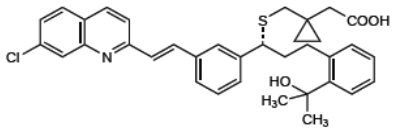
For the use of a Registered Medical Practitioner or Hospital or a Laboratory only

ASTHATOR
(Montelukast Sodium Tablets 5 mg & 10 mg)

BRAND OR PRODUCT NAME
ASTHATOR

NAME AND STRENGTH

ASTHATOR
Each uncoated tablet contains:
Montlukast Sodium Ph.Eur equivalent to Montelukast ……5 mg & 10 mg



DESCRIPTION
Montelukast is a selective leukotriene receptor antagonist. Chemically it is 1-[({(*R*)-*m*-[(*E*)-2-(7-chloro-2-quinolyl)-vinyl]-α-[*o*-(1-hydroxy-1-methylethyl) phenethyl]-benzyl} thio)methyl] cyclopropaneacetate.

CLINICAL PHARMACOLOGY
PHARMACODYNAMICS
Pharmacotherapeutic group: Leukotriene receptor antagonist

ATC-code: R03D C03

Mechanism of action

The cysteinyl leukotrienes (LTC_4, LTD_4, LTE_4) are potent inflammatory eicosanoids released from various cells including mast cells and eosinophils. These important pro-asthmatic mediators 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 bronchoconstriction, mucous secretion, vascular permeability, and eosinophil recruitment. 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.

Pharmacodynamic effects

Montelukast is an orally active compound which binds with high affinity and selectivity to the $CysLT_1$ receptor. In clinical studies, montelukast inhibits bronchoconstriction due to inhaled LTD_4 at doses as low as 5 mg. Bronchodilation was observed within 2 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 FEV_1 (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 nighttime 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 FEV_1: 5.43% vs 1.04%; β-agonist use: -8.70% vs 2.64%). Compared with inhaled beclomethasone (200 μg 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 FEV_1: 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 FEV_1 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.

In an 8-week study in paediatric patients 6 to 14 years of age, montelukast 5 mg once daily, compared with placebo, significantly improved respiratory function (FEV_1 8.71% vs 4.16% change from baseline; AM PEFR 27.9 L/min vs 17.8 L/min change from baseline) and decreased "as-needed" β-agonist use (-11.7% vs +8.2% change from baseline).

Significant reduction of exercise-induced bronchoconstriction (EIB) was demonstrated in a 12-week study in adults (maximal fall in FEV_1 22.33% for montelukast vs 32.40% for placebo; time to recovery to within 5% of baseline FEV_1 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 FEV_1 18.27% vs 26.11%; time to recovery to within 5% of baseline FEV_1 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 (FEV_1 8.55% vs -1.74% change from baseline and decrease in total β-agonist use -27.78% vs 2.09% change from baseline).

PHARMACOKINETICS

Absorption

Montelukast is rapidly absorbed following oral administration. For the 10 mg film-coated tablet, the mean peak plasma concentration (C_{max}) is achieved 3 hours (T_{max}) after administration in adults in the fasted state. The mean oral bioavailability is 64%. The oral bioavailability and C_{max} are not influenced by a standard meal. Safety and efficacy were demonstrated in clinical trials where the 10 mg film-coated tablet was administered without regard to the timing of food ingestion.

For the 5 mg chewable tablet, the C_{max} is achieved in 2 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 8-11 litres. Studies in rats with radiolabelled montelukast indicate minimal distribution across the blood-brain barrier. In addition, concentrations of radiolabelled material at 24 hours post-dose were minimal in all other tissues.

Biotransformation

Montelukast is extensively metabolised. In studies with therapeutic doses, plasma concentrations of metabolites of montelukast are undetectable at steady state in adults and children.

Cytochrome P450 2C8 is the major enzyme in the metabolism of montelukast. Additionally CYP 3A4 and 2C9 may have a minor contribution, although itraconazole, an inhibitor of CYP 3A4, was shown not to change pharmacokinetic variables of montelukast in healthy subjects that received 10 mg 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 faecal 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.

INDICATION
Montelukast is indicated in the treatment of asthma as add-on therapy in those patients with mild to moderate persistent asthma who are inadequately controlled on inhaled corticosteroids and in whom "as-needed" short acting β-agonists provide inadequate clinical control of asthma. In those asthmatic patients in whom Montelukast is indicated in asthma, Montelukast can also provide symptomatic relief of seasonal allergic rhinitis.

Montelukast is also indicated in the prophylaxis of asthma in which the predominant component is exercise-induced bronchoconstriction.

DOSE AND METHOD OF ADMINISTRATION
Posology

The recommended dose for adults and adolescents 15 years of age and older with asthma, or with asthma and concomitant seasonal allergic rhinitis, is one 10 mg tablet daily to be taken in the evening.
General recommendations

The therapeutic effect of Montelukast on parameters of asthma control occurs within one day. Montelukast may be taken with or without food. Patients should be advised to continue taking Montelukast even if their asthma is under control, as well as during periods of worsening asthma. Montelukast should not be used concomitantly with other products containing the same active ingredient, montelukast.

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.

Therapy with Montelukast in relation to other treatments for asthma

Montelukast can be added to a patient's existing treatment regimen.

Inhaled corticosteroids: Treatment with Montelukast can be used as add-on therapy in patients when inhaled corticosteroids plus "as needed" short acting β-agonists provide inadequate clinical control Montelukast should not be abruptly substituted for inhaled corticosteroids.

Paediatric population

Do not give Montelukast 10 mg film-coated tablets to children less than 15 years of age. The safety and efficacy of Montelukast 10 mg film-coated tablets in children less than 15 years has not been established.

5 mg chewable tablets are available for paediatric patients 6 to 14 years of age.

4 mg chewable tablets are available for paediatric patients 2 to 5 years of age.

4 mg granules are available for paediatric patients 6 months to 5 years of age.

Method of administration

Oral use.

CONTRAINDICATIONS

Hypersensitivity to the active substance or to any of the excipients.

WARNINGS AND PRECAUTIONS

Patients should be advised never to use oral montelukast to treat acute asthma attacks and to keep their usual appropriate rescue medication for this purpose readily available. If an acute attack occurs, a short-acting inhaled β-agonist should be used. Patients should seek their doctors' advice as soon as possible if they need more inhalations of short-acting β-agonists than usual.

Montelukast should not be substituted abruptly for inhaled or oral corticosteroids.

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

In rare cases, patients on therapy with anti-asthma agents including 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 cases have been sometimes associated with the reduction or withdrawal of oral corticosteroid therapy. Although a causal relationship with leukotriene receptor antagonism has not been established, physicians should be alert to eosinophilia, vasculitic rash, worsening pulmonary symptoms, cardiac complications, and/or neuropathy presenting in their patients. Patients who develop these symptoms should be reassessed and their treatment regimens evaluated.

Treatment with montelukast does not alter the need for patients with aspirin-sensitive asthma to avoid taking aspirin and other non-steroidal anti-inflammatory drugs.

Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicine.

Effects on ability to drive and use machines

Montelukast has no or negligible influence on the ability to drive and use machines. However, individuals have reported drowsiness or dizziness.

DRUG INTERACTIONS

Montelukast may be administered with other therapies routinely used in the prophylaxis and chronic treatment of asthma. In drug-interactions studies, the recommended clinical dose of montelukast did not have clinically important effects on the pharmacokinetics of the following medicinal products: theophylline, prednisone, prednisolone, oral contraceptives (ethinyl estradiol/ norethindrone 35/1), terfenadine, digoxin and warfarin.

The area under the plasma concentration curve (AUC) for montelukast was decreased approximately 40% in subjects with co-administration of phenobarbital. Since montelukast is 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.

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

In vitro studies have reported 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.

USE IN SPECIFIC POPULATIONS

Pregnancy

Use during pregnancy

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.

Use during lactation

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

Montelukast may be used in breast-feeding only if it is considered to be clearly essential.

ADVERSE REACTIONS

Montelukast has been evaluated in clinical studies as follows:

• 10 mg film-coated tablets in approximately 4,000 adult and adolescent asthmatic patients 15 years of age and older.

• 10 mg film-coated tablets in approximately 400 adult and adolescent asthmatic patients with seasonal allergic rhinitis 15 years of age and older.

• 5 mg chewable tablets in approximately 1,750 paediatric asthmatic patients 6 to 14 years of age.

The following drug-related adverse reactions in clinical studies were reported commonly (≥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
Gastro-intestinal disorders	abdominal pain	

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 6 to 14 years of age, the safety profile did not change.

Tabulated list of Adverse Reactions

Adverse reactions reported in post-marketing use are listed, by System Organ Class and specific Adverse Reactions, in the table below. Frequency Categories were estimated based on relevant clinical trials.

System Organ Class	**Adverse Experience Term**	**Frequency Category***
Infections and infestations	upper respiratory infection †	Very Common
Blood and lymphatic system disorders	increased bleeding tendency	Rare
Immune system disorder	hypersensitivity reactions including anaphylaxis	Uncommon
	hepatic eosinophilic infiltration	Very Rare
Psychiatric disorders	dream abnormalities including nightmares, insomnia, somnambulism, anxiety, agitation including aggressive behaviour or hostility, depression, psychomotor hyperactivity (including irritability, restlessness, tremor §)	Uncommon
	disturbance in attention, memory impairment	Rare
	hallucinations, disorientation, suicidal thinking and behaviour (suicidality)	Very Rare
Nervous system disorder	dizziness, drowsiness paraesthesia/hypoesthesia, seizure	Uncommon

Cardiac disorders	palpitations	Rare
Respiratory, thoracic and mediastinal disorders	epistaxis	Uncommon
	Churg-Strauss Syndrome (CSS)	Very Rare
	Pulmonary eosinophilia	Very rare
Gastrointestinal disorders	diarrhoea ‡, nausea‡, vomiting‡	Common
	dry mouth, dyspepsia	Uncommon
Hepatobiliary disorders	elevated levels of serum transaminases (ALT, AST)	Common
	Hepatitis (including cholestatic, hepatocellular, and mixed-pattern liver injury).	Very Rare
Skin and subcutaneous tissue disorders	rash	Common
	bruising, urticaria, pruritus	Uncommon
	angiooedema	Rare
	erythema nodosum, erythema multiforme	Very Rare
Musculoskeletal, connective tissue and bone disorders	arthralgia, myalgia including muscle cramps	Uncommon
General disorders and administration site conditions	pyrexia‡	Common
	asthenia/fatigue, malaise, oedema,	Uncommon

* Frequency Category: Defined for each Adverse Reaction by the incidence reported in the clinical trials data base: Very Common (≥1/10), Common (≥1/100 to <1/10), Uncommon (≥1/1,000 to <1/100), Rare (≥1/10,000 to <1/1,000), Very Rare (<1/10,000).

† This adverse experience, reported as Very Common in the patients who received montelukast, was also reported as Very Common in the patients who received placebo in clinical trials.

‡ This adverse experience, reported as Common in the patients who received montelukast, was also reported as Common in the patients who received placebo in clinical trials.

§ Frequency Category: Rare

STORAGE CONDITIONS
Store below 30°C. Protect from Light & moisture.
Keep out of reach of children

PRESENTATION AND AVAILIBILITY
Asthator tablets are packed in 3 blister strips of 10 tablets.

Manufactured by:
TORRENT PHARMACEUTICALS LTD.
Indrad-382 721, Dist. Mehsana, INDIA.

Marketed by:
Chanrai Health Care Limited,
Chanrai Health Care Limited
122-132 Oshodi Apapa Expressway
Isolo, Lagos, Nigeria.