Montelukast sodium
Levocetirizine dihydrochloride

Rx

Prescription (Rx) Drug

Monterizine
10 mg / 5 mg Capsule
Antihistamine + Leukotriene Receptor Antagonist

【Product Description】
Beige cap and body hard capsule containing two beige film-coated tablets and one white film-coated tablet

【Formulation】 Each capsule contains
Active ingredient : Montelukast sodium (EP) ····· 10.40mg (10mg as montelukast)
Levocetirizine dihydrochloride ····· 5.00mg
Additives (tar color) : FD&C Yellow No. 6
Excipient(animal derivative) : lactose hydrate (cow, milk)

【Pharmacodynamics】
Monterizine capsule falls into the pharmacotherapeutic groups as follow: Leukotriene receptor antagonist and Anti-histamine.
Monterizine capsule is a combination of a leukotriene receptor antagonist, Montelukast sodium, and a third generation antihistamine, Levocetirizine dihydrochloride. The former treats late phase of rhinitis and the latter effectively blocks the early phase responses of rhinitis. Taken together, combination of these ingredients has alleviation effect to rhinitis symptoms.

○ Mechanism of action
○ Montelukast
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.

○ Levocetirizine
Levocetirizine, the (R) enantiomer of cetirizine, is a potent and selective antagonist of peripheral H1-receptors.
Binding studies revealed that levocetirizine has high affinity for human H1-receptors (K_i = 3.2 nmol/l). Levocetirizine has an affinity 2-fold higher than that of cetirizine (K_i = 6.3 nmol/l). Levocetirizine dissociates from H1-receptors with a half-life of 115 ± 38 min.
After single administration, levocetirizine shows a receptor occupancy of 90% at 4 hours and 57% at 24 hours.

【Pharmacokinetics】
○ Montelukast
○ Absorption
Montelukast is rapidly absorbed following oral administration. After administration of the 10-mg film-coated tablet to fasted adults, 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.
○ 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 post-dose 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 CYP3A4, 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.
○ Excretion
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%).

○ Levocetirizine
○ Absorption
Levocetirizine is rapidly and extensively absorbed following oral administration. In adults, peak plasma concentrations are achieved 0.9 hour after administration of the oral tablet. The accumulation ratio following daily oral administration is 1.12 with steady state achieved after 2 days. Peak concentrations are typically 270 ng/mL and 308 ng/mL following a single and a repeated 5 mg once daily dose, respectively. Food had no effect on AUC of the levocetirizine tablet, but Tmax was delayed by about 1.25 hours and Cmax 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 oral solution is bioequivalent to a 5 mg dose of levocetirizine tablets. Following oral administration of a 5 mg dose of levocetirizine oral solution to healthy adult subjects, the mean peak plasma concentrations were achieved approximately 0.5 hour 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 hepatic drug metabolizing 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 CYP3A4 while aromatic oxidation involves multiple and/or unidentified CYP isoforms.
○ Excretion
The plasma half-life in adult healthy subjects was about 8 to 9 hours after administration of oral tablets and oral solution, and the mean oral total body clearance for levocetirizine was approximately 0.63 mL/kg/min. The major route of excretion of levocetirizine and its metabolites is via urine, accounting for a mean of 85.4% of the dose. Excretion via feces 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.

【Indication(s)】
Alleviation of symptoms of allergic rhinitis in patients with both asthma and perennial allergic rhinitis

【Dosage and Mode/Route of Administration】
This drug is administered to asthma patients with allergic rhinitis who require treatment with montelukast.
Adults and adolescents at the age of 15 or older: Administer orally one capsule, once a day, in the evening.
A patient concomitantly taking montelukast and levocetirizine can be switched to this drug for convenient medication (fixed-dose combination containing the same content of the individual active ingredients).

【Contraindication(s)】
1. This drug is contraindicated for use in the following patients.
1) Patient with hypersensitivity reactions to this drug or any of its components, hydroxyzine, or piperazine derivatives
2) Patient with renal failure (CL_{CR} < 10mL/min) or on hemodialysis
3) Pregnant woman, woman who might be pregnant, or lactating woman
4) This drug contains lactose, and therefore, must not be administered to patients with hereditary problems such as galactose intolerance, Lapp lactase deficiency or glucose-galactose malabsorption.

【Precautions】
1. Caution should be exercised if this drug is administered to the following patients.
1) Patient with renal impairment (a high blood level of levocetirizine may persist.)
2) Patient with hepatic impairment (a high blood level of levocetirizine may persist.)
3) The elderly (a high blood level of levocetirizine may persist.)
4) This drug contains Yellow 5 (Sunset Yellow FCF), and therefore, must be administered with caution to patients with hypersensitivity or history of allergy to this substance.

2. General precautions
○ Montelukast
(1) Montelukast is not indicated for the treatment of bronchospasm which occurs during acute asthmatic attack such as status asthmaticus.
(2) Patients should be instructed to carry appropriate emergency drugs. Montelukast treatment may be continued in the event of acute exacerbation of asthma.
(3) While inhaled corticosteroids may be tapered under the supervision of the physician, abrupt switching from inhaled or oral corticosteroids to montelukast should be avoided.
(4) Neuropsychiatric symptoms were reported in patients treated with montelukast. Causal relationship between these symptoms and montelukast is unknown. The physician should discuss these AEs with the patients or their guardians. The patients and their guardians should be instructed to notify the physician if these changes occur.
(5) Montelukast should not be used as monotherapy for the treatment of exercise-induced bronchospasm. For patients with exacerbated asthma after exercise, usual dose of inhaled β-agonist should continue to be used for prophylactic purpose, and fast-acting inhaled β-agonist may be used for emergency.
(6) Patients with hypersensitivity reactions to aspirin should not take aspirin or other non-steroidal anti-inflammatory drugs (NSAIDs)during treatment with montelukast. Although montelukast effectively improves airway functions during asthmatic attacks in patients with a history of hypersensitivity reations to aspirin, it is unknown whether montelukast can treat bronchoconstriction induced by aspirin or other NSAIDs in aspirin-sensitive patients with asthma.
(7) Eosinophilia
Asthma patients who are treated with montelukast may rarely experience systemic eosinophilia manifested by vasculitis, the same clinical symptom as Churg-Strauss syndrome. This symptom can be treated with systemic corticosteroids. Systemic eosinophilia is occasionally associated with reduced oral dose of corticosteroids. The physician should thoroughly monitor the patient for eosinophilia, vascular inflammatory rash, exacerbation of pulmonary symptoms, cardiac complications and/or neuropathy. Causal relationship between montelukast and these symptoms has not been established.

○ Levocetirizine
(1) Drowsiness, fatigue, and asthenia may occur after levocetirizine administration. The patient should pay more attention if he/she has to perform any activities requiring alertness such as driving and operating machinery.
(2) Co-administration of levocetirizine with alcohol or antidepressants should be avoided because this may result in a decrease in alertness or an additional decrease in central nervous system activities.
(3) As levocetirizine may increase the risk of urinary retention, caution should be exercised if this drug is administered to patients with predisposing factors of urinary retention (e.g., spinal cord disorder, prostatic hyperplasia).

3. Use in children
The safety and efficacy of this drug have not been established in chidren aged less than 15 years old.

4. Use in the elderly
The following information is based on the results of studies on each of the individual components, i.e., montelukast and levocetirizine.

○ Montelukast
Among all subjects in montelukast clinical studies, 3.5% were the elderly at the age of 65 years old or older; 0.4% were the elderly at the age of 75 years old or older. There was no overall difference in safety and efficacy, nor other clinical difference, between the elderly and younger patients. Howevere, potential increase in responses to montelukast in the elderly cannot be ruled out.

○ Levocetirizine
As levocetirizine is excreted primarily through the kidney, elevated blood concentrations may persist in the elderly who generally tend to have decreased renal function. For this reason, treatment should be initiated with care at a lower dose in the elderly; if any abnormality is observed, dose reduction or interruption should be implemented, and other appropriate actions should be taken.

5. Impact on clinical test results
As levocetirizine inhibits intradermal allergen tests, it is desirable not to administer this drug for 3-5 days before intradermal allergen tests.

6. Precautions for application
This drug is unstable to light. Do not open the drug until administration can be prepared.

【Pregnancy and Lactation】

1. Use in pregnant and lactating women and women of childbearing potential

1) When montelukast was orally administered to rats at a dose up to 400mg/kg/day (equivalent to 100-fold exposure of AUC of maximum oral daily dose in adults) and to rabbits at a dose up to 300mg/kg/day (equivalent to 110-fold exposure of AUC of maximum oral daily dose in adults), teratogenicity was not observed. Montelukast was reported to cross the placenta after oral administration to rats and rabbits. However, no controlled studies have been conducted in pregnant women, and results of reproductive toxicity studies in animals are not always consistent with the results in humans. In addition, teratogenicity was not reported in animal experiments on levocetirizine. Nevertheless, as relevant research is still insufficient, this drug should not be administered to pregnant women.
2) In the worldwide post-marketing surveillance, in a rare case, congenital amelia was reported in the children of women treated with montelukast during pregnancy. Most of these women were treated with other antiasthmatics during pregnancy, and causal relationship between this AE and montelukast has not been established.
3) The impact of levocetirizine on fertility has not been studied in animals.
4) In rats, montelukast was excreted in milk. Although it is unknown whether montelukast is secreted into human milk, this drug should not be administered to lactating women because many drugs are excreted in milk.

【Interactions】

1) There were no clinically significant pharmacokinetic interractions between montelukast and levocetirizine, the active ingredients of this drug, upon co-administration.
2) No studies have been conducted to investigate interractions between montelukast/levocetirizine fixed-combination therapy and other drugs. Based on the label of each component, information on drug interactions is as follows.

○ Montelukast

(1) There were no reports of increased AEs upon co-administration of montelukast with other drugs for the prevention and long-term treatment of asthma. In drug interaction studies, usual dose of montelukast had no clincially significant impact on the pharmacokinetics of the following drugs:
theophylline, prednisone, prednisolone, oral contraceptives (norethisterone 1mg/ etinyl estradiol 35ug), terfenadine, digoxin, warfarin
(2) Although no drug interaction studies were additionally conducted, no clinically meaningful interactions were observed when montelukast was co-administered with a wide range of commonly prescribed drugs in clinical studies. Drugs co-administered in clinical studies include thyroid hormone, sedative hypnotics, NSAIDs, benzodiazepine, decongestants, etc.
(3) Phenobarbital, a liver enzyme inducer, reduces montelukast AUC by approximately 40% after one dose of montelukast 10mg
Although montelukast dose adjustment is not required, it is desirable to implement appropriate clinical monitoring when montelukast is co-administered with strong CYP-450 inducers such as phenobarbital, rifampicin, or phenytoin.
(4) In an *in vitro* study, montelukast was found to be an inhibitor of CYP2C8. However, in a clinical study on interactions between montelukast and rosiglitazone (a representative drug primarily metabolied by CYP2C8), montelukast did not inhibit CYP2C8 *in vivo*.
Based on this, montelukast is thought not to inhibit metabolism of drugs primarily metabolized by CYP2C8 (e.g., paclitaxel, rosiglitazone, repaglinide).
(5) An *in vitro* study demonstrated that montelukast was a substrate of CYP2C8, CYP2C9, and CYP3A4. In a clinical study to examine interactions between montelukast and gemfibrozil (inhibitor of CYP2C8 and CYP2C9), gemfibrozil increased systemic exposure of montelukast by 4.4 folds. In addition, when itraconazole, a strong CYP3A4 inhibitor, was co-administered with gemfibrozil and montelukast, there was no further increase in systemic exposure of montelukast. Results from the safety study which used higher doses than the approved dose of 10mg for adults (200mg/day, 22 weeks, approximately 1 week of treatment at an increased dose up to 900mg/day in adults) indicated no clinically significant drug interactions, based on which the impact of gemfibrozil on systemic exposure of montelukast is considered to be of no clinical significance. Therefore, dose adjustment for montelukast is not necessary upon co-administration with gemfibrozil. Based on *in vitro* results, montelukast is thought to have no clinically significant interactions with other known CYP2C8 inhibitors such as trimethoprim. Additionally, co-administration of only montelukast and itraconazole did not result in a significant increase in systemic exposure of montelukast.

○ Levocetirizine

(1) As with other antihistamines, this drug should not be co-administered with excessive alcohol.
(2) Cetirizine, a lacemate (optical isomers), does not appear to increase the impact of alcohol (0.5g/L blood level), co-administration of levocetirizine with alcohol or other CNS inhibitors may result in an additional decrease in alertness and cause performance impairment.
(3) Although no studies have been conducted to anlayze interactions with levocetirizine, some studies were conducted to analyze interactions with the isomer, cetirizine; there were no interactions with antipyrine, pseudoephedrine, erythromycin, azithromycin, ketoconazole, or cimetidine. A high-dose study with theophylline (400mg/day) showed a slight decrease (16%) in cetirizine clearance.
(4) Ritonavir resulted in an increase in plasma AUC of cetirizine by 42% as well as an increase in half-life (53%) and a decrease in clearance (29%) of cetirizine. There was a slight change in the pharmacokinetics of ritonavir (11% decrease) upon co-administration with cetirizine.
(5) When the drug is administered with food, drug absorpation rate deminishes, but the total amount of drug absorption does not decline.

【Adverse Reactions】

1) Adolescents aged 15 or older and adults who have asthma with symptoms of perennial allergic rhinitis
The safety of this drug was assessed in a controlled clinical study of montelukast in 224 asthma patients with symptoms of perennial allergic rhinitis who were adolescents aged 15 or older or adults. During the 4-week treatment period, commonly reported adverse events [AEs] among those treated with this drug were upper respiratory infection (3.51%), nasopharyngitis (2.63%), gastrointestinal disturbance (1.75%), tonsillitis (1.75%). Hydrodipsomania and prolonged QT on ECG, 1 event each, were adverse drug reactions (ADRs) related to this drug, both of which were mild in severity. The following table summarizes the frequency of AEs that were reported in ≥1% of all 224 subjects (110 in montelukast group and 114 in this drug group)or at a higher rate in this drug group than in montelukast group in this study, regardless of causal relationship.

AE by system organ class	Montelukast (n=110) N(%)	This drug (n=114) N(%)	Total (n=224) N(%)
Gastrointestinal disorders			
dyspepsia	0(0%)	1(0.88%)	1(0.45%)
gastritis	0(0%)	1(0.88%)	1(0.45%)
gastrointestinal disturbance	0(0%)	2(1.75%)	2(0.89%)
gastroesophageal reflux disease	0(0%)	1(0.88%)	1(0.45%)
irritable bowel syndrome	0(0%)	1(0.88%)	1(0.45%)
colonic polyp	0(0%)	1(0.88%)	1(0.45%)
Generalised disorders and treatment site conditions			
facial edema	0(0%)	1(0.88%)	1(0.45%)
pain	0(0%)	1(0.88%)	1(0.45%)
hydrodipsomania	0(0%)	1(0.88%)	1(0.45%)
Infections			
nasopharyngitis	0(0%)	3(2.63%)	3(1.34%)
pharyngitis	0(0%)	1(0.88%)	1(0.45%)
nasosinusitis	0(0%)	1(0.88%)	1(0.45%)
tonsillitis	1(0.91%)	2(1.75%)	3(1.34%)
upper respiratory infection	4(3.64%)	4(3.51%)	8(3.57%)
Investigations			
prolonged QT on ECG	0(0%)	1(0.88%)	1(0.45%)
Metabolism and nutrition disorders			
hypercholesterolemia	0(0%)	1(0.88%)	1(0.45%)
Benign, malignant, and unclassified tumors			
gastric cancer	0(0%)	1(0.88%)	1(0.45%)
Neurological disorders			
Alzheimer's dementia	0(0%)	1(0.88%)	1(0.45%)
lacunar infarction	0(0%)	1(0.88%)	1(0.45%)
Psychiatric disorders			
insomnia	0(0%)	1(0.88%)	1(0.45%)
Respiratory disorders			
dyspnea	0(0%)	1(0.88%)	1(0.45%)

2) Adolescents aged 15 or older and adults who have perennial allergic rhinitis
The safety of this drug was assessed in a clinical study in which combination therapy of montelukast and levocetirizine was compared with monotherapy of each individual component in 283 patients with perennial allergic rhinitis who were adolescents aged 15 or older or adults. During the 4-week treatment period, commonly reported AEs in the combination therapy group were upper respiratory infection (2.20%), headache (2.20%), dysmenorrhea (2.20%), dry nose (2.20%), urticaria (2.20%), ventricular extrasystole (1.10%), blepharospasm (1.10%), cheilitis (1.10%), diarrhea (1.10%), dry mouth (1.10%), hematochezia (1.10%), nasopharyngitis (1.10%), tonsillitis (1.10%), ALT elevated (1.10%), AST elevated (1.10%), asthma (1.10%), oropharyneal pain (1.10%), and skin lesions (1.10%). ADRs related to this drug included 1 event of dry mouth, 1 event of alanine aminotransferase (ALT) elevated, 1 event of aspartate aminotransferase (AST) elevated, and 2 events of dry nose, all of which were mild in severity. The following table summarizes the frequency of AEs that were reported in ≥1% of all 283 subjects (98 in montelukast group, 94 in levocetirizine group, and 91 in combination group) or at a higher rate in the combination group than in each monotherapy group in this study, regardless of causal relationship.

AE by system organ class	Montelukast (n=98) N(%)	Levocetirizine (n=94) N(%)	Combination (n=91) N(%)	Total (n=283) N(%)
Cardiac disorders				
ventricular extrasystole	0(0%)	0(0%)	1(1.10%)	1(0.35%)
Eye disorders				
blepharospasm	0(0%)	0(0%)	1(1.10%)	1(0.35%)
Gastrointestinal disorders				
cheilitis	0(0%)	0(0%)	1(1.10%)	1(0.35%)
diarrhea	1(1.02%)	0(0%)	1(1.10%)	2(0.71%)
dry mouth	0(0%)	0(0%)	1(1.10%)	1(0.35%)
hematochezia	0(0%)	0(0%)	1(1.10%)	1(0.35%)
Infections				
nasopharyngitis	1(1.02%)	1(1.06%)	1(1.10%)	3(1.06%)

tonsillitis	0(0%)	0(0%)	1(1.10%)	1(0.35%)
upper respiratory infection	2(2.04%)	5(5.32%)	2(2.20%)	9(3.18%)
Investigations				
ALT elevated	1(1.02%)	1(1.06%)	1(1.10%)	3(1.06%)
AST elevated	0(0%)	1(1.06%)	1(1.10%)	2(0.71%)
Neurological disorders				
headache	0(0%)	2(2.13%)	2(2.20%)	4(1.41%)
drowsiness	2(2.04%)	3(3.19%)	0(0%)	5(1.77%)
Reproductive system and breast disorders				
dysmenorrhea	2(2.04%)	0(0%)	2(2.20%)	4(1.41%)
Respiratory disorders				
asthma	0(0%)	0(0%)	1(1.10%)	1(0.35%)
dry nose	0(0%)	0(0%)	2(2.20%)	2(0.71%)
oropharyneal pain	1(1.02%)	0(0%)	1(1.10%)	2(0.71%)
Skin and subcutaneous tissue disorders				
skin lesions	0(0%)	0(0%)	1(1.10%)	1(0.35%)
urticaria	3(3.06%)	0(0%)	2(2.20%)	5(1.77%)

【Overdose and Treatment】

The following information is based on the results of studies on each of the individual components, i.e., montelukast and levocetirizine.

o Montelukast

(1) When a single dose of montelukast was orally administered to mice at at dose up to 5,000mg/kg (equivalent to 335-fold exposure of AUC of maximum oral daily dose in adults) and to rats at a dose up to 5,000mg/kg (equivalent to 230-fold exposure of AUC of maximum oral daily dose in adults), no animals died.

(2) There is no specific treatment of montelukast overdose. When montelukast was administered to patients at a dose up to 200mg/day for 22 weeks in a long-term asthma study and at a dose up to 900mg/day for 1 week in a short-term study, no clinically significant AEs were observed. In the event of overdose, it is reasonable to provide general symptomatic treatment (e.g., remove unabsorbed drug from the gastrointestinal system, implement monitoring, and if necessary, provide supportive care).

(3) In post-marketing surveillance and clinical studies, montelukast overdose up to 1,000mg was reported in adults and children, but the observed clinical symptoms and clinical test results did not differ from the safety information in adult and pediatric patients. The most commonly reported AEs were abdominal pain, drowsiness, thirst, headache, vomiting, and psychomotor hyperactivity, which were consistent with safety information on this drug.

(4) It is unknown whether this drug can be removed by peritoneal dialysis or hemodialysis.

o Levocetirizine

(1) Overdose results in drowsiness in adults, and agitation and restlessness are followed by drowsiness in children.

(2) There is no specific antidote to levocetirizine; overdose should be treated with symptomatic therapy or supportive care. Provide gastric lavage for short-term overdose.

(3) Levocetirizine is not effectively removed by hemodialysis.

【Storage Condition(s)】

Store at temperatures not exceeding 30℃.

【Package Unit】

Alu/Alu Blister Pack x 10's (Box of 30's)

【Instructions and Special Precautions for Handling and Disposal】

1) Keep out of reach of children.
2) Note that keeping the drug in another container instead of its original container may cause an accident and is also undesirable for quality maintenance.

【Others】

Refer to the label of each component of this drug.

【Product Information Center】

Hanmi Pharmaceutical Co., Ltd.
Customer service: 080-916-9000 (toll-free)

【Caution Statement】

Foods, Drugs, Devices and Cosmectics Act prohibits dispensing without prescription.
※ Seek medical attention immediately at the first sign of any adverse drug reaction.
※ This product can be compensated according to the guidelines for consumer dispute resolution, Notification of Fair Trade Commission.
(If the product is expired, spoiled, deteriorated, contaminated, or damaged at the time of purchase, please ask for the exchange of the product or get a refund from the pharmacy or retailer of purchase.)
※ Do not administer expired product.

※ Cautions

1. Do not use this product for any purpose other than prescribed symptoms and prescribed patients.
2. Administer this drug with sufficient water.
3. Once the product is opened, if there are fillers, remove them completely before using the drug. Once the product is opened, keep the product sealed during storage. (Do not eat silica gel (desiccant).

【ADR Reporting Statement】

For suspected adverse drug reactions, report to the FDA: www.fda.gov.ph

Care should be taken to avoid any injury by packages (container, case) while opening or handling the product.

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※ Please carefully read the package insert before using the drug, and keep the package insert with the drug.