

**UTTARANCHAL BIOTECH LTD.****Jai Nagar No 3, Dineshpur Road Rudrapur (U.S Nagar) Uttarakhand****1.3 PRODUCT INFORMATION****1.3.1 Summary of Product Characteristics (Prescribing Information)**

1. Name of the medical product

Drug Product : ONTIME

Generic Name : Montelukast Sodium and Levocetirizine Dihydrochloride Tablets

Strength : 10 mg & 5 mg

2. Qualitative and Quantitative Formula Composition

Each film-coated tablet contains:

Montelukast Sodium BP

Equivalent to Montelukast 10 mg

Levocetirizine Dihydrochloride USP 5 mg

Excipients: q.s.

Colour : Titanium Dioxide B.P.

STANDARD BATCH SIZE: 1.00 Lac

Sr. No .	Material code	Materials	Spec.	Claim /Tab.	U O M	Standard Quantity (Kg)	Ovg %	Required Quantity (Kg)	Category
I	DRY MIXING								
1	RAW0000464	Montelukast Sodium eq. to Montelukast	BP	10 mg	Kg	1.040	3	1.070	Active
2	RAW0000707	Levocetirizine Dihydrochloride	USP	5 mg	Kg	0.500	3	0.515	Active
3	EXP0000337	Microcrystalline cellulose - PH 101	BP		Kg	4.400		4.400	Diluent
4	EXP0000245	Maize Starch	BP		Kg	3.250		3.250	Diluent
II	BINDER								
1	EXP0000251	Methyl Paraben	BP		Kg	0.025		0.025	Preservative
2	EXP0000265	Propyl Paraben	BP		Kg	0.010		0.010	Preservative
3	EXP0000245	Maize Starch (Paste)	BP		Kg	0.300		0.300	Binder

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4	EXP00002 77	PVPK- 30	BP		Kg	0.100		0.100	Binder
5	-NA-	Purified Water	BP		Litr	6.600		6.600	Solvent for binder
III	LUBRICANT								
1	EXP00000 22	Purified Talc	BP		Kg	0.500		0.500	Glidant
2	EXP00002 59	Crospovidone	BP		Kg	0.550		0.550	Disintegrant
3	EXP00002 27	Sodium Starch Glycolate	BP		Kg	0.400		0.400	Disintegrant
4	EXP00002 45	Starch	BP		Kg	0.480		0.480	Disintegrant
5	EXP00002 74	Colloidal silicon dioxide	BP		Kg	0.100		0.100	Disintegrant
6	EXP00000 05	Magnesium Stearate	BP		Kg	0.300		0.300	Lubricant
7	EXP00002 45	Maize Starch	BP		Kg	0.400		0.400	Disintegrant
IV	COATING MATERIAL								
1	EXP00003 21	Isopropyl Alcohol	BP		Ltr.	3.000		3.000	Solvent
2	RAW0000 531	Methylene Di Chloride	BP		Kg	7.860		7.860	Solvent
3	EXP00002 20	HPMC-15	USP		Kg	0.240		0.240	Coating material
4	EXP00000 22	Purified Talc	BP		Kg	0.015		0.015	Glidant
5	EXP00002 23	Propylene glycol	USP		Kg	0.060		0.060	Solvent
6	EXP00000 27	Titanium dioxide	BP		Kg	0.100		0.100	Colouring agent

3. Pharmaceutical form Film-coated tablet**4. Clinical particulars****4.1 Therapeutic indications**

It contains combination of montelukast sodium which is a leukotriene receptor antagonist and levocetirizine dihydrochloride which is an antihistamine. It is used for relief of symptoms of allergic rhinitis (seasonal and perennial). Tablets are indicated for relief of



symptoms of allergic rhinitis [seasonal or perennial], as prophylaxis in seasonal allergic rhinitis and treatment of comorbid asthma and allergic rhinitis in patients 15 years of age and over.

4.2 Posology and method of administration

Adults and adolescents (>15 years): 1 tablet once daily

Method of Administration

For Oral use

General Recommendations

No dosage adjustment is necessary for the elderly, or for patients with renal insufficiency, or mild to moderate hepatic impairment. There are no data on patients with severe hepatic impairment. The dosage is the same for both male and female patients.

4.3 Contraindications

It is contraindicated in patients with known hypersensitivity to montelukast sodium, levocetirizine or cetirizine or to any other component of this product. Its also contraindicated in patients with severe renal impairment at less than 10ml/min creatinine clearance. Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medication.

4.4 Special warnings and precautions for use

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, obsessive-compulsive symptoms, 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 coordination 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 Levocetirizine if urinary retention occurs.

4.5 Interaction with other medicinal products and other forms of interaction**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 medicinal drugs: theophylline, prednisone, prednisolone, oral contraceptives (norethindrone 1 mg/ethinyl estradiol 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, 2C8 and 2C9, caution should be exercised, particularly in



children, when montelukast is co-administered with inducers of CYP 3A4, 2C8 and 2C9 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 C_{max} 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.

4.6 Fertility, pregnancy and lactation

Patients with 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.

Patients with 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.

Pregnant Women

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

Animal studies do not indicate harmful effects with respect to effects on pregnancy or embryonal/foetal development.

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.

Montelukast may be used during pregnancy only if it is considered to be clearly essential.

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.

Risk Summary

Available data from published literature and postmarketing experience with levocetirizine use in pregnant women are insufficient to identify any drug-associated risks of miscarriage, birth defects, or adverse maternal or fetal outcomes. In animal reproduction studies, there was no evidence of fetal harm with administration of levocetirizine by the oral route to pregnant rats and rabbits, during the period of organogenesis, at doses up to 390 times and 470 times, respectively, the maximum recommended human dose (MRHD) in adults. In rats treated during late gestation and the lactation period, cetirizine had no effects on pup development at oral doses up to approximately 60 times the MRHD in adults. In mice treated during late gestation and the lactation period, cetirizine administered by the oral route to the dams had no effects on pup development at a dose that was approximately 25 times the MRHD in adults; however, lower pup weight gain during lactation was observed at a dose that was 95 times the MRHD in adults .

The estimated background risk of major birth defects and miscarriage for the indicated population is unknown. All pregnancies have a background risk of birth defect, loss, or other adverse outcomes. In the U.S. general population, the estimated background risks of major birth defects and miscarriage in clinically recognized pregnancies is 2% to 4% and 15% to 20%, respectively.

Data

Animal data

In embryo-fetal development studies, pregnant rats received daily doses of levocetirizine up to 200 mg/kg/day from gestation days 6 to 15 and pregnant rabbits received daily doses of levocetirizine up to 120 mg/kg/day from gestation days 6 to 18. Levocetirizine produced no evidence of fetal harm in rats and rabbits at doses up to 390 and 470 times the MRHD, respectively (on a mg/m² basis with maternal oral doses of 200 and 120 mg/kg/day in rats and rabbits, respectively).



No prenatal and postnatal development (PPND) studies in animals have been conducted with levocetirizine. In a PPND study conducted in mice, cetirizine was administered at oral doses up to 96 mg/kg/day from gestation day 15 through lactation day 21. Cetirizine lowered pup body weight gain during lactation at an oral dose in dams that was approximately 95 times the MRHD (on a mg/m² basis with a maternal oral dose of 96 mg/kg/day); however, there were no effects on pup weight gain at an oral dose in dams that was approximately 25 times the MRHD (on a mg/m² basis with a maternal oral dose of 24 mg/kg/day). In a PPND study conducted in rats, cetirizine was administered at oral doses up to 180 mg/kg/day from gestation day 17 to lactation day 22. Cetirizine did not have any adverse effects on rat dams or offspring development at doses up to approximately 60 times the MRHD (on a mg/m² basis with a maternal oral dose of 30 mg/kg/day). Cetirizine caused excessive maternal toxicity at an oral dose in dams that was approximately 350 times the MRHD (on a mg/m² basis with a maternal oral dose of 180 mg/kg/day).

Lactating Women

Montelukast

Studies in rats have shown that montelukast is excreted in milk. It is not known if montelukast is excreted in human milk. Montelukast may be used in breast-feeding mothers only if it is considered to be clearly essential.

Levocetirizine

No peri 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.

Risk Summary

There are no data on the presence of levocetirizine in human milk, the effects on the breastfed infant, or the effects on milk production. However, cetirizine has been reported to be present in human breast milk. In mice and beagle dogs, studies indicated that cetirizine was excreted in milk. When a drug is present in animal milk, it is likely the drug will be present in human milk. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for



Levocetirizine and any potential adverse effects on the breastfed child from Levocetirizine or from the underlying maternal condition.

Data

Animal data

Cetirizine was detected in the milk of mice. No adverse developmental effects on pups were seen when cetirizine was administered orally to dams during lactation at a dose that was approximately 25 times the MRHD in adults. Studies in beagle dogs indicated that approximately 3% of the dose of cetirizine was excreted in milk. The concentration of drug in animal milk does not necessarily predict the concentration of drug in human milk.

Pediatric Patients

Montelukast

Safety and efficacy of montelukast have been established in adequate and well-controlled studies in pediatric patients with asthma 6 to 14 years of age. Safety and efficacy profiles in this age group are similar to those seen in adults. The efficacy of montelukast for the treatment of seasonal allergic rhinitis in pediatric patients 2 to 14 years of age and for the treatment of perennial allergic rhinitis in pediatric patients 6 months to 14 years of age is supported by extrapolation from the demonstrated efficacy in patients 15 years of age and older with allergic rhinitis as well as the assumption that the disease course, pathophysiology and the drug's effect are substantially similar among these populations.

The safety of montelukast 4-mg and 5-mg chewable tablets in pediatric patients aged 2 to 14 years with allergic rhinitis is supported by data from studies conducted in pediatric patients aged 2 to 14 years with asthma. A safety study in pediatric patients 2 to 14 years of age with seasonal allergic rhinitis demonstrated a similar safety profile.

The safety of montelukast 4-mg oral granules in pediatric patients as young as 6 months of age with perennial allergic rhinitis is supported by extrapolation from safety data obtained from studies conducted in pediatric patients 6 months to 23 months of age with asthma and from pharmacokinetic data comparing systemic exposures in patients 6 months to 23 months of age to systemic exposures in adults.



The safety and efficacy of montelukast in children below the age of 12 months with asthma, 6 months with perennial allergic rhinitis, and 6 years with exercise-induced bronchoconstriction has not been established. The safety and effectiveness of levocetirizine in pediatric patients under 2 years of age have not been established.

Levocetirizine

The recommended dose of levocetirizine for the treatment of the uncomplicated skin manifestations of chronic idiopathic urticaria in patients 6 months to 17 years of age is based on extrapolation of efficacy from adults 18 years of age and older. The recommended dose of levocetirizine in patients 6 months to 2 years of age for the treatment of the symptoms of perennial allergic rhinitis and 6 months to 11 years of age with chronic idiopathic urticaria is based on cross-study comparisons of the systemic exposure of levocetirizine in adults and pediatric patients and on the safety profile of levocetirizine in both adult and pediatric patients at doses equal to or higher than the recommended dose for patients 6 months to 11 years of age.

The safety of levocetirizine 5 mg once daily was evaluated in 243 pediatric patients 6 to 12 years of age in two placebo-controlled clinical trials lasting 4 and 6 weeks. The safety of levocetirizine 1.25 mg twice daily was evaluated in one 2-week clinical trial in 114 pediatric patients 1 to 5 years of age and the safety of levocetirizine 1.25 mg once daily was evaluated in one 2-week clinical trial in 45 pediatric patients 6 to 11 months of age.

The effectiveness of levocetirizine 1.25 mg once daily (6 months to 5 years of age) for the treatment of the symptoms of perennial allergic rhinitis is supported by the extrapolation of demonstrated efficacy of levocetirizine 5 mg once daily in patients 12 years of age and older based on the pharmacokinetic comparison between adults and children.

Cross-study comparisons indicate that administration of a 5 mg dose of levocetirizine to 6 to 12 year old pediatric patients resulted in about 2-fold the systemic exposure (AUC) observed when 5 mg of levocetirizine was administered to healthy adults. Therefore, in children 6 to 11 years of age the recommended dose of 2.5 mg once daily should not be exceeded. In a population pharmacokinetics study the administration of 1.25 mg once



daily in children 6 months to 5 years of age resulted in systemic exposure comparable to 5 mg once daily in adults.

Geriatric Patients

Montelukast

No overall differences in safety or effectiveness were observed between these subjects and younger subjects, and other reported clinical experience has not identified differences in responses between the elderly and younger patients, but greater sensitivity of some older individuals cannot be ruled out. 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. No dosage adjustment in the elderly is required.

Levocetirizine

Clinical studies of levocetirizine for each approved indication did not include sufficient numbers of patients aged 65 years and older to determine whether they respond differently than younger patients. Other reported clinical experience has not identified differences in responses between the elderly and younger patients. In general, dose selection for an elderly patient should be cautious usually starting at the low end of the dosing range reflecting the greater frequency of decreased hepatic, renal or cardiac function and of concomitant disease or other drug therapy.

4.7 Effects on ability to drive and use machines

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.

**4.8 Undesirable effects**

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

Montelukast

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 trials of another drug and may not reflect the rates observed in clinical practice.

The most common adverse reactions (incidence $\geq 5\%$ and greater than placebo; listed in descending order of frequency) in controlled clinical trials were: upper respiratory infection, fever, headache, pharyngitis, cough, abdominal pain, diarrhea, otitis media, influenza, 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 placebo-controlled clinical trials, the following adverse experiences reported with montelukast 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 aspartate amino transaminase (AST) and pyuria



The frequency of less common adverse events was comparable between montelukast and 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 consistent 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 experience profile did not significantly change.

Seasonal Allergic Rhinitis

Montelukast has been evaluated for safety in 2199 adult and adolescent patients with seasonal allergic rhinitis 15 years of age and older in clinical trials. Montelukast administered 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 $\geq 1\%$ 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 $\geq 1\%$ 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 $\geq 2\%$ 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 $\geq 2\%$ 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 $\geq 2\%$ 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 6 to 23 Months of Age

Asthma

Safety and effectiveness in pediatric patients younger than 12 months of age with asthma have not been established. 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 pediatric patients 2 to 14 years of age. In pediatric patients 6 to 23 months of age receiving montelukast, the following events occurred with a frequency $\geq 2\%$ 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.

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 $\geq 2\%$ 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 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), , 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, Churg-Strauss Syndrome (CSS)

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.

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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

Renal and urinary disorders: Enuresis in children

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.

The following drug-related adverse reactions in clinical studies were reported commonly ($\geq 1/100$ to $< 1/10$) in asthmatic patients treated with montelukast and at a greater incidence than in patients treated with placebo:

Body System Class	Adult and Adolescent Patients 15 years and older (two 12-week studies; n=795)	Paediatric Patients 6 to 14 years old (one 8-week study; n=201) (two 56-week studies; n=615)
Nervous system disorders	Headache	headache
Gastrointestinal disorders	abdominal pain	
General disorders and administration site conditions		



With prolonged treatment in clinical trials with a limited number of patients for up to 2 years for adults, and up to 12 months for paediatric patients and adolescents 6 to 14 years of age, the safety profile did not change.

Levocetirizine

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

Clinical Trials Experience

The safety data described below reflect exposure to levocetirizine in 2708 patients with allergic rhinitis in 14 controlled clinical trials of 1 week to 6 months duration.

The short-term (exposure up to 6 weeks) safety data for adults and adolescents are based upon eight clinical trials in which 1896 patients (825 males and 1071 females aged 12 years and older) were treated with levocetirizine 2.5, 5, or 10 mg once daily in the evening.

The short-term safety data from pediatric patients are based upon two clinical trials in which 243 children with allergic rhinitis (162 males and 81 females 6 to 12 years of age) were treated with levocetirizine 5 mg once daily for 4 to 6 weeks, one clinical trial in which 114 children (65 males and 49 females 1 to 5 years of age) with allergic rhinitis were treated with levocetirizine 1.25 mg twice daily for 2 weeks, and one clinical trial in which 45 children (28 males and 17 females 6 to 11 months of age) with symptoms of allergic rhinitis were treated with levocetirizine 1.25 mg once daily for 2 weeks.

The long-term (exposure of 4 or 6 months) safety data in adults and adolescents are based upon two clinical trials in which 428 patients (190 males and 238 females) with allergic rhinitis were exposed to treatment with levocetirizine 5 mg once daily. Long term safety data are also available from an 18-month trial in 255 levocetirizine -treated subjects 12-24 months of age.

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.

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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 below 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.

Adverse reactions reported in $\geq 2\%$ * 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	25 (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%)

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* 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 below 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.

Adverse reactions reported in $\geq 2\%$ * 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 below lists adverse reactions that were reported in greater than or equal to 2%

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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.

Adverse reactions reported in $\geq 2\%$ * of subjects aged 1-5 years exposed to levocetirizine 1.25 mg twice daily in a 2-week placebo-controlled clinical trial

Adverse Reactions	Levocetirizine 1.25 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

A total of 45 pediatric patients 6 to 11 months of age received levocetirizine 1.25 mg once daily in a two week placebo-controlled double-blind safety trial. The mean age of the patients was 9 months, 51% were Caucasian and 31% were Black. 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.



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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, urticaria

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 exanthematous pustulosis (AGEP); rebound pruritus - pruritus within a few days after discontinuation of cetirizine, usually after long-term use (e.g. months to years) of cetirizine.

4.9 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.

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 one week without clinically important adverse experiences.

There have been reports of acute overdose in post-marketing experience and clinical studies with montelukast. These include reports in adults and children with a dose as high as 1000 mg (approximately 61 mg/Kg in a 42 month old child). The clinical and laboratory findings observed were consistent with the safety profile in adults and paediatric patients.

There were no adverse experiences in the majority of overdose reports.

Symptoms of Overdose

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.

Management of overdose

No specific information is available on the treatment of overdose with montelukast. It is not known whether montelukast is dialysable by peritoneal- or haemo-dialysis.

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. 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/m² 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/m² basis).

5. Pharmacological properties

5.1 Pharmacodynamic properties

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

Mechanism of Action

The cysteinyl leukotrienes (LTC₄, LTD₄, LTE₄) are potent inflammatory eicosanoids released from various cells including mast cells and eosinophils. These important pro-asthmatic mediators bind to cysteinyl leukotriene receptors (CysLT) found in the human airway and cause airway actions, including bronchoconstriction, mucous secretion, vascular permeability, and eosinophil recruitment.

The CysLT type-1 (CysLT₁) 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 allergic rhinitis. 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. Intranasal challenge with CysLTs has been shown to increase nasal airway resistance and symptoms of nasal obstruction.

Montelukast sodium is an orally active compound that binds with high affinity and selectivity to the CysLT type-1 (CysLT₁) receptor. Montelukast inhibits physiologic actions of LTD₄ at the CysLT₁ receptor without any agonist activity. It therefore acts as a leukotriene receptor antagonist.

Levocetirizine, the active enantiomer of cetirizine, is an antihistamine; its principal effects are mediated via selective inhibition of H₁ receptors. The antihistaminic activity of levocetirizine has been documented in a variety of animal and human models. In vitro binding studies revealed that levocetirizine has an affinity for the human H₁-receptor 2-



fold higher than that of cetirizine ($K_i = 3 \text{ nmol/L}$ vs. 6 nmol/L , respectively). The clinical relevance of this finding is unknown.

Pharmacodynamic Properties

Montelukast

The cysteinyl leukotrienes (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 (CysLT₁) 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 which binds with high affinity and selectivity to the CysLT₁ receptor. Montelukast inhibits physiologic actions of LTD_4 at the CysLT₁ 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.

In clinical studies, montelukast inhibits bronchoconstriction due to inhaled LTD_4 at doses as low as 5 mg. Bronchodilation was observed within two hours of oral administration. The bronchodilation effect caused by a β -agonist was additive to that caused by montelukast. Treatment with montelukast inhibited both early- and late-phase bronchoconstriction due to antigen challenge. Montelukast, compared with placebo, decreased peripheral blood



eosinophils in adult and paediatric patients. In a separate study, treatment with montelukast significantly decreased eosinophils in the airways (as measured in sputum) and in peripheral blood while improving clinical asthma control.

Clinical Efficacy and Safety

In studies in adults, montelukast 10 mg once daily, compared with placebo, demonstrated significant improvements in morning FEV₁ (10.4% vs 2.7% change from baseline), AM peak expiratory flow rate (PEFR) (24.5 L/min vs 3.3 L/min change from baseline), and significant decrease in total β -agonist use (-26.1% vs -4.6% change from baseline). Improvement in patient-reported daytime and night-time asthma symptoms scores was significantly better than placebo.

Studies in adults demonstrated the ability of montelukast to add to the clinical effect of inhaled corticosteroid (% change from baseline for inhaled beclomethasone plus montelukast vs beclomethasone, respectively for FEV₁ : 5.43% vs 1.04%; β -agonist use: -8.70% vs 2.64%). Compared with inhaled beclomethasone (200 μ g twice daily with a spacer device), montelukast demonstrated a more rapid initial response, although over the 12-week study, beclomethasone provided a greater average treatment effect (% change from baseline for montelukast vs beclomethasone, respectively for FEV₁ : 7.49% vs 13.3%; β -agonist use: -28.28% vs -43.89%). However, compared with beclomethasone, a high percentage of patients treated with montelukast achieved similar clinical responses (e.g. 50% of patients treated with beclomethasone achieved an improvement in FEV₁ of approximately 11% or more over baseline while approximately 42% of patients treated with montelukast achieved the same response).

A clinical study was conducted to evaluate montelukast for the symptomatic treatment of seasonal allergic rhinitis in adult and adolescent asthmatic patients 15 years of age and older with concomitant seasonal allergic rhinitis. In this study, montelukast 10 mg tablets administered once daily demonstrated a statistically significant improvement in the Daily Rhinitis Symptoms score, compared with placebo. The Daily Rhinitis Symptoms score is the average of the Daytime Nasal Symptoms score (mean of nasal congestion, rhinorrhea, sneezing, nasal itching) and the Nighttime Symptoms score (mean of nasal congestion upon awakening, difficulty going to sleep, and nighttime awakenings scores). Global evaluations



of allergic rhinitis by patients and physicians were significantly improved, compared with placebo. The evaluation of asthma efficacy was not a primary objective in this study.

Significant reduction of exercise-induced bronchoconstriction (EIB) was demonstrated in a 12-week study in adults (maximal fall in FEV1 22.33% for montelukast vs 32.40% for placebo; time to recovery to within 5% of baseline FEV1 44.22 min vs 60.64 min). This effect was consistent throughout the 12-week study period. Reduction in EIB was also demonstrated in a short term study in paediatric patients (maximal fall in FEV1 18.27% vs 26.11%; time to recovery to within 5% of baseline FEV1 17.76 min vs 27.98 min). The effect in both studies was demonstrated at the end of the once-daily dosing interval.

In aspirin-sensitive asthmatic patients receiving concomitant inhaled and/or oral corticosteroids, treatment with montelukast, compared with placebo, resulted in significant improvement in asthma control (FEV1 8.55% vs -1.74% change from baseline and decrease in total β -agonist use -27.78% vs 2.09% change from baseline).

Levocetirizine

Levocetirizine, the active enantiomer of cetirizine, is an antihistamine its principal effects are mediated via selective inhibition of H₁-receptors. Binding studies revealed that levocetirizine has affinity for human H₁ -receptors 2-fold higher than that of cetirizine (K_i = 3 nmol/L vs. 6 nmol/L). Levocetirizine dissociates from H₁ -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.

5.2 Pharmacokinetic properties

Montelukast

Absorption



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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.

For the 5 mg chewable tablet, the C_{max} is achieved in two hours after administration 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. 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.

Cytochrome P450 2C8 is the major enzyme in the metabolism of montelukast.

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.

Additionally CYP3A4 and 2C9 may have a minor contribution, although itraconazole, an inhibitor of CYP3A4, was shown not to change pharmacokinetic variables of montelukast in healthy subjects that received 10mg montelukast daily. Based on 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 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. Because montelukast and its metabolites are eliminated by the biliary route, no dose adjustment is anticipated to be necessary in patients with renal impairment. There are no data on the pharmacokinetics of montelukast in patients with severe hepatic insufficiency (Child-Pugh score >9).

With high doses of montelukast (20-and 60-fold the recommended adult dose), a decrease in plasma theophylline concentration was observed. This effect was not seen at the recommended dose of 10 mg once daily.

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 film-coated tablet is similar in adolescents ≥ 15 years of age and young adults. The 10-mg film-coated 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 C_{max} 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 levocetirizine dihydrochloride 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.

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 healthy adult subjects was about 8 to 9 hours after administration of oral tablets and oral solution. 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.

Drug Interaction Studies

In vitro data on metabolite interaction indicate that levocetirizine is unlikely to produce, or be subject to metabolic interactions. Levocetirizine at concentrations well above C_{max} 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 formal in vivo drug interaction studies have been performed with levocetirizine. Studies have been performed with the racemic cetirizine.

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 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 pediatric population than in adults.

Dedicated pharmacokinetic studies have not been conducted in pediatric 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 results in plasma concentrations similar to those of adults receiving 5 mg once daily.

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.

5.3 Preclinical safety data

Carcinogenesis, Mutagenesis, Impairment of Fertility

Montelukast

In animal toxicity studies, minor serum biochemical alterations in ALT, glucose, phosphorus and triglycerides were observed which were transient in nature. The signs of toxicity in animals were increased excretion of saliva, gastro-intestinal symptoms, loose stools and ion imbalance. These occurred at dosages which provided >17-fold the systemic exposure seen at the clinical dosage. In monkeys, the adverse effects appeared at doses from 150 mg/kg/day (>232-fold the systemic exposure seen at the clinical dose). In animal studies, montelukast did not affect fertility or reproductive performance at systemic exposure exceeding the clinical systemic exposure by greater than 24-fold. A slight decrease in pup body weight was noted in the female fertility study in rats at 200 mg/kg/day (>69-fold the clinical systemic exposure). In studies in rabbits, a higher incidence of



incomplete ossification, compared with concurrent control animals, was seen at systemic exposure >24-fold the clinical systemic exposure seen at the clinical dose. No abnormalities were seen in rats. Montelukast has been shown to cross the placental barrier and is excreted in breast milk of animals.

No deaths occurred following a single oral administration of montelukast sodium at doses up to 5,000 mg/kg in mice and rats (15,000 mg/m² and 30,000 mg/m² in mice and rats, respectively) the maximum dose tested. This dose is equivalent to 25,000 times the recommended daily adult human dose (based on an adult patient weight of 50 kg).

Montelukast was determined not to be phototoxic in mice for UVA, UVB or visible light spectra at doses up to 500 mg/kg/day (approximately >200-fold based on systemic exposure).

Montelukast was neither mutagenic in in vitro and in vivo tests nor tumorigenic in rodent species.

Levocetirizine

No carcinogenicity studies have been performed with levocetirizine. However, evaluation of cetirizine carcinogenicity studies is relevant for determination of the carcinogenic potential of levocetirizine. In a 2-year carcinogenicity study, in rats, cetirizine was not carcinogenic at dietary doses up to 20 mg/kg (approximately 40, 40, 25, and 10 times the MRHDs in adults, children 6 to 11 years of age, children 2-5 years, and children 6 months to 2 years of age, respectively, on a mg/m² basis).

In a 2-year carcinogenicity study in mice, cetirizine caused an increased incidence of benign hepatic tumors in males at a dietary dose of 16 mg/kg (approximately 15, 15, 9, and 5 times the MRHDs in adults, children 6 to 11 years of age, children 2-5 years, and children 6 months to 2 years of age, respectively, on a mg/m² basis). No increased incidence of benign tumors was observed at a dietary dose of 4 mg/kg (approximately 4, 4, 2, and 1 times the MRHDs in adults, children 6 to 11 years of age, children 2-5 years, and children 6 months to 2 years of age, respectively on a mg/m² basis). The clinical significance of these findings during long-term use of Levocetirizine is not known.



Levocetirizine was not mutagenic in the Ames test, and not clastogenic in the human lymphocyte assay, the mouse lymphoma assay, and in vivo micronucleus test in mice.

Fertility and reproductive performance were unaffected in male and female mice and rats that received cetirizine at oral doses up to 64 and 200 mg/kg/day, respectively (approximately 60 and 390 times the MRHD in adults on a mg/m² basis).

6. Pharmaceutical particulars

6.1 List of excipients

Microcrystalline cellulose - PH 101, Maize Starch, Methyl Paraben, Propyl Paraben, PVPK- 30, Purified Talc, Crospovidone, Sodium Starch Glycolate, Colloidal silicon dioxide, Magnesium Stearate, Isopropyl Alcohol, Methylene Di Chloride, HPMC-15, Purified Talc, Propylene glycol, Titanium dioxide

6.2 Incompatibilities

Not Applicable.

6.3 Shelf life

36 Months

6.4 Special precautions for storage

Store below 30°C, protected from light & moisture.

6.5 Nature and contents of container

Tablets are White circular biconvex film coated tablets plain on both sides of each tablet. 10 tablets are packed in one Alu-Alu blister pack and such 3 blister packs are packed in one-unit carton along with pack insert.

6.6 Special precautions for disposal and other handling

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.



UTTARANCHAL BIOTECH LTD.

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7. Marketing authorisation holder

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8. Marketing authorisation number(s)

N/A

9. Date of first authorisation/renewal of the authorisation

N/A

10. Date of revision of the text

N/A