Important information. Please read carefully.

# *XEPA ALTRA*

***Chewable Tablets 4mg & 5mg***

**COMPOSITION**
XEPA ALTRA Chewable Tablets 5mg:
Each tablet contains 5mg Montelukast (as Montelukast Sodium).

XEPA ALTRA Chewable Tablets 4mg:
Each tablet contains 4mg Montelukast (as Montelukast Sodium).

**PHARMACODYNAMICS**
Pharmacotherapeutic Group: Leukotriene receptor antagonist
ATC Code: R03D C03

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 (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 a number of airway actions, including 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.

Montelukast is a potent, orally active compound that significantly improves parameters of asthmatic inflammation. Based on biochemical and pharmacological bioassays, it binds with high affinity and selectivity to the CysLT1 receptor (in preference to other pharmacologically important airway receptors such as the prostanoid, cholinergic, or β-adrenergic receptor). Montelukast potently inhibits physiologic actions of LTC4, LTD4, and LTE4 at the CysLT1 receptor without any agonist activity.

Montelukast causes potent inhibition of airway cysteinyl leukotriene receptors as demonstrated by the ability to inhibit bronchoconstriction due to inhaled LTD4 in asthmatic patients. Doses as low as 5-mg cause substantial blockage of LTD4-induced bronchoconstriction.

Montelukast causes bronchodilation within 2 hours of oral administration; these effects were additive to the bronchodilation caused by a β-agonist.

**PHARMACOKINETICS**
Absorption
Montelukast is rapidly and nearly completely absorbed following oral administration.

For the 5-mg chewable tablet, the $C_{max}$ is achieved 2 hours after administration in adults in the fasted state. The mean oral bioavailability is 73%. Food does not have a clinically important influence with chronic administration.

For the 4-mg chewable tablet, $C_{max}$ is achieved 2 hours after administration in pediatric patients 2 to 5 years of age in the fasted state.
Safety and efficacy were demonstrated in clinical studies where the 4-mg chewable tablet and 5-mg chewable tablet were administered without regard to the timing of food ingestion.

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

Metabolism
Montelukast is extensively metabolized. In studies with therapeutic doses, plasma concentrations of metabolites of

montelukast are undetectable at steady state in adults and pediatric patients.

*In vitro* studies using human liver microsomes indicate that cytochrome P450 3A4, 2C8 and 2C9 are involved in the metabolism of montelukast. Based on further *in vitro* results in human liver microsomes, therapeutic plasma concentrations of montelukast do not inhibit cytochromes P450 3A4, 2C9, 1A2, 2A6, 2C19, or 2D6.

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 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 are nearly linear for oral doses up to 50 mg. No difference in pharmacokinetics was noted between dosing in the morning or in the evening.

Characteristic in Patients
*Gender*
The pharmacokinetics of montelukast are similar in males and females.

*Elderly*
The plasma half-life of montelukast is slightly longer in the elderly. No dosage adjustment in the elderly is required.

*Race*
Pharmacokinetic differences due to race have not been studied. In clinical studies, there do not appear to be any differences in clinically important effects.

*Hepatic Insufficiency*
The elimination of montelukast is 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. There are no clinical data in patients with severe hepatic insufficiency (Child-Pugh score > 9).

*Renal Insufficiency*
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.

**INDICATIONS**
For the prophylaxis and chronic treatment of asthma in pediatric patients 2 to 14 years of age.

Montelukast is indicated in pediatric patients 2 to 14 years of age for the relief of daytime and nighttime symptoms of seasonal allergic rhinitis.

**DOSAGE AND ADMINISTRATION**
Montelukast should be taken once daily. For asthma, the dose should be taken in the evening. For allergic rhinitis, the time of administration may be individualized to suit patient needs.

Patients with both asthma and allergic rhinitis should take only one tablet daily in the evening.

*Pediatric Patients 6 to 14 Years of Age with Asthma and/or Seasonal Allergic Rhinitis*
The dosage for pediatric patients 6 to 14 years of age is one 5-mg chewable tablet daily.

*Pediatric Patients 2 to 5 Years of Age with Asthma and/or Seasonal Allergic Rhinitis*
The dosage for pediatric patients 2 to 5 years of age is one 4-mg chewable tablet daily.

General Recommendations:
The therapeutic effect of montelukast on parameters of asthma control occurs within one day.
Montelukast can be taken with or without food. Patients should be advised to continue taking montelukast while their asthma is controlled, as well as during periods of worsening asthma.

No dosage adjustment is necessary for pediatric patients, for the elderly, for patients with renal insufficiency, or mild-

to-moderate hepatic impairment, or for patients of either gender.

Montelukast is a long term-controller medication which should not be substituted for short acting beta-agonists. It is effective alone or in combination with other prophylactic agent.

Montelukast is a preventive agent, which should be used in addition to other drugs for the management of asthma.

*Therapy with montelukast in Relation to Other Treatments for Asthma:*
Montelukast can be added to a patient's existing treatment regimen.
Reduction in Concomitant Therapy:
*Bronchodilator Treatments:* Montelukast can be added to the treatment regimen of patients who are not adequately controlled on bronchodilator alone. When a clinical response is evident (usually after the first dose), the patient's bronchodilator therapy can be reduced as tolerated.
*Inhaled Corticosteroids:* Treatment with montelukast provides additional clinical benefit to patients treated with inhaled corticosteroids. A reduction in the corticosteroid dose can be made as tolerated. The dose should be reduced gradually with medical supervision. In some patients, the dose of inhaled corticosteroids can be tapered off completely. Montelukast should not be abruptly substituted for inhaled corticosteroids.

**CONTRAINDICATIONS**
Hypersensitivity to any component of this product.

**WARNING AND PRECAUTIONS**
The efficacy of oral Montelukast for the treatment of acute asthma attacks has not been established. Therefore, oral Montelukast should not be used to treat acute asthma attacks. Patients should be advised to have appropriate rescue medication available.

While the dose of concomitant inhaled corticosteroid may be reduced gradually under medical supervision, Montelukast should not be abruptly substituted for inhaled or oral corticosteroids. Neuropsychiatric events have been reported in patients taking Montelukast (see SIDE EFFECTS). Since other factors may have contributed to these events, it is not known if they are related to Montelukast. Physicians should discuss these adverse experiences with their patients and/or caregivers. Patients and/or caregivers should be instructed to notify their physician if these changes occur.

In rare cases patients receiving anti-asthma agents, including leukotriene receptor antagonists, have experienced one or more of the following: eosinophilia, vasculitic rash, worsening pulmonary symptoms, cardiac complications, and/or neuropathy sometimes diagnosed as Churg-Strauss syndrome, a systemic eosinophilic vasculitis. 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, caution
and appropriate clinical monitoring are recommended in patients receiving Montelukast.

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 documented aspirin sensitivity.

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

The area under the plasma concentration-time curve (AUC) for montelukast was decreased approximately 40% in subjects with co-administration of phenobarbital. No dosage adjustment for Montelukast is recommended.

In vitro studies have shown that montelukast is an inhibitor of CYP2C8. However, data from a clinical drug-drug interaction study involving montelukast and rosiglitazone (a probe substrate representative of drugs primarily metabolized by CYP2C8) demonstrated that montelukast does not inhibit CYP2C8 in vivo. Therefore, montelukast is not anticipated to alter the metabolism of drugs metabolized by this enzyme (e.g., paclitaxel, rosiglitazone, repaglinide).

In vitro studies have shown that montelukast is a substrate of CYP 2C8, 2C9, and 3A4. Data from a clinical drug-drug interaction study involving montelukast and gemfibrozil (an inhibitor of both CYP 2C8 and 2C9) demonstrated that gemfibrozil increased the systemic exposure of montelukast by 4.4-fold. Co-administration of itraconazole, a strong CYP 3A4 inhibitor, with gemfibrozil and montelukast did not further increase the systemic exposure of montelukast. The effect of gemfibrozil on systemic exposure of montelukast is not considered to be clinically meaningful based on clinical safety data with doses greater than the 10 mg approved dose in adults (e.g., 200 mg/day to adult patients for 22 weeks, and up to 900 mg/day to patients for approximately one week) where clinically important adverse experiences were not observed. Therefore, no dosage adjustment of montelukast is required upon co-administration with gemfibrozil. Based on in vitro data, clinically important drug interactions with other known inhibitors of CYP 2C8 (e.g., trimethoprim) are not anticipated. In addition, co-administration of montelukast with itraconazole alone resulted in no significant increase in the systemic exposure of montelukast.

**PREGNANCY AND LACTATION**

*Pregnancy*
Montelukast should be used during pregnancy only if clearly needed. Available data from published prospective and retrospective cohort studies with montelukast use in pregnant women evaluating major birth defects have not established a drug-associated risk. Available studies have methodologic limitations, including small sample size, in some cases retrospective data collection, and inconsistent comparator groups.

*Lactation*
It is not known if Montelukast is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when Montelukast is given to a nursing mother.

**SIDE EFFECTS**

Montelukast has been generally well tolerated. Side effects, which usually were mild, generally did not require discontinuation of therapy.

**Postmarketing Experience**
The following side effects have been reported in postmarketing use:

| **System Organ Class** | **Adverse Effects** |
|---|---|
| Infections and infestations | Upper respiratory infection |
| Blood and lymphatic system disorders | Increased bleeding tendency, thrombocytopenia |
| Immune system disorders | Hypersensitivity reactions including anaphylaxis, very rarely hepatic eosinophilic infiltration |
| Psychiatric disorders | Agitation including aggressive behavior or hostility, anxiousness, depression disorientation, disturbances in attention, dream abnormalities dysphemia (stuttering), hallucinations, insomnia, memory impairment, obsessive-compulsive symptoms, psychomotor hyperactivity (including irritability, restlessness, and tremor), somnambulism, suicidal thinking and behavior (suicidality), tic |
| Nervous system disorders | Dizziness, drowsiness, paraesthesia/hypoesthesia, very rarely seizure |
| Cardiac disorders | Palpitations |
| Respiratory, thoracic and mediastinal disorders | Epistaxis; pulmonary eosinophilia |
| Gastrointestinal disorders | Diarrhea, dyspepsia, nausea, vomiting |
| Hepatobiliary disorders | Increased ALT and AST, very rarely hepatitis (including cholestatic, hepatocellular, and mixed-pattern liver injury) |
| Skin and subcutaneous tissue disorders | Angioedema, bruising, erythema multiforme, erythema nodosum, pruritus, rash, urticaria |
| Musculoskeletal and connective tissue disorders | Arthralgia, myalgia including muscle cramps |
| Renal and urinary disorders | Enuresis in children |
| General disorders and administration site conditions | Asthenia/fatigue, edema, pyrexia |

**SYMPTOMS AND TREATMENT FOR OVERDOSAGE**
No specific information is available on the treatment of overdosage with montelukast.

There have been reports of acute overdosage in postmarketing experience and clinical studies 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.

It is not known whether montelukast is dialysable by peritoneal- or haemodialysis.

**SHELF-LIFE**
The expiry date is indicated on the packaging.

**STORAGE CONDITION**
Store below 30°C. Protect from light and moisture.

**PRODUCT DESCRIPTION, DOSAGE FORM AND PACKAGING AVAILABLE**
XEPA ALTRA Chewable Tablets 5mg:
Mottled pink, round tablet with 'crown' logo on one side and plain on the other side.
Available as Alu-Alu blister strips of 10's in packing of 30 tablets per box.

XEPA ALTRA Chewable Tablets 4mg:
Mottled pink, round tablet with 'Z' logo on one side and plain on the other side.
Available as Alu-Alu blister strips of 10's in packing of 30 tablets per box.

**KEEP OUT OF REACH OF CHILDREN/ JAUHI DARI KANAK-KANAK**

For further information, please consult your pharmacist or physician.

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Manufacturer and Product Registration Holder (in Malaysia)
**Xepa-Soul Pattinson (Malaysia) Sdn. Bhd.**
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