Aireez®

(Montelukast Sodium USP)

ایئریز

COMPOSITION

Aireez 4 mg Chewable Tablet
Each chewable tablet contains: Montelukast ……..4 mg (as Montelukast sodium USP)
Aireez 4 mg Sachet
Each sachet of oral granules contains: Montelukast …..4 mg (as Montelukast sodium USP)
Aireez 5 mg Chewable Tablet
Each chewable tablet contains: Montelukast ……..5 mg (as Montelukast sodium USP)
Aireez 10 mg Tablet
Each film-coated tablet contains: Montelukast ……10 mg (as Montelukast sodium USP)
(USP Specs.)

WARNING: SERIOUS NEUROPSYCHIATRIC EVENTS
Serious neuropsychiatric (NP) events have been reported with the use of AIREEZ. Monitor for neuropsychiatric symptoms in patients taking AIREEZ and discontinue if neuropsychiatric symptoms occur. Because the benefits of AIREEZ may not outweigh the potential risk of neuropsychiatric symptoms in patients with allergic rhinitis, reserve use for patients who have an inadequate response or intolerance to alternative therapies. [See WARNINGS AND PRECAUTIONS].

DESCRIPTION

Montelukast sodium is selective leukotriene receptor antagonist which inhibits the cysteine leukotriene CysLT 1 receptor. Montelukast sodium is described chemically as [R-(E)]-1-[[[1-[3-[2-(7-chloro-2-quinolinyl) ethenyl]phenyl]-3-[2-(1-hydroxy-1-methylethyl)phenyl] propyl]thio] methyl]cyclopropaneacetic acid, monosodium salt. The empirical formula is $C_{35}H_{35}C_1NNaO_3S$, and its molecular weight is 608.18.

CLINICAL PHARMACOLOGY

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). Leukotrienes (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.
Montelukast is an orally active compound which binds with high affinity and selectivity to the CysLT1 receptor. Montelukast inhibits physiologic actions of LTD4 at the CysLT1 receptor without any agonist activity. As a result, bronchoconstriction is inhibited with decreased airway and blood eosinophils leading to improved control over asthma and allergic rhinitis.

Pharmacokinetics
Absorption
Montelukast is rapidly absorbed following oral administration. For the 10 mg film-coated tablet, the mean peak plasma concentration (Cmax) is achieved 3 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.
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.
In paediatric patients 6 months to 2 years of age, Cmax is achieved 2 hours after administration of the 4 mg granules formulation. Cmax is nearly 2-fold greater than in adults receiving a 10 mg tablet. The co-administration of high-fat standard meal with the granule formulation did not have a clinically meaningful effect on the pharmacokinetics of montelukast as determined by AUC (1191.8 vs 1148.5 ng.hr/mL with and without a high-fat standard meal, respectively)

Distribution
Montelukast is more than 99% bound to plasma proteins. The steady-state volume of distribution of montelukast averages 8-11 litres.

Metabolism
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. 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 radiolabelled 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. In several studies, the mean plasma half-life of montelukast ranged from 2.7 to 5.5 hours in healthy young adults.

INDICATIONS

Asthma
AIREEZ is indicated for the prophylaxis and chronic treatment of asthma in adults and pediatric patients 12 months of age and older.

Exercise-Induced Bronchoconstriction (EIB)
AIREEZ is indicated for prevention of exercise-induced bronchoconstriction (EIB) in patients 6 years of age and older.

Allergic Rhinitis
AIREEZ is indicated for the relief of symptoms of seasonal allergic rhinitis in patients 2 years of age and older and for perennial allergic rhinitis in patients 6 months of age and older. Because the benefits of AIREEZ may not outweigh the risk of neuropsychiatric symptoms in patients with allergic rhinitis, reserve use for patients who have an inadequate response or intolerance to alternative therapies.

DOSAGE AND ADMINISTRATION

General considerations
The therapeutic effect of Aireez on parameters of asthma control occurs within one day. Aireez may be taken with or without food. Patients should be advised to continue taking Aireez even if their asthma is under control, as well as during periods of worsening asthma.
Asthma
AIREEZ should be taken once daily in the evening. The following doses are recommended:
For adults and adolescents 15 years of age and older: one 10mg tablet.
For pediatric patients 6 to 14 years of age: one 5-mg chewable tablet.
For pediatric patients 2 to 5 years of age: one 4-mg chewable tablet or one sachet of 4-mg oral granules.
For pediatric patients 12 to 23 months of age: one sachet of 4-mg oral granules.

Safety and effectiveness in pediatric patients less than 12 months of age with asthma have not been established.

Exercise- Induced Bronchoconstriction (EIB)
For prevention of EIB, a single dose of AIREEZ should be taken at least 2 hours before exercise.
The following doses are recommended:
For adults and adolescents 15 years of age and older: one 10-mg tablet.
For pediatric patients 6 to 14 years of age: one 5-mg chewable tablet.
An additional dose of AIREEZ should not be taken within 24 hours of a previous dose. Patients already taking AIREEZ daily for another indication (including chronic asthma) should not take an additional dose to prevent EIB. All patients should have available for rescue a short-acting β-agonist. Safety and efficacy in patients younger than 6 years of age have not been established. Daily administration of AIREEZ for the chronic treatment of asthma has not been established to prevent acute episodes of EIB.

Allergic Rhinitis
For allergic rhinitis, Aireez should be taken once daily. Efficacy was demonstrated for seasonal allergic rhinitis when montelukast was administered in the morning or the evening without regard to time of food ingestion. The time of administration may be individualized to suit patient needs.

The following doses for the treatment of symptoms of seasonal allergic rhinitis are recommended:
For adults and adolescents 15 years of age and older: one 10-mg tablet.
For pediatric patients 6 to 14 years of age: one 5-mg chewable tablet.
For pediatric patients 2 to 5 years of age: one 4-mg chewable tablet or one sachet of 4-mg oral granules.
Safety and effectiveness in pediatric patients younger than 2 years of age with seasonal allergic rhinitis have not been established.

The following doses for the treatment of symptoms of perennial allergic rhinitis are recommended:
For adults and adolescents 15 years of age and older: one 10-mg tablet.
For pediatric patients 6 to 14 years of age: one 5-mg chewable tablet.
For pediatric patients 2 to 5 years of age: one 4-mg chewable tablet or one sachet of 4-mg oral granules.
For pediatric patients 6 to 23 months of age: one sachet of 4-mg oral granules.
Safety and effectiveness in pediatric patients younger than 6 months of age with perennial allergic rhinitis have not been established.

Asthma and Allergic Rhinitis
Patients with both asthma and allergic rhinitis should take only one Aireez dose daily in the evening.

Dosing Consideration in Special populations

Elderly
No dosage adjustment is necessary for the elderly.

Hepatic impairment
No dosage adjustment is necessary for patients with mild to moderate hepatic insufficiency. There are no data on the pharmacokinetics of montelukast in patients with severe hepatic insufficiency.

Renal impairment
No dose adjustment is anticipated to be necessary in patients with renal impairment.

Administration instructions for Aireez 4mg sachet (oral granules)
AIREEZ 4 mg sachet (oral) granules can be administered either directly in the mouth, dissolved in 1 teaspoonful (5 mL) of cold or room temperature baby formula or breast milk or mixed with a spoonful of cold or room temperature soft food (only applesauce, ice cream, carrots and rice should be used). The sachet should not be opened until ready to use. After opening the sachet, the full dose (with or without mixing with baby formula, breast milk, or food) must be administered within 15 minutes. If mixed with baby formula, breast milk or food, AIREEZ granules must not be stored for future use. Discard any unused portion. Aireez oral granules are not intended to be dissolved in any liquid other than baby formula or breast milk for administration. AIREEZ granules are not intended to be dissolved in liquid for administration other than baby formula or breast milk. However, liquids may be taken subsequent to administration. AIREEZ granules can be administered without regard to the timing of food ingestion.

CONTRAINDICATIONS

Hypersensitivity to montelukast

WARNINGS AND PRECAUTIONS

Neuropsychiatric Events
Serious neuropsychiatric (NP) events have been reported with use of AIREEZ. These postmarketing reports have been highly variable and included, but were not limited to, agitation, aggressive behavior or hostility, anxiousness, depression, disorientation, disturbance in attention, dream abnormalities, dysphemia (stuttering), hallucinations, insomnia, irritability, memory impairment, obsessive-compulsive symptoms, restlessness, somnambulism, suicidal thoughts and behavior (including suicide), tic, and tremor. NP events have been reported in adult, adolescent, and pediatric patients with and without a previous history of psychiatric disorder. NP events have been reported mostly during AIREEZ treatment, but some were reported after AIREEZ discontinuation. Because of the risk of NP events, the benefits of AIREEZ may not outweigh the risks in some patients, particularly when the symptoms of disease may be mild and adequately treated with alternative therapies. Reserve use of AIREEZ for patients with allergic rhinitis who have an inadequate response or intolerance to alternative therapies. In patients with asthma or exercise-induced bronchoconstriction, consider the benefits and risks before prescribing AIREEZ. Discuss the benefits and risks of AIREEZ use with patients and caregivers when

prescribing AIREEZ. Advise patients and/or caregivers to be alert for changes in behavior or for new NP symptoms when taking AIREEZ. If changes in behavior are observed, or if new NP symptoms or suicidal thoughts and/or behavior occur, advise patients to discontinue AIREEZ and contact a healthcare provider immediately. In many cases, symptoms resolved after stopping AIREEZ therapy; however, in some cases symptoms persisted after discontinuation of AIREEZ. Therefore, continue to monitor and provide supportive care until symptoms resolve. Re-evaluate the benefits and risks of restarting treatment with AIREEZ if such events occur.

Acute Asthma
Montelukast is not indicated for use in the reversal of bronchospasm in acute asthma attacks, including status asthmaticus. Patients should be advised to have appropriate rescue medication available. Therapy with Montelukast can be continued during acute exacerbations of asthma. Patients who have exacerbations of asthma after exercise should have available for rescue a short-acting inhaled β-agonist.

Concomitant Corticosteroid Use
While the dose of inhaled corticosteroid may be reduced gradually under medical supervision, Montelukast should not be abruptly substituted for inhaled or oral corticosteroids.

Aspirin Sensitivity
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 non-steroidal anti- Inflammatory drugs in aspirin-sensitive asthmatic patients.

Eosinophilic Conditions
Patients with asthma on therapy with 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 events have been sometimes associated with the reduction of oral corticosteroid therapy. Physicians should be alert to eosinophilia, vasculitic rash, worsening pulmonary symptoms, cardiac complications, and/or neuropathy presenting in their patients. A causal association between Montelukast and these underlying conditions has not been established.

Phenylketonuria
Phenylketonuric patients and their care givers should be informed that the 4-mg and 5-mg chewable tablets and Aireez sachet (oral granules) contain aspartame, and these should not be used for such patients.

Effects on ability to drive and use machines
Montelukast is not expected to affect a patient's ability to drive a car or operate machinery. However, in very rare cases, individuals have reported drowsiness or dizziness.

ADVERSE REACTIONS

Infections and infestations
Very Common: upper respiratory infection
Blood and lymphatic system disorders
Rare: increased bleeding tendency
Very rare: Thrombocytopenia
Immune system disorder
Uncommon: hypersensitivity reactions including anaphylaxis
Very Rare: hepatic eosinophilic infiltration.
Psychiatric disorders
Uncommon: dream abnormalities including nightmares, insomnia, somnambulism, irritability, anxiety, restlessness, agitation including aggressive behaviour or hostility, depression, psychomotor hyperactivity (including irritability, restlessness, and tremor).
Rare: disturbance in attention, memory impairment, tic.
Very Rare: hallucinations, disorientation, suicidal thinking and behaviour (suicidality) , dysphemia, obsessive-compulsive symptoms.
Nervous system disorder
Uncommon: dizziness, drowsiness paraesthesia/hypoesthesia, seizure.
Cardiac disorders
Rare: palpitations
Respiratory, thoracic and mediastinal disorders
Uncommon: epistaxis.
Very Rare: Churg-Strauss Syndrome, pulmonary eosinophilia
Gastrointestinal disorders
Common: diarrhoea, nausea, vomiting
Uncommon: dry mouth, dyspepsia.
Hepatobiliary disorders
Common: elevated levels of serum transaminases (ALT, AST).
Very Rare: hepatitis (including cholestatic, hepatocellular, and mixed-pattern liver injury).
Skin and subcutaneous tissue disorders
Common: rash
Uncommon: bruising, urticaria, pruritus
Rare: angioedema
Very Rare: erythema nodosum, erythema multiforme.
Musculoskeletal, connective tissue and bone disorders
Uncommon: arthralgia, myalgia including muscle cramps
General disorders and administration site conditions
Common: pyrexia
Uncommon: asthenia, fatigue, malaise, edema

Other adverse reactions reported commonly with Montelukast in specific age groups are given below:
Adults & Adolescents 15 years and older: headache, abdominal pain
Pediatric patients 6-14 years of age: headache
Pediatric patients 2-5 years of age: abdominal pain, thirst
Pediatric patients 6 months - 2 years of age: hyperkinesia, asthma, diarrhea, eczematous dermatitis, rash

DRUG INTERACTIONS
• Montelukast may be administered with other therapies routinely used in the prophylaxis and chronic treatment of asthma. The recommended dose of montelukast did not have clinically important effects on the pharmacokinetics of the following drugs: theophylline, prednisone, prednisolone, oral contraceptives (ethinyl estradiol/ norethindrone), 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 metabolized 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 shown that montelukast is a potent inhibitor of CYP 2C8. However, data from a clinical drug-drug interaction study demonstrated that montelukast does not inhibit CYP 2C8 in vivo. Therefore, montelukast is not anticipated to markedly alter the metabolism of drugs metabolized by this enzyme (e.g., paclitaxel, rosiglitazone, and repaglinide.)
• In vitro studies have shown 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 SPECIAL POPULATIONS

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.

Nursing Mothers
Studies in rats have shown that montelukast is excreted in milk. 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. Montelukast 10 mg film-coated tablets may be used in breast-feeding only if it is considered to be clearly essential

Geriatric Use
No dosage adjustment in the elderly is required. The pharmacokinetic profile and the oral bioavailability of a single 10-mg oral dose of montelukast is similar in elderly and younger adults. The plasma half-life of montelukast is slightly longer in the elderly.

Hepatic Insufficiency
No dosage adjustment is required in patients with mild-to-moderate hepatic insufficiency. No data is available for severe hepatic insufficiency.

Renal Insufficiency
No dosage adjustment is recommended in patients with renal insufficiency.

OVERDOSAGE
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 1,000 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.

Treatment
No specific information is available on the treatment of overdose with montelukast. In the event of overdose, it is reasonable to employ the usual supportive measures; e.g., remove unabsorbed material from the gastrointestinal tract, employ clinical monitoring, and institute supportive therapy, if required. It is not known whether montelukast is dialyzable by peritoneal- or haemo-dialysis.

PRESENTATION
Aireez 4mg: Pack of 14 chewable tablets
Aireez 4mg: Pack of 14 sachets
Aireez 5mg: Pack of 30 chewable tablets
Aireez 10mg: Pack of 30 film coated tablets

INSTRUCTIONS
Use as advised by the physician.
Keep all medicines out of the reach of children.
To be sold on the prescription of a registered medical practitioner only.
Protect from light, heat and moisture.
Store below 30°C.
For suspected adverse drug reaction, email us at reports@pharmevo.biz

For more information on our products
call PharmAssist helpline 0800-82222
Monday to Friday 9:00 am to 6:00 pm
or email us at : pharmassist@pharmevo.biz

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