikely to produce pharmacokinetic interactions through inhibition or induction of liver drug-metabolizing enzymes. No in-vivo drug-drug interaction studies have been performed with Levocetirizine. In pharmacokinetic interaction studies performed with racemic cetirizine, cetirizine did not interact with antipyrine, pseudoephedrine, erythromycin, azithromycin, ketoconazole, or cimetidine. A small decrease in the clearance of cetirizine was caused by a 400mg dose of theophylline. Ritonavir increased the plasma AUC, half-life and decreased the clearance 42%, 53% and 29% respectively. The disposition of ritonavir was not altered by administration of cetirizine.

SPECIAL PRECAUTIONS FOR STORAGE:
Store at temperatures not exceeding 30˚C

ADR Reporting Statement:
For suspected adverse drug reaction, report to the FDA: www.fda.gov.ph
Seek medical attention immediately at the ·rst sign of any adverse drug reaction.

DOSAGE FORM AND PACKAGING AVAILABLE:
Film-Coated tablet, Alu/PVC Blister pack x 10's (Box of 100's and 30's).

CAUTION
Foods, Drugs, Devices and Cosmetics Act prohibits dispensing without prescription.

Mfg.Lic.No.: TN00002269

DRP-13136

Date of First Authorization: 07 DEC 2022

TM: STELIX is a Trademark of Natrapharm

Date of Leaflet Revision: 12 DEC 2022

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Imported by:
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Distributed by:
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PENC 3630

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