1. NAME OF THE MEDICINALPRODUCT

MONTIZINE TABLETS
(LevocetirizineDihydrochloride USP 5 mg and Montelukast Sodium BP 10 mg)

2. QUALITATIVE AND QUANTITATIVECOMPOSITION

Each uncoated tablet contains:
Montelukast Sodium BP
Equivalent to Montelukast 10 mg
Levocetirizine Di hydrochloride USP 5 mg
Colour - Yellow Oxide of Iron

3. PHARMACEUTICAL FORM

Pharmaceutical form: Tablets
Description:Light yellow coloured circular biconvex uncoated tablets.

3.1 Therapeuticindications

- Allergic rhinitis (seasonal or perennial)
- Symptoms of allergic reactions such as running nose, itchy and watery eyes and sneezing
- Urticaria

3.2 Posology and method ofadministration

As directed by the physician

3.3 Contraindications

MontizineTablets is contraindicated in patients with known hypersensitivity to montelukast, levocetirizine or cetirizine, or to any of the excipients. Also, contradicted in patients with end stage renal disease at less than 10 ml/min creatinine clearance, and patients undergoing haemodialysis. Children 6 months to 11 years of age with impaired renal function should not be administered. Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose- galactosemalabsoprtion should not take this medicine.

3.4 Special warnings and precautions foruse

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. While the dose of inhaled corticosteroid may be reduced gradually under medical supervision, montelukast should not be abruptly substituted for

inhaled or oral corticosteroids. There are no data demonstrating that oral corticosteroids can be reduced when montelukast is given concomitantly.

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 hyperplasia) as levocetirizine may increase the risk of urinary retention. Discontinue, if urinary retention occurs.

3.5 Interaction with other medicinal products and other forms ofinteraction

Montelukast

Montelukast may be administered with other therapies routinely used in the prophylaxis and chronic treatment of asthma. In drug-interaction 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 (norethindrone 1 mg/ethinylestradiol 35 mcg), terfenadine, digoxin and warfarin, gemfibrozil, itraconazole, thyroid hormones, sedative hypnotics, non-steroidal anti-inflammatory agents, benzodiazepines, decongestants, and CYP 450 enzyme inducers.

The area under the plasma concentration curve (AUC) for montelukast was decreased approximately 40% in subjects with co-administration of phenobarbital. Since montelukast is metabolised by CYP 3A4, caution should be exercised, particularly in children, when montelukast is co-administered with inducers of CYP 3A4, such as phenytoin, phenobarbital and rifampicin.

Although additional specific interaction studies were not performed, montelukast was used concomitantly with a wide range of commonly prescribed drugs in clinical studies without evidence of clinical adverse interactions. These medications included thyroid hormones, sedative hypnotics, non-steroidal anti-inflammatory agents, benzodiazepines, and decongestants.

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 medicinal products primarily metabolised by CYP 2C8) demonstrated that montelukast does not inhibit CYP 2C8 in vivo. Therefore, montelukast is not anticipated to markedly alter the metabolism of medicinal products metabolised by this enzyme (e.g., paclitaxel, rosiglitazone, and repaglinide.)

In vitro studies have shown that montelukast is a substrate of CYP 2C8, and to a less significant extent, of 2C9, and 3A4. In a clinical drug-drug interaction study involving

montelukast and gemfibrozil (an inhibitor of both CYP 2C8 and 2C9) gemfibrozil increased the systemic exposure of montelukast by 4.4-fold. No routine dosage adjustment of montelukast is required upon co-administration with gemfibrozil or other potent inhibitors of CYP 2C8, but the physician should be aware of the potential for an increase in adverse reactions.

Based on in vitro data, clinically important drug interactions with less potent inhibitors of CYP 2C8 (e.g., trimethoprim) are not anticipated. Co-administration of montelukast with itraconazole, a strong inhibitor of CYP 3A4, resulted in no significant increase in the systemic exposure of montelukast.

Levocetirizine

In vitro data on metabolite interaction indicate that levocetirizine is unlikely to produce, or be subject to metabolic interactions. Levocetirizine at concentrations well above Cmax level achieved within the therapeutic dose ranges is not an inhibitor of CYP isoenzymes 1A2, 2C9, 2C19, 2A1, 2D6, 2E1, and 3A4, and is not an inducer of UGT1A or CYP isoenzymes 1A2, 2C9 and 3A4. No in vivo drug-drug interaction studies have been performed with levocetirizine. Drug interaction studies have been performed with racemic cetirizine, Antipyrine, Azithromycin, Cimetidine, Erythromycin, Ketoconazole, Theophylline, and Pseudoephedrine

Pharmacokinetic interaction studies performed with racemic cetirizine demonstrated that cetirizine did not interact with antipyrine, pseudoephedrine, erythromycin, glipizide and diazepam, azithromycin, ketoconazole and cimetidine. There was a small decrease (~16%) in the clearance of cetirizine caused by a 400 mg dose of theophylline. It is possible that higher theophylline doses could have a greater effect.
The extent of absorption of levocetirizine is not reduced with food although the rate of absorption is decreased.

Ritonavir
Ritonavir increased the plasma AUC of cetirizine by about 42% accompanied by an increase in half-life (53%) and a decrease in clearance (29%) of cetirizine. The disposition of ritonavir was not altered by concomitant cetirizine administration.
In sensitive patients the simultaneous administration of cetirizine or levocetirizine and alcohol or other CNS depressants may have effects on the central nervous system, although it has been shown that the racemate cetirizine does not potentiate the effect of alcohol.

Renal Impairment

Montelukast

No dosage adjustment is recommended for montelukast in patients with renal impairment.

Levocetirizine

Levocetirizine is known to be substantially excreted by the kidneys and the risk of adverse reactions to this drug may be greater in patients with impaired renal function. Dosage adjustment may be required in patients with impaired renal function. Hence this

combination is not recommended in patients with impaired renal function. Because elderly patients are more likely to have decreased renal function, care should be taken in dose selection and it may be useful to monitor renal function.

Hepatic Impairment

Montelukast

No dosage adjustment is required in patients with mild-to-moderate hepatic insufficiency. The pharmacokinetics of montelukast in patients with more severe hepatic impairment or with hepatitis have not been evaluated.

Levocetirizine

As levocetirizine is mainly excreted unchanged by the kidneys, it is unlikely that the clearance of levocetirizine is significantly decreased in patients with solely hepatic impairment.

3.6 Pregnancy and Lactation

Pregnancy

There are no adequate and well controlled studies of either montelukast or levocetirizine in pregnant women. Animal studies do not indicate harmful effects with respect to effects on pregnancy or embryonal/ foetal development.

Montelukast

Limited data from available pregnancy databases do not suggest a causal relationship between Montelukast and malformations (i.e. limb defects) that have been rarely reported in worldwide post marketing experience.

Levocetirizine

In rats and rabbits, levocetirizine was not teratogenic at oral doses approximately 320 and 390, respectively, times the maximum recommended daily oral dose in adults on a mg/m2 basis.

Because animal reproduction studies are not always predictive of human response, this combination should be used during pregnancy only if it is considered to be clearly essential.

Lactation

Montelukast

Studies in rats have shown that montelukast is excreted in milk. It is not known if montelukast is excreted in human milk.

Levocetirizine

No pre and postnatal animal studies have been conducted with levocetirizine. Cetirizine has been reported to be excreted in human breast milk. Because levocetirizine is also expected to be excreted in human milk this combination is not recommended during lactation.

3.7 Effects on ability to drive and usemachines

Montelukast

Montelukast is not expected to affect a patient's ability to drive a car or operate machinery. However, in very rare cases, individuals have reported drowsiness or dizziness.

Levocetirizine

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

3.8 Undesirableeffects

There is no data available on undesirable effects of this combination. However, side effe cts have been reported with individual molecules.

Montelukast

Because clinical trials are conducted under widely varying conditions, adverse reactionrates observed in the clinical trials of a drug cannot be directly compared to rates in theclinical trials of another drug and may not reflect the rates observed in clinical pra ctice.

The most common adverse reactions (incidence ≥ 5% and greater than placebo; listed in descending order of frequency) in controlled clinical trials were: upper respiratory infect ion, fever, headache, pharyngitis, cough, abdominal pain, diarrhea, otitis media, influenz a, rhinorrhea, sinusitis, otitis.

Adults and Adolescents 15 Years of Age and Older

Asthma

Montelukast has been evaluated for safety in approximately 2950 adult and adolescent patients with asthma 15 years of age and older in clinical trials. In placebocontrolled clinical trials, the following adverse experiences reported with montel ukast occurred in greater than or equal to 1% of patients and at an incidence greater than that in patients treated with placebo:

Body as a whole: Abdominal pain, asthenia/fatigue, fever, trauma
Digestive system disorders: Dyspepsia, dental pain, infectious gastroenteritis Nervous/ Psychiatric disorders: Headache, dizziness
Respiratory system disorders: Influenza, cough, nasal congestion
Skin/Skin appendages disorder: Rash
Laboratory adverse experiences: Increased alanine amino transaminase (ALT) and asp artate amino transaminase (AST) and pyuria

The frequency of less common adverse events was comparable between montelukastand placebo. The safety profile of montelukast, when administered as a single dose for prevention of EIB in adult and adolescent patients 15 years of age and older, was consist ent with the safety profile previously described for montelukast.

Cumulatively, 569 patients were treated with montelukast for at least 6 months, 480 for one year, and 49 for two years in clinical trials. With prolonged treatment, the adverse e xperience profile did not significantly change.

Seasonal Allergic Rhinitis
Montelukast has been evaluated for safety in 2199 adult and adolescent patients withseas onal allergic rhinitis 15 years of age and older in clinical trials. Montelukast administere d once daily in the morning or in the evening had a safety profile similar to that of placebo. In placebo-controlled clinical trials, the following event was reported with montelukast with a frequency ≥ 1% and at an incidence greater than placebo: upper respiratory infection, 1.9% of patients receiving montelukast vs. 1.5% of patients receiving placebo. In a 4-week, placebo-controlled clinical study, the safety profile was consistent with that observed in 2-week studies. The incidence of somnolence was similar to that of placebo in all studies.

Perennial Allergic Rhinitis
Montelukast has been evaluated for safety in 3357 adult and adolescent patients 15 years of age and older with perennial allergic rhinitis of whom 1632 received montelukast in two, 6-week, clinical studies. Montelukast administered once daily had a safety profile consistent with that observed in patients with seasonal allergic rhinitis and similar to that of placebo. In these two studies, the following events were reported with montelukast with a frequency ≥ 1% and at an incidence greater than placebo: sinusitis, upper respiratory infection, sinus headache, cough, epistaxis, and increased ALT. The incidence of somnolence was similar to that of placebo.

Pediatric Patients 6 to 14 Years of Age

Asthma
Montelukast has been evaluated for safety in 476 pediatric patients with asthma 6 to 14 years of age. Cumulatively, 289 pediatric patients were treated with montelukast for at least 6 months, and 241 for one year or longer in clinical trials. The safety profile of montelukast in the 8-week, double-blind, pediatric efficacy trial was generally similar to the adult safety profile. In pediatric patients 6 to 14 years of age receiving montelukast, the following events occurred with a frequency ≥ 2% and more frequently than in pediatric patients who received placebo: pharyngitis, influenza, fever, sinusitis, nausea, diarrhea, dyspepsia, otitis, viral infection, and laryngitis. The other adverse effect reported frequently in clinical trials with montelukast in this age group was headache.

The frequency of less common adverse events was comparable between montelukast and placebo. With prolonged treatment, the adverse experience profile did not significantly change.
The safety profile of montelukast tablets when administered as a single dose for prevention of EIB in pediatric patients 6 years of age and older, was consistent with the safety profile previously described for montelukast tablets

In studies evaluating growth rate, the safety profile in these pediatric patients was consistent with the safety profile previously described for montelukast. In a 56-week, double-blind study evaluating growth rate in pediatric patients 6 to 8 years of age receiving montelukast, the following events not previously observed with the use of montelukast in this age group occurred with a frequency ≥ 2% and more frequently than in pediatric patients who received placebo: headache, rhinitis (infective), varicella, gastroenteritis, atopic dermatitis, acute bronchitis, tooth infection, skin infection, and myopia.

Pediatric Patients 2 to 5 Years of Age

Asthma

Montelukast has been evaluated for safety in 573 pediatric patients 2 to 5 years of age in single- and multiple-dose studies. Cumulatively, 426 pediatric patients 2 to 5 years of age were treated with montelukast for at least 3 months, 230 for 6 months or longer, and 63 patients for one year or longer in clinical trials. In pediatric patients 2 to 5 years of age receiving montelukast, the following events occurred with a frequency ≥ 2% and more frequently than in pediatric patients who received placebo: fever, cough, abdominal pain, diarrhea, headache, rhinorrhea, sinusitis, otitis, influenza, rash, ear pain, gastroenteritis, eczema, urticaria, varicella, pneumonia, dermatitis, and conjunctivitis. Another adverse effect commonly reported in the clinical trials with montelukast in this age-group was thirst.

Pediatric Patients 2 to 14 Years of Age

Seasonal Allergic Rhinitis

Montelukast has been evaluated in 280 pediatric patients with seasonal allergic rhinitis 2 to 14 years of age in a 2-week, multicenter, double-blind, placebo-controlled, parallel-group safety study. Montelukast administered once daily in the evening had a safety profile similar to that of placebo. In this study, the following events occurred with a frequency ≥2% and at an incidence greater than placebo: headache, otitis media, pharyngitis, and upper respiratory infection.

The safety in patients 2 to 14 years of age with perennial allergic rhinitis is supported by the safety in patients 2 to 14 years of age with seasonal allergic rhinitis.

Pediatric Patients 6 to 23 Months of Age with Asthma
The safety in patients 6 to 23 months of age is supported by data from pharmacokinetic and safety and efficacy studies in asthma in this pediatric population and from adult pharmacokinetic studies.

Montelukast has been evaluated for safety in 175 pediatric patients 6 to 23 months of age with asthma. The safety profile of montelukast in a 6-week, double-blind, placebo-controlled clinical study was generally similar to the safety profile in adults and pediatricpatients 2 to 14 years of age. In pediatric patients 6 to 23 months of age receiving montelukast, the following events occurred with a frequency ≥ 2% and more frequently than in pediatric patients who received placebo: upper respiratory infection, wheezing; otitis media; pharyngitis, tonsillitis, cough; and rhinitis. The frequency of less common adverse events was comparable between montelukast and placebo.

Safety and effectiveness in pediatric patients younger than 12 months of age with asthma have not been established.

Pediatric Patients 6 Months to 14 Years of Age

Perennial Allergic Rhinitis

The safety in patients 2 to 14 years of age with perennial allergic rhinitis is supported by the safety in patients 2 to 14 years of age with seasonal allergic rhinitis. The safety in patients 6 to 23 months of age is supported by data from pharmacokinetic and safety and efficacy studies in asthma in this pediatric population and from adult pharmacokinetic studies.

Postmarketing Experience

The following adverse reactions have been reported in post-marketing use:

Blood and lymphatic system disorders: Increased bleeding tendency, thrombocytopenia.
Immune system disorders: Hypersensitivity reactions including anaphylaxis, hepatic eosinophilic infiltration.

Psychiatric disorders: Agitation including aggressive behavior or hostility, anxiousness, depression, disorientation, psychomotor hyperactivity dream abnormalities including nightmares, hallucinations, insomnia, irritability, memory impairment, restlessness, somnambulism, suicidal thinking and behavior (including suicide), tic, and tremor, disturbance in attention. These events were reported in all age groups. However, nightmare/night terrors, aggression and behavioural changes are more frequently reported in the paediatric population.

Nervous system disorders: Drowsiness dizziness, paraesthesia/hypoesthesia, seizures.
Respiratory, thoracic and mediastinal disorders: Epistaxis, pulmonary eosinophilia

Cardiac disorders: Palpitations.

Gastro-intestinal disorders: Diarrhoea, dry mouth, dyspepsia, nausea, vomiting, pancreatitis.

Hepatobiliary disorders: Cases of cholestatic hepatitis, hepatocellular liver-injury, and mixed-pattern liver injury have been reported in patients treated with montelukast. Most of these occurred in combination with other confounding factors, such as use of other

medications, or when montelukast was administered to patients who had underlying potential for liver disease, such as alcohol use or other forms of hepatitis.
Skin and subcutaneous tissue disorders: Angioedema, bruising, urticaria, pruritus, erythema nodosum, erythema multiforme, Stevens-Johnson syndrome/toxic epidermal necrolysis.

Musculoskeletal and connective tissue disorders: Arthralgia, myalgia including muscle cramps

General disorders and administration site conditions: Pyrexia, asthenia/fatigue, malaise, oedema.

Patients with asthma 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.

Levocetirizine

Use of levocetirizine has been associated with somnolence, fatigue, asthenia, and urinary retention.

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trial of another drug and may not reflect the rates observed in practice.

Adults and Adolescents 12 years of Age and Older

In studies up to 6 weeks in duration, the mean age of the adult and adolescent patients was 32 years, 44% of the patients were men and 56% were women, and the large majority (more than 90%) was Caucasian.

In these trials 43% and 42% of the subjects in the levocetirizine 2.5 mg and 5 mg groups, respectively, had at least one adverse event compared to 43% in the placebo group.

In placebo-controlled trials of 1-6 weeks in duration, the most common adverse reactions were somnolence, nasopharyngitis, fatigue, dry mouth, and pharyngitis, and most were mild to moderate in intensity. Somnolence with levocetirizine showed dose ordering between tested doses of 2.5, 5 and 10 mg and was the most common adverse reaction leading to discontinuation (0.5%).

Table 1 lists adverse reactions that were reported in greater than or equal to 2% of subjects aged 12 years and older exposed to levocetirizine 2.5 mg or 5 mg in eight placebo-controlled clinical trials and that were more common with levocetirizine than placebo.

Table 1: Adverse Reactions Reported in ≥2%* of Subjects Aged 12 Years and Older Exposed to levocetirizine 2.5 mg or 5 mg Once Daily in Placebo-Controlled Clinical Trials 1-6 Weeks in Duration

Adverse Reactions	Levocetirizine 2.5 mg (n = 421)	Levocetirizine 5 mg (n = 1070)	Placebo (n = 912)
Somnolence	22 (5%)	61 (6%)	16 (2%)
Nasopharyngitis	24 (6%)	40 (4%)	28 (3%)
Fatigue	5 (1%)	46 (4%)	20 (2%)
Dry mouth	12 (3%)	26 (2%)	11 (1%)
Pharyngitis	10 (2%)	12 (1%)	9 (1%)

* Rounded to the closest unit percentage

Additional adverse reactions of medical significance observed at a higher incidence than in placebo in adults and adolescents aged 12 years and older exposed to levocetirizine were syncope (0.2%) and weight increased (0.5%).

Pediatric Patients 6 to 12 Years of Age

A total of 243 pediatric patients 6 to 12 years of age received levocetirizine 5 mg once daily in two short-term placebo controlled double-blind trials. The mean age of the patients was 9.8 years, 79 (32%) were 6 to 8 years of age, and 50% were Caucasian. Table 2 lists adverse reactions that were reported in greater than or equal to 2% of subjects aged 6 to 12 years exposed to levocetirizine 5 mg in placebo-controlled clinical trials and that were more common with levocetirizine than placebo.

Table 2: Adverse Reactions Reported in ≥2%* of Subjects Aged 6-12 Years Exposed to levocetirizine 5 mg Once Daily in Placebo-Controlled Clinical Trials 4 and 6 Weeks in Duration

Adverse Reactions	Levocetirizine 5 mg (n = 243)	Placebo (n = 240)
Pyrexia	10 (4%)	5 (2%)
Cough	8 (3%)	2 (<1%)
Somnolence	7 (3%)	1 (<1%)
Epistaxis	6 (2%)	1 (<1%)

* Rounded to the closest unit percentage

Pediatric Patients 1 to 5 Years of Age

A total of 114 pediatric patients 1 to 5 years of age received levocetirizine 1.25 mg twice daily in a two-week placebo-controlled double-blind safety trial. The mean age of the patients was 3.8 years, 32% were 1 to 2 years of age, 71% were Caucasian and 18% were Black. Table 3 lists adverse reactions that were reported in greater than or equal to 2% of subjects aged 1 to 5 years exposed to levocetirizine 1.25 mg twice daily in the

placebo-controlled safety trial and that were more common with levocetirizine than placebo.

Table 3: Adverse Reactions Reported in ≥2%* of Subjects Aged 1-5 Years Exposed to levocetirizine 1.25 mg Twice Daily in a 2-Week Placebo-Controlled Clinical Trial

Adverse Reactions	Levocetirizine1.25 mg twice daily (n=114)	Placebo (n=59)
Pyrexia	5 (4%)	1 (2%)
Diarrhea	4 (4%)	2 (3%)
Vomiting	4 (4%)	2 (3%)
Otitis Media	3 (3%)	0 (0%)

* Rounded to the closest unit percentage

Pediatric Patients 6 to 11 Months of Age

Adverse reactions that were reported in more than 1 subject (i.e. greater than or equal to 3% of subjects) aged 6 to 11 months exposed to levocetirizine 1.25 mg once daily in the placebo-controlled safety trial and that were more common with levocetirizine than placebo included diarrhea and constipation which were reported in 6 (13%) and 1 (4%) and 3 (7%) and 1 (4%) children in the levocetirizine and placebo-treated groups, respectively.

Long-Term Clinical Trials Experience

In two controlled clinical trials, 428 patients (190 males and 238 females) aged 12 years and older were treated with levocetirizine 5 mg once daily for 4 or 6 months. The patient characteristics and the safety profile were similar to that seen in the short-term studies. Ten (2.3%) patients treated with levocetirizine discontinued because of somnolence, fatigue or asthenia compared to 2 (<1%) in the placebo group.
There are no long-term clinical trials in children below 12 years of age with allergic rhinitis or chronic idiopathic urticaria.

Laboratory Test Abnormalities
Elevations of blood bilirubin and transaminases were reported in <1% of patients in the clinical trials. The elevations were transient and did not lead to discontinuation in any patient.

Postmarketing Experience
In addition to the adverse reactions reported during clinical studies and listed above, the following adverse drug reactions have been identified during postapproval use of levocetirizine. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

Cardiac disorders: Palpitations, tachycardia

Ear and labyrinth disorders: vertigo

Eyes disorders: Visual disturbances, blurred vision

Gastrointestinal disorders: Nausea, vomiting

General disorders and administration site conditions: edema

Hepatobiliary disorders: Hepatitis

Immune system disorders: Hypersensitivity and anaphylaxis

Metabolism and nutrition disorders: increased appetite

Musculoskeletal, connective tissues, and bone disorders: Arthralgia, myalgia

Nervous system disorders: Dizziness, dysgeusia, febrile seizure, movement disorders (including dystonia and oculogyric crisis), paraesthesia, seizure (reported in subjects with and without a known seizure disorder), tremor Psychiatric disorders: Aggression, agitation, hallucinations, depression, insomnia, nightmare, suicidal ideation

Renal and urinary disorders: dysuria urinary retention

Respiratory, thoracic, and mediastinal disorders: Dyspnoea
Skin and subcutaneous tissue disorders: Angioedema, fixed drug eruption, pruritus, rash, urticarial

Besides these events reported under treatment with levocetirizine, other potentially severe adverse events have been reported from the post-marketing experience with cetirizine. Since levocetirizine is the principal pharmacologically active component of cetirizine, one should take into account the fact that the following adverse events could also potentially occur under treatment with levocetirizine:

Cardiac disorders: severe hypotension

Gastrointestinal disorders: cholestasis

Nervous system disorders: extrapyramidal symptoms, myoclonus, orofacial dyskinesia, tic

Pregnancy, puerperium and perinatal conditions: stillbirth

Renal and urinary disorders: glomerulonephritis

Skin and subcutaneous tissue disorders: acute generalized exanthematouspustulosis (AGEP); rebound pruritus - pruritus within a few days after discontinuation of cetirizine, usually after long-term use (e.g. months to years) of cetirizine.

If you experience any side-effects, talk to your doctor or pharmacist.

3.9 Overdose

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. In chronic asthma studies, montelukast has been administered at doses up to 200 mg/day to adult patients for 22 weeks and, in short-term studies, up to 900 mg/day to patients for approximately a week without clinically important adverse experiences.

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.

The acute maximal non-lethal oral dose of levocetirizine was 240 mg/kg in mice (approximately 190 times the maximum recommended daily oral dose in adults, approximately 230 times the maximum recommended daily oral dose in children 6 to 11 years of age, and approximately 180 times the maximum recommended daily oral dose in children 6 months to 5 years of age on a mg/m^2 basis). In rats the maximal non-lethal oral dose was 240 mg/kg (approximately 390 times the maximum recommended daily oral dose in adults, approximately 460 times the maximum recommended daily oral dose in children 6 to 11 years of age, and approximately 370 times the maximum recommended daily oral dose in children 6 months to 5 years of age on a mg/m^2 basis).

4. PHARMACOLOGICALPROPERTIES

4.1 Pharmacodynamics properties

As MONTIZINETABLETS is a combination of montelukast and levocetirizine, the pharmacological properties of both the molecules are given separately:

Montelukast

The cysteinylleukotrienes (LTC_4, LTD_4, LTE_4) are products of arachidonic acid metabolism and are released from various cells including mast cells and eosinophils. These eicosanoids bind to cysteinyl leukotriene (CysLT) receptors. The CysLT type-1 ($CysLT_1$) receptor is found in the human airway (including airway smooth muscle cells and airway macrophages) and on other pro-inflammatory cells (including eosinophils and certain myeloid stem cells). CysLTs have been correlated with the pathophysiology of asthma and allergic rhinitis.

In asthma, leukotriene-mediated effects include airway edema, smooth muscle contraction, and altered cellular activity associated with the inflammatory process. In allergic rhinitis, CysLTs are released from the nasal mucosa after allergen exposure during both early- and late-phase reactions and are associated with symptoms of allergic rhinitis.

Montelukast is an orally active compound that binds with high affinity and selectivity to the $CysLT_1$ receptor. Montelukast inhibits physiologic actions of LTD_4 at the $CysLT_1$ receptor without any agonist activity.

In patients with seasonal allergic rhinitis aged 15 years and older who received montelukast, a mean increase of 0.2% in peripheral blood eosinophil counts was noted, compared with a mean increase of 12.5% in placebo-treated patients, over the double-blind treatment periods; this reflects a mean difference of 12.3% in favor of montelukast. The relationship between these observations and the clinical benefits of montelukast noted in the clinical trials is not known.

Levocetirizine

Levocetirizine, the active enantiomer of cetirizine, is an antihistamine its principal effects are mediated via selective inhibition ofH_1-receptors. Binding studies revealed that levocetirizine has affinity for human H_1 -receptors 2-fold higher than that of cetirizine (Ki = 3 nmol/L vs. 6 nmol/L). Levocetirizine dissociates from H_1 -receptors with a half-life of 115 ± 38 min. After single administration, levocetirizine shows receptor occupancy of 90% at 4 hours and 57% at 24 hours.

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) show that levocetirizine inhibits eotaxin-induced eosinophil transendothelial 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.

The efficacy and safety of levocetirizine has 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.

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. Pharmacokinetic/pharmacodynamic relationship 5 mg levocetirizine provide a similar pattern of inhibition of histamine-induced wheal and flare than 10 mg cetirizine. As for cetirizine, the action on histamine-induced skin reactions was out of phase with the plasma concentrations. ECGs did not show relevant effects of levocetirizine on QT interval.

Studies in adult healthy subjects showed that levocetirizine at doses of 2.5 mg and 5 mg inhibited the skin wheal and flare caused by the intradermal injection of histamine. In contrast, dextrocetirizine exhibited no clear change in the inhibition of the wheal and flare reaction. Levocetirizine at a dose of 5 mg inhibited the wheal and flare caused by intradermal injection of histamine in 14 pediatric subjects (aged 6 to 11 years) and the activity persisted for at least 24hours. The clinical relevance of histamine wheal skin testing is unknown.

A QT/QTc study using a single dose of 30 mg of levocetirizine did not demonstrate an effect on the QTc interval. While a single dose of levocetirizine had no effect, the effects of levocetirizine may not be at steady state following single dose. The effect of levocetirizine on the QTc interval following multiple dose administration is unknown. Levocetirizine is not expected to have QT/QTc effects because of the results of QTc studies with cetirizine and the long postmarketing history of cetirizine without reports of QT prolongation.

4.2 Pharmacokinetic properties

Montelukast

Absorption

Montelukast is rapidly absorbed following oral administration. After administration of the 10 mg film-coated tablet to fasted adults, the mean peak montelukast plasma concentration

(C_{max}) is achieved in 3 to 4 hours (T_{max}). The mean oral bioavailability is 64%. The oral bioavailability and C_{max} are not influenced by a standard meal in the morning.

For the 4 mg chewable tablet, the mean C_{max} is achieved 2 hours after administration in pediatric patients 2 to 5 years of age in the fasted state.

The safety and efficacy of montelukast in patients with asthma were demonstrated in clinical trials in which the 10 mg film-coated tablets were administered in the evening without regard to the time of food ingestion. The safety of montelukast in patients with asthma was also demonstrated in clinical trials in which the 4 mg chewable tablets were administered in the evening without regard to the time of food ingestion.

The safety of montelukast in patients with asthma was also demonstrated in clinical trials in which the 4 mg chewable tablet and 4 mg oral granule formulations were administered in the evening without regard to the time of food ingestion. The safety and efficacy of montelukast in patients with seasonal allergic rhinitis were demonstrated in clinical trials in which the 10 mg film-coated tablet was administered in the morning or evening without regard to the time of food ingestion.

Distribution

Montelukast is more than 99% bound to plasma proteins. The steady-state volume of distribution of montelukast averages 8 to 11 liters. Studies in rats with radiolabeled montelukast indicate minimal distribution across the blood-brain barrier. In addition, concentrations of radiolabeled material at 24 hours postdose 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 pediatric patients.

In vitro studies using human liver microsomes indicate that cytochromes P450 3A4, 2C8, and 2C9 are involved in the metabolism of montelukast. At clinically relevant concentrations, 2C8 appears to play a major role in the metabolism of montelukast. Clinical studies investigating the effect of known inhibitors of cytochromes P450 3A4 (e.g., ketoconazole, erythromycin) or 2C9 (e.g., fluconazole) on montelukast pharmacokinetics have not been conducted. 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. However, in vitro studies have shown that montelukast is a potent inhibitor of cytochrome P450 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, and therefore is not anticipated to alter the metabolism of drugs metabolized by this enzyme.

Elimination

The plasma clearance of montelukast averages 45 mL/min in healthy adults. Following an oral dose of radiolabeled 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.

In several studies, the mean plasma half-life of montelukast ranged from 2.7 to 5.5 hours in healthy young adults. The pharmacokinetics of montelukast is nearly linear for oral doses up to 50 mg. During once-daily dosing with 10 mg montelukast, there is little accumulation of the parent drug in plasma (14%).

Special Population

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 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. The pharmacokinetics of montelukast in patients with more severe hepatic impairment or with hepatitis have not been evaluated.

Renal Impairment

Since montelukast and its metabolites are not excreted in the urine, the pharmacokinetics of montelukast were not evaluated in patients with renal insufficiency. No dosage adjustment is recommended in these patients.

Gender

The pharmacokinetics of montelukast are similar in males and females.

Race

Pharmacokinetic differences due to race have not been studied.

Adolescents and Pediatric Patients

Pharmacokinetic studies evaluated the systemic exposure of the 4-mg oral granule formulation in pediatric patients 6 to 23 months of age, the 4-mg chewable tablets in pediatric patients 2 to 5 years of age, the 5-mg chewable tablets in pediatric patients 6 to 14 years of age, and the 10-mg film-coated tablets in young adults and adolescents ≥15 years of age.

The plasma concentration profile of montelukast following administration of the 10-mg tablet is similar in adolescents ≥15 years of age and young adults. The 10-mg tablet is recommended for use in patients ≥15 years of age.

The mean systemic exposure of the 4-mg chewable tablet in pediatric patients 2 to 5 years of age and the 5-mg chewable tablets in pediatric patients 6 to 14 years of age is similar to the mean systemic exposure of the 10-mg film-coated tablet in adults. The 5-mg chewable tablet should be used in pediatric patients 6 to 14 years of age and the 4-mg chewable tablet should be used in pediatric patients 2 to 5 years of age.

In children 6 to 11 months of age, the systemic exposure to montelukast and the variability of plasma montelukast concentrations were higher than those observed in adults. Based on population analyses, the mean AUC (4296 ng•hr/mL) was 60% higher and the mean C_{max} (667 ng/mL) was 89% higher than those observed in adults (mean AUC 2689 ng•hr/mL) and mean C_{max} (353 ng/mL). The systemic exposure in children 12 to 23 months of age was less variable, but was still higher than that observed in adults. The mean AUC (3574 ng•hr/mL) was 33% higher and the mean C_{max} (562 ng/mL) was 60% higher than those observed in adults. Safety and tolerability of montelukast in a single-dose pharmacokinetic study in 26 children 6 to 23 months of age were similar to that of patients two years and above. The 4-mg oral granule formulation should be used for pediatric patients 12 to 23 months of age for the treatment of asthma, or for pediatric patients 6 to 23 months of age for the treatment of perennial allergic rhinitis. Since the 4-mg oral granule formulation is bioequivalent to the 4-mg chewable tablet, it can also be used as an alternative formulation to the 4-mg chewable tablet in pediatric patients 2 to 5 years of age.

Levocetirizine

The pharmacokinetics of levocetirizine is 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. Peak plasma concentrations are achieved 0.9 g hour after dosing. Steady state is achieved after two days. Peak concentrations are typically 270ng/ml and 308ng/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 T_{max} was delayed by about 1.25 hours and Cmax was decreased by about 36% after administration with a high fat meal; therefore, levocetirizine can be administered with or without food. A dose of 5 mg (10 ml) of levocetirizinedihydrochloride oral solution is bioequivalent to a 5mg dose of levocetirizine tablets. Following oral administration of a 5mg dose of levocetirizine oral solution to healthy adult subjects, the mean peak plasma concentrations were achieved approximately 0.5 hours post-dose.

Distribution

The mean plasma protein binding of levocetirizine in vitro ranged from 91 to 92%, independent of concentration in the range of 90-5000 ng/mL, which includes the therapeutic plasma levels observed. Following oral dosing, the average apparent volume of distribution is approximately 0.4 L/kg, representative of distribution in total body water.

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 healthy adult subjects was about 8 to 9 hours after administration of oral tablets. The mean apparent total body clearance is 0.63 ml/ kg/ min. 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. Renal clearance of levocetirizine correlates with that of creatinine clearance. In patients with renal impairment the clearance of levocetirizine is reduced

Special Population

Pediatric Patients

Data from a pediatric 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 Cmax and AUC values are about 2-fold greater than that reported in healthy adult subjects in a cross-study comparison. The mean Cmax 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 pediatric population than in adults.

Geriatric Patients

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.

Renal Impairment
Levocetirizine exposure (AUC) exhibited 1.8-, 3.2-, 4.3-, and 5.7-fold increase in mild, moderate, severe, renal impaired, and end-stage renal disease patients, respectively, compared to healthy subjects. The corresponding increases of half-life estimates were 1.4-, 2.0-, 2.9-, and 4-fold, respectively.

The total body clearance of levocetirizine after oral dosing was correlated to the creatinine clearance and was progressively reduced based on severity of renal impairment. It is, therefore, recommended to adjust the dosing intervals of levocetirizine, based on the creatinine clearance in patients with moderate and severe renal impairment. In end-stage renal disease subjects, the total body clearance is decreased by approximately 80% when compared to normal subjects. The amount of levocetirizine removed during a standard 4-hour haemodialysis procedure was <10%.

The dosage of levocetirizine should be reduced in patients with mild renal impairment. Both the dosage and frequency of administration should be reduced in patients with moderate or severe renal impairment.

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 with solely hepatic impairment.

4.3 Preclinical safety data

Not applicable

5 PHARMACEUTICALPARTICULARS

5.1 List ofexcipients

Core Tablet

Lactose, Starch, MCCP, yellow oxide of iron, Povidone PVP-K 30, talc and Magnesium

Stearate.

5.2 Incompatibilities

Not applicable

5.3 Shelflife

36 Months from the date of Manufacture.

5.4 Special precautions for storage

Store protected from light and moisture at a temperature not exceeding 30° C. Keep out of reach of children.

5.5 Nature and contents of container <and special equipment for use, administration or implantation>

Not applicable

5.6 Special precautions for disposal <and otherhandling>

No special requirements.

APPLICANT/MANUFACTURER

APPLICANT	**MANUFACTURER**
M/s. Sterling Lab	M/s. Sterling Lab
104-105, Midford House,	57, Sipcot Industrial Complex,
Midford Gardens, M.G.Road,	Hosur-635 126 (T.N),
Bangalore-560001,	Tamilnadu, India
Karnataka, India	
Telephone : +91-080-25585748/25587163	Telephone: +91-04344-276071
Telefax : +91-080-25583712	Telefax : +91-04344-278303
E-Mail : qa@sterlinglab.com	**E-Mail : works@sterlinglab.com**