1.6 PRODUCT INFORMATION

1.6.1 SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE FINISHED PHARMACEUTICAL PRODUCT
MONTIKAST-10 (Montelukast Tablets BP 10 mg)

2. QUALITATIVE AND QUANTITATIVE COMPOSITION
Each uncoated tablet contains:
Montelukast Sodium BP Equivalent to Montelukast BP 10 mg
Colour: Sunset Yellow

3. PHARMACEUTICAL FORM
Tablet, Solid dosage form

4. CLINICAL PARTICULARS
4.1 Therapeutic indications
Montelukast 10 mg tablets is indicated in the treatment of asthma as add-on therapy in adults and adolescents from 15 years of age and older with mild to moderate persistent asthma who are inadequately controlled on inhaled corticosteroids and in whom "as needed" short acting beta-agonists provide inadequate clinical control of asthma. In those asthmatic patients in whom Montelukast 10 mg tablets is indicated in asthma, Montelukast 10 mg tablets can also provide symptomatic relief of seasonal allergic rhinitis.
Montelukast 10 mg tablets is also indicated in the prophylaxis of asthma in which the predominant component is exercise-induced bronchoconstriction.

4.2 Posology and method of administration
Prophylaxis of asthma
By Mouth
Child 6 months-5 years: 4 mg once daily, dose to be taken in the evening
Child 6-14 years: 5 mg once daily, dose to be taken in the evening
Child 15-17 years: 10 mg once daily, dose to be taken in the evening
Adult: 10 mg once daily, dose to be taken in the evening

Symptomatic relief of seasonal allergic rhinitis in patients with asthma.
By Mouth
Child 15-17 years: 10 mg once daily, dose to be taken in the evening
Adult: 10 mg once daily, dose to be taken in the evening

Method of administration
Oral use
Chewable: The tablets are to be chewed before swallowing.
Uncoated: The tablet should not be chewed before swallowing.

4.3 Contraindications
Hypersensitivity to the active substance or to any of the excipients

4.4 Special warnings and precaution for use
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 doctor's advice as soon as possible if they need more inhalations of short-acting β-agonists than usual.

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.

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.

4.5 Interaction with other medicinal products and other forms of interaction
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 (ethinyloestradiol/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,and2C9,such as phenytoin, phenobarbital and rifampicin.
In vitro studies have shown that montelukast is a potent inhibitor of CYP 2C8.
However, data from a clinical drug-drug interaction study involving montelukast and rosiglitazone (a probe substrate representative of 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 (eg., paclitaxel, rosiglitazone, and repaglinide).
In vitro studies have shown that montelukast is asubstrate of CYP2C8, and to a less significant extent, of 2C ,and 3A4. In aclinical drug drug interaction study involving montelukast and gemfibrozil (an inhibitor of both CYP2C8 and 2C9) gemfibrozil increased the systemic exposure of montelukast by 4.4-fold. No routine dosage adjustment of montelukast is required up on co administration with gemfibrozil or other potent inhibitors of CYP2C8,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 CYP2C8 (e.g.,trimethoprim) are not anticipated. Co-administration of montelukast with itraconazole, a strong inhibitor of CYP3A4, resulted in no significant increase in the systemic exposure of montelukast.

4.6 Pregnancy and Lactation
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.

Breastfeeding
Studies in rats have shown that montelukast is excreted in milk. It is unknown whether montelukast/metabolites are is excreted in human milk. Montelukast may be used in breast-feeding mothers only if it is considered to be clearly essential.

4.7 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.

4.8 Undesirable effects
Abdominal or stomach pain
Diarrhea
Diziness
Fever
Headache
Scaly and itchy skin
Skin rash
Thirst
Weakness or unusual redness

4.9 Overdose
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.

5. PHARMACOLOGICAL PROPERTIES

Pharmacotherapeutic group: Other systemic drugs for obstructive airway diseases, Leukotriene receptor antagonists,
ATC Code: RO3D CO3

5.1 Pharmacodynamic Properties

Montelukast is an orally active compound which binds with high affinity and selectivity to the Cys LT1 receptor. In clinical studies, montelukast inhibits bronchoconstriction due to inhaled LTD4 at doses as low as 5 mg. Bronchodilation was observed within two hours of oral administration. The bronchodilation effect caused by a beta-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 inperipheral blood while improving clinical asthma control.

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.

5.2 Pharmacokinetic Properties

Absorption: Montelukast is rapidly absorbed following oral administration. For the 10 mg film-coated tablet, the mean peak plasma concentration (Cmax) is achieved three hours (Tmax) after administration in adults in the fasted state. The mean oral bioavailability is 64%. The oral bioavailability and Cmax are not influenced by a standard meal. Safety and efficacy were demonstrated in clinical trials where the 10 mg film-coated tablet was administered without regard to the timing of food ingestion.
For the 5 mg chewable tablet, the Cmax 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.
After administration of the 4 mg chewable tablet to paediatric patients 2 to 5 years of age in the fasted state, Cmax is achieved 2 hours after administration. The mean Cmax is 66% higher while mean C min is lower than in adults receiving a 10 mg tablet.

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 radiolabelledmontelukast 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 paediatric patients. Cytochrome P450 2C8isthemajorenzyme in the metabolism of montelukast. Additionally CYP3A4 and2C9 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 radio labelled 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.

Characteristics in patients:
No dosage adjustment is necessary for the elderly or mild to moderate hepatic insufficiency. Studies in patients with renal impairment have not been undertaken. 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

5.3 Preclinical safety data
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/m^2 and 30,000 mg/m^2 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.

6. PHARMACEUTICAL PARTICULARS
6.1 List of Excipients
Mannitol
Crosspovidone
Colour Tartrazine Lake
Aspartame
Low substituted Hydroxy propyl cellulose LH11
Flavour Pineapple
Magnesium Stearate

6.2 Incompatibilities
Not applicable

6.3 Shelf life
36 months

6.4 Special precautions for storage
Store below 30^0 C. Protect from light and moisture.
Keep Medicine Out of Reach of Children

6.5 Nature and contents of container
1 Blisters of 10 tablets each are packed in carton along with Product insert. (1×10's Alu-Alu Blisters pack)

7. MARKETING AUTHORISATION HOLDER

Star Biotech Limited

Address: 1st floor, Prestige House, Rwandex, Kigali-Rwanda

Telephone: (+250) 785377688 / (+250) 787229914

Email: shantilal.bhanderi@yahoo.com

8. MARKETING AUTHORISATION NUMBER
Not Applicable

9. DATE OF FIRST REGISTRATION/RENEWAL OF THE REGISTRATION
Not Applicable