Montelukast sodium

Kastair® EZTab®

4 mg Tablet
5 mg Tablet

Anti-asthma / Anti-allergic rhinitis

FORMULATIONS
Each tablet contains:
Montelukast (as sodium)…… 4 mg or 5 mg

PRODUCT DESCRIPTIONS
Montelukast (Kastair® EZTab®) 4 mg tablet contains 4.2 mg montelukast sodium equivalent to 4 mg of montelukast. It is a white, round tablet with red specks, with EZ logo on one side and plain on the other side. Easy to swallow, cherry-flavored tablet that melts in the mouth in less than 30 seconds without chewing.

Montelukast (Kastair® EZTab®) 5 mg tablet contains 5.2 mg montelukast sodium equivalent to 5 mg of montelukast. It is a white, round tablet with red specks, with EZ logo on one side and plain on the other side. Easy to swallow, cherry-flavored tablet that melts in the mouth in less than 30 seconds without chewing.

CLINICAL PHARMACOLOGY
PHARMACODYNAMICS
Montelukast is a selective leukotriene-receptor antagonist that specifically inhibits the cysteinyl leukotriene $CysLT_1$ receptor. The cysteinyl leukotrienes [CysLT (LTC_4, LTD_4, and LTE_4)] are potent inflammatory eicosanoids released from various cells including mast cells and eosinophils that bind to CysLT receptors. The CysLT type 1 ($CysLT_1$) receptor is present in the human airway (including airway smooth muscle cells and airway macrophages). CysLTs contribute to the pathophysiology of asthma and allergic rhinitis. In asthma, CysLTs are found to increase mucus secretion, vascular permeability, and bronchoconstriction. In allergic rhinitis, CysLTs are released from the nasal mucosa after exposure to allergens and are associated with symptoms of allergic rhinitis. Montelukast inhibits bronchoconstriction and reduces inflammation of the nasal mucosa induced by exposure to known precipitants.

PHARMACOKINETICS
In two pharmacokinetic trials in asthmatic pediatric patients aged 2 to 5 years and 6 to 14 years, peak plasma concentrations of montelukast 4 mg (471 ± 65 ng/mL) and 5 mg (495 ± 129 ng/mL) as chewable tablets are attained within 2.07 ± 0.3 hours and 2.6 ± 1 hours, respectively.

Montelukast's steady state volume of distribution is 8 to 11 liters. Plasma protein binding is more than 99%.

Montelukast is extensively metabolized in the liver by cytochrome P450 isoenzymes CYP2C8, CYP3A4, and CYP2C9, and is excreted principally in the feces via the bile.

Bioequivalence Study

Montelukast sodium (Kastair® EZTab®) 5 mg tablet was shown to be bioequivalent to the reference product (innovator) in adults under fasting conditions. The following are important pharmacokinetic parameters of montelukast in adult volunteers who received montelukast sodium (Kastair® EZTab®) 5 mg tablet (as a single oral dose) under fasting conditions:

Pharmacokinetic Parameters	Montelukast (Kastair® EZTab®) 5 mg Tablet	90% Confidence Interval
T_{max} ± S.D. (h)	2.75 ± 0.77	
C_{max} ± S.D. (ng/mL)	252.71 ± 63.6	81.99 – 97.841
AUC_{0-inf} ± S.D (ng-h/mL)	1690.29 ± 571.97	88.615 – 103.932
AUC_{0-t} ± S.D (ng-h/mL)	1839.49 ± 581.94	88.442 – 103.048
Kel (h)	0.1778 ± 0.051	
$T_{1/2}$ (h)	4.23 ± 1.238	

T_{max} = time the drug reached its maximum concentration in the blood
C_{max} = maximum plasma concentration of the drug at peak time
AUC_{0-inf} = area under the curve from blood level profile(from zero to sampling time point)
AUC_{0-t} = area under the curve from blood level profile(extrapolated to infinity)
Kel = elimination rate constant
$T_{1/2}$ = elimination half life

INDICATIONS
- For the relief of symptoms of allergic rhinitis:
  - Seasonal allergic rhinitis in children 2 years and older and in adults
  - Perennial allergic rhinitis in children 6 months old and older and in adults

- For the prophylaxis and chronic treatment of asthma in children 6 months old and older and in adults

Montelukast is effective alone or when used together with other agents for the management of chronic asthma. Montelukast may be used concomitantly with inhaled corticosteroids to control asthma and to reduce the dose of inhaled corticosteroids required by patients with moderate to severe asthma.

- For the prevention of exercise-induced bronchoconstriction in children 2 years and older and in adults

DOSAGE AND ADMINISTRATION

Age Group	Once daily dose of Montelukast (Kastair® EZTab®) for Allergic Rhinitis, Asthma and/or Exercise-induced Bronchoconstriction	
	4 mg	5 mg
Children 6 months to 5 years	1 tablet	-
6 to 14 years	-	1 tablet
Adults and children 15 years and older	-	2 tablets
	Or, as prescribed by a physician	

Directions for Use:
- **For patients with allergic rhinitis:**
  - The time of administration may be individualized to suit patient needs.
  - Take everyday, at about the same time each day, or, as prescribed by a physician.

- **For patients with asthma with or without coexisting allergic rhinitis:**
  - The dose should be taken in the evening to obtain simultaneous peak plasma concentration and peak airway reactivity in the morning.
  - Take at regular intervals (i.e., daily) to be therapeutically effective, even if the patient has no asthma symptoms, or, as prescribed by a physician.

- **For the prevention of exercise-induced bronchoconstriction:**
  - Take at least 2 hours before exercise.
  - Do not take an additional dose within 24 hours of a previous dose.
  - Do not take an additional dose to prevent exercise-induced bronchoconstriction if the patient is taking daily for chronic asthma or allergic rhinitis. Consult a physician about treatment of exercise-induced bronchoconstriction.

- Montelukast 4 mg and 5 mg tablet can be dissolved in the mouth or chewed before swallowing.

- May be taken with or without food.

- **For younger children (6 months to 2 years old), montelukast 4 mg tablet can be crushed and:**
  - administered directly in the mouth
  - dissolved in 5 mL (1 teaspoonful) of cold or room temperature breast milk or baby formula
  - mixed with a spoonful of one of the following soft foods at cold or room temperature: applesauce, mashed carrots, rice, or ice cream
  - The tablet should not be crushed until ready for use.
  - The entire dose of the crushed tablet must be administered within 15 minutes. The crushed tablet should not be stored for future use if mixed with food or dissolved in breast milk or baby formula.
  - The crushed tablet should not be dissolved in liquid other than breast milk or baby formula. However, liquids can be taken after administration.

CONTRAINDICATION
Hypersensitivity to montelukast or other ingredients in the product

WARNINGS AND PRECAUTIONS
Acute Asthma
Montelukast is not indicated for the treatment of acute asthma attacks, including status asthmaticus. Patients should have appropriate short-acting inhaled beta-agonist medication available to treat asthma exacerbations. However, therapy with montelukast can be continued during acute asthmatic attacks.

Patients taking montelukast should not discontinue or reduce the dosage of other medicines for asthma unless directed by a physician.

Aspirin Sensitivity
Avoid aspirin or nonsteroidal anti-inflammatory drugs (NSAIDs) while taking montelukast in patients with known aspirin sensitivity.

Neuropsychiatric Events
Neuropsychiatric events have been reported in patients taking montelukast. These postmarketing reports include agitation, aggressive behavior or hostility, anxiousness, depression, disorientation, disturbance in attention, dream abnormalities, hallucinations, insomnia, irritability, memory impairment, restlessness, somnambulism, suicidal thinking and behavior (including suicide), and tremor. Patients should inform their physician if these changes occur.

Eosinophilic Conditions
Eosinophilia, vasculitic rash, worsening pulmonary symptoms, cardiac complications, and/or neuropathy consistent with Churg-Strauss syndrome have been reported in patients with asthma being treated with montelukast.

Effects on Ability to Drive and Use Machines
Montelukast is not expected to affect patients' physical coordination (e.g., driving, operating machinery). However, in very rare cases, individuals have reported dizziness or drowsiness.

INTERACTIONS WITH OTHER MEDICAMENTS
Montelukast may be administered with other drugs routinely used in the prophylaxis and chronic treatment of asthma and in the treatment of allergic rhinitis.

No clinically important effects were observed when montelukast was concomitantly administered with: benzodiazepines, decongestants, digoxin, nonsteroidal anti-inflammatory agents, oral contraceptives (ethinyl estradiol with norethindrone), prednisone, prednisolone, sedative hypnotics, terfenadine, theophylline, thyroid hormones, and warfarin.

Montelukast-treated patients with known aspirin sensitivity should continue to avoid aspirin and other NSAIDs. Although montelukast can improve airway function in asthmatics with aspirin sensitivity, the drug has not been shown to shorten the bronchoconstrictor response to aspirin or other NSAIDs in such patients.

The area under the plasma concentration-time curve of montelukast decreased by approximately 40% with coadministration of phenobarbital. No dosage adjustment for montelukast is recommended. However, appropriate clinical monitoring should be initiated with concomitant administration of montelukast with potent cytochrome P450 enzyme inducers such as phenobarbital, phenytoin, and rifampicin.

STATEMENT ON USAGE FOR HIGH RISK GROUPS
Pregnancy: Pregnancy Category B. No adequate and well-controlled studies in pregnant women are available for montelukast. Montelukast should only be used during pregnancy when clearly needed.

There have been reports of congenital limb defects in children of patients treated with montelukast. Some of the mothers, however, were receiving various medications in the course of their pregnancies. Since there is no consistent pattern of congenital abnormality development, a relationship between the use of montelukast and the development of congenital anomalies cannot be established.

Lactation: It is not known if montelukast is excreted in human milk. Therefore, do not administer to breastfeeding women unless, in the opinion of a physician, the potential benefit of the drug justifies the possible risk to the infant.

Children: The safety and efficacy of montelukast in infants younger than 6 months old have not been established.

Elderly: There were no age-related differences in the efficacy or safety profile of montelukast, but greater sensitivity of some older individuals cannot be ruled out.

UNDESIRABLE EFFECTS
The most frequently reported adverse effects with montelukast include upper respiratory infection, fever, headache, pharyngitis, cough, abdominal pain, diarrhea, otitis media, influenza, rhinorrhea, sinusitis, and otitis.
Infection and Infestations: Pyuria, skin infection, tooth infection, varicella, viral infection
Blood and lymphatic system disorders: Increased bleeding tendency, thrombocytopenia
Immune system disorders: Hypersensitivity reactions including anaphylaxis
Psychiatric disorders: Agitation including aggressive behavior or hostility, anxiousness, depression, disorientation, disturbance in attention, dream abnormalities, hallucinations, insomnia, irritability, memory impairment, restlessness, somnambulism, suicidal thinking and behavior (including suicide), tic, tremor
Nervous system disorders: Dizziness, drowsiness, hyperkinesia, hypoesthesia, paresthesia, seizure
Eye disorders: Conjunctivitis, myopia
Ear and labyrinth disorders: Ear pain
Cardiac disorders: Palpitations
Vascular disorders: Vasculitis
Respiratory, thoracic and mediastinal disorders: Acute bronchitis, asthma, Churg-Strauss syndrome, epistaxis, laryngitis, nasal congestion, pneumonia, pulmonary eosinophilia, rhinitis/infective rhinitis, sinus headache, tonsillitis, wheezing
Gastrointestinal disorders: Dry mouth, dyspepsia, gastroenteritis/infectious gastroenteritis, nausea, pancreatitis, vomiting
Hepatobiliary disorders: Hepatic infiltration eosinophilic, cholestastic hepatitis, hepatocellular liver injury, mixed-pattern liver injury, increased alanine aminotransferase (ALT) and aspartate aminotransferase (AST)
Skin and subcutaneous tissue disorders: Angioedema, atopic dermatitis, bruising, dermatitis, eczema, erythema multiforme, erythema nodosum, Stevens-Johnson syndrome, pruritus, rash, toxic epidermal necrolysis, 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, dental pain, edema, fatigue, leg pain, malaise, thirst
Injury, poisoning and procedural complications: Trauma

OVERDOSE AND TREATMENT
Montelukast given in doses up to 200 mg/day for 22 weeks and up to 900 mg/day for approximately a week to adult patients showed no clinically important adverse reactions. Acute overdosages in adults and children given montelukast with a dose as high as 1000 mg have been reported. There were no adverse effects reported in majority of overdosage reports. The most frequent adverse effects observed were abdominal pain, headache, psychomotor hyperactivity, somnolence, thirst, vomiting, and less frequently convulsion.

There is no specific information available on the treatment of overdosage with montelukast. In case of overdose, institute supportive and symptomatic therapy, i.e., remove unabsorbed material from the gastrointestinal tract. There is no adequate evidence to support the use of dialysis in the treatment of montelukast overdose.

STORAGE CONDITION
Keep the product out of sight and reach of children
Store at temperatures not exceeding 30°C

AVAILABILITY
*Montelukast (Kastair® EZTab®) 4 mg tablet in box of 28's (in flex foil) (DR-XY31298)
**Montelukast (Kastair® EZTab®) 5 mg tablet in box of 28's (in flex foil) (DRP-2957-01)

DATE OF FIRST AUTHORIZATION (DR-XY31298): August 2007
DATE OF FIRST AUTHORIZATION (DRP-2957-01): July 2012
DATE OF REVISION OF PACKAGE INSERT: June 2017

CAUTION
Foods, Drugs, Devices, and Cosmetics Act prohibits dispensing without prescription

ADVERSE DRUG REACTION REPORTING STATEMENT
For suspected adverse drug reaction, seek medical attention immediately and report to the FDA at www.fda.gov.ph AND Unilab at (+632) 858-1000 or productsafety@unilab.com.ph. By reporting undesirable effects, you can help provide more information on the safety of this medicine.

*Manufactured by AMHERST LABORATORIES, INC.
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for UNILAB, Inc.
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