APPROVED PACKAGE INSERT:

BelAIR 4 & 5 (chewable tablets)

SCHEDULING STATUS:

S3

PROPRIETARY NAMES (AND DOSAGE FORMS)

BelAIR 4 (chewable tablets)

BelAIR 5 (chewable tablets)

COMPOSITION

BelAIR 4: Each chewable tablet contains 4 mg montelukast as montelukast sodium.

BelAIR 5: Each chewable tablet contains 5 mg montelukast as montelukast sodium.

The inactive ingredients are: aspartame, cherry flavour, croscarmellose sodium, hydroxypropyl cellulose, iron oxide red, magnesium stearate, mannitol and microcrystalline cellulose

PHARMACOLOGICAL CLASSIFICATION

A 10.2.2 Other anti-asthmatics (Leukotriene receptor antagonist).

PHARMACOLOGICAL ACTION

Pharmacodynamics:

The cysteinyl leukotrienes (LTC_4, LTD_4, LTE_4) are products of arachidonic acid metabolism that are released from various cells, including mast cells and eosinophils. They bind to cysteinyl leukotriene receptors (CysLT) found in the human airway.

Binding of cysteinyl leukotrienes to leukotriene receptors has been correlated with the pathophysiology of asthma, including airway oedema, smooth muscle contraction, and altered cellular activity associated with the inflammatory process, factors that contribute to the signs and symptoms of asthma.

Montelukast binding to the $CysLT_1$ receptor is high affinity and selective, preferring the $CysLT_1$ receptor to other pharmacologically important airway receptors, such as the prostanoid, cholinergic, or beta-adrenergic receptor. Montelukast inhibits physiologic actions of LTD_4 at the $CysLT_1$ receptors, without any antagonist activity.

Pharmacokinetics

Absorption

Montelukast is absorbed rapidly following oral administration.

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

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.

Distribution

Montelukast is highly protein bound (99 %). The steady-state volume of distribution averages 8 to 11 litres.

Metabolism

Montelukast is metabolised extensively in the liver by cytochrome P450 3A4, and 2C9. Plasma concentrations of montelukast metabolites are undetectable at steady state following therapeutic doses in adults and paediatric patients. Therapeutic plasma concentrations of montelukast do not inhibit cytochromes P450 3A4, 2C9, 1A2, 2A6, 2C19, or 2D6.

Elimination

The half-life of montelukast is between approximately 3 and 6 hours. The duration of action of a single dose is 24 hours.

Montelukast is excreted principally in the faeces via bile (86 %), with less than 0, 2 % eliminated via the renal route. Plasma clearance averages 45 ml per minute in healthy adults. It is not known whether montelukast is removable by peritoneal dialysis or haemodialysis.

The pharmocokinetics of montelukast are nearly linear at doses of up to 50 mg. No difference in pharmacokinetics was found between dosing in the morning and evening.

Special Populations

Hepatic and renal impairment

Metabolism was reduced and the elimination half-life prolonged in patients with mild to moderate hepatic impairment and those with clinical evidence of cirrhosis. No clinical data is available in patients with severe hepatic insufficiency (Child-Pugh score greater than 9).

No dosage adjustment is required in patients with mild to moderate hepatic insufficiency.

No dosage adjustment is expected to be necessary in patients with renal impairment.

Elderly

The pharmacokinetics and oral bioavailability of montelukast are similar in elderly and younger adults. The plasma half-life is slightly longer in the elderly, but no dosage adjustment is necessary.

INDICATIONS

BelAIR is indicated for the prophylaxis and chronic treatment of atopic asthma, as follows:

- **BelAIR 4** chewable tablets in paediatric patients 2 to 5 years of age;
- **BelAIR 5** chewable tablets in paediatric patients over 6 years of age.

CONTRA-INDICATIONS

Hypersensitivity to montelukast or any of the excipients of **BelAIR.**

Pregnancy and lactation.

BelAIR 4 should not be given to children less than 2 years of age as safety and efficacy has not been demonstrated.

BelAIR 5 should not be given to children less than 6 years of age as safety and efficacy has not been demonstrated.

WARNINGS

BelAIR is not indicated in the reversal of bronchospasm in acute asthma attacks, including status asthmaticus. See SPECIAL PRECAUTIONS. The efficacy of **BelAIR** has not been established for the treatment of acute asthma attacks.

INTERACTIONS

Monitoring is recommended during concurrent use with potent cytochrome P450 enzyme inducers, such as phenytoin, phenobarbital and rifampicin, due to the potential for interactions.

Concurrent use with phenobarbital results in significant decreases (approximately 40 %) in the area under the curve (AUC) for **BelAIR**, as a result of induction of hepatic metabolism; however, no dosage adjustment is necessary.

Studies have not found that **BelAIR** causes significant changes in the pharmacokinetics of theophylline, warfarin, immunoreactive digoxin, fexofenadine, oral contraceptives containing norethindrone and ethinyl oestradiol, prednisone or prednisolone.

PREGNANCY AND LACTATION

BelAIR should not be used during pregnancy and lactation. It is not known whether montelukast is excreted in breast milk.

DOSAGE AND DIRECTIONS FOR USE

BelAIR should be taken once daily in the evening with or without food. Patients should be advised of the importance of compliance with therapy and using **BelAIR** every day even during symptom-free periods, as well as not to discontinue treatment without discussing it with their medical practitioners.

BelAIR 4 mg Chewable tablet

Paediatric patients 2 to 5 years of age: One chewable tablet daily.

BelAIR 5 mg Chewable tablet

Paediatric patients 6 to 14 years of age: One chewable tablet daily.

No dosage adjustment is necessary for patients with mild to moderate hepatic impairment, renal impairment, the elderly or patients of either gender.

BELAIR can be added to a patient's existing treatment regimen.

SIDE EFFECTS AND SPECIAL PRECAUTIONS

Side Effects

The following undesirable effects have been observed during treatment with **BelAIR**:

Blood and lymphatic system disorders

The following side-effects have been reported and frequencies are unknown:

Increased bleeding tendency, agranulocytocis.

Systemic eosinophilia has occurred in patients taking **BelAIR**, sometimes presenting with the clinical features of vasculitis consistent with Churg-Strauss syndrome, a

condition that is often treated with systemic corticosteroid therapy. (see **SPECIAL PRECAUTIONS – Eosinophilic Conditions**).

Immune system disorders

The following side-effects have been reported and frequencies are unknown:

Hypersensitivity reactions including anaphylaxis, angioedema, hepatic eosinophilic infiltration.

Psychiatric disorders

The following side-effects have been reported and frequencies are unknown:

Abnormal dreams and hallucinations, agitation including aggressive behaviour, anxiousness, depression, insomnia, irritability, restlessness, suicidal thinking and behaviour (suicidality), tremor**.**

Nervous system disorders

Frequent: Headache, dizziness, insomnia.

The following side-effects have been reported and frequencies are unknown:

Drowsiness, paraesthesia/hypoesthesia, seizure.

Cardiac disorders

Less frequent: Palpitations, chest pain.

Respiratory, thoracic and mediastinal disorders

Frequent: Congestion (nasal), cough, influenza.

The following have been reported and frequencies are unknown:

Epistaxis.

Gastro-intestinal disorders

Frequent: Dyspepsia, gastroenteritis (infectious), pain (dental), diarrhoea, thirst, abdominal pain.

The following side-effects have been reported and frequencies are unknown:

Nausea, vomiting, diarrhoea, dyspepsia.

Hepato-biliary disorders

Less frequent: Cholestatic hepatitis, increased alanine aminotransferase (ALT) and aspartate aminotransferase (AST).

Skin and subcutaneous tissue disorders

Frequent: Rash.

The following side-effects have been reported and frequencies are unknown:

Pruritus, urticaria, erythema nodosum, bruising.

Musculoskeletal, connective tissue and bone disorders

The following side-effects have been reported and frequencies are unknown:

Arthralgia, myalgia including muscle cramps.

Renal and urinary disorders

Frequent: Pyuria.

Ear and labyrinth disorders

Frequent: Vertigo.

General disorders and administration site disorders

Frequent: Asthenia/fatigue, trauma.

The following side-effects have been reported and frequencies are unknown:

Oedema, pyrexia and increased sweating.

Investigations

Laboratory value alterations

Frequent: Serum values of alanine aminotransferase (ALT[SGPT]) and aspartate aminotransferase (AST[SGOT]) may infrequently be increased.

Mean peripheral eosinophils may be increased by approximately 13 to 15 % from baseline.

Special precautions

Eosinophilic conditions

Systemic eosinophilia has occurred in patients taking **BelAIR**, sometimes presenting with the clinical features of vasculitis consistent with Churg-Strauss syndrome, a condition that is often treated with systemic corticosteroid therapy. These events have usually, but not always, occurred in association with the reduction of oral corticosteroid therapy.

It is recommended that medical practitioners be alert for signs of eosinophilia, vasculitic rash, worsening of pulmonary symptoms, cardiac complications, and/or neuropathy in these patients. A causal relationship between **BelAIR** and these underlying conditions has not been established.

Neuropsychiatric Events

Neuropsychiatric events have been reported in some patients taking **BelAIR**. These include agitation, aggression, anxiousness, dream abnormalities, hallucinations, depression, insomnia, irritability, restlessness, suicidal thinking and behaviour (including suicide), and tremor. Patients and healthcare professionals should be aware of the potential for neuropsychiatric events. Patients should be instructed to notify their healthcare professionals if these events occur. Healthcare professionals should carefully evaluate the risks and benefits of continuing treatment with **BelAIR** if such events occur.

Hypersensitivity to aspirin

Patients with a known hypersensitivity for aspirin should continue avoiding aspirin and NSAIDs while taking **BelAIR**. Although **BelAIR is** effective in improving airway function in asthmatics, it has not been shown to reduce the bronchoconstrictor response to aspirin or other non-steroidal anti-inflammatory drugs (NSAIDs) in aspirin-sensitive asthmatic patients.

Hepatic function impairment

The metabolism of montelukast may be decreased in patients with mild to moderate hepatic function impairment and clinical evidence of cirrhosis. The half-life may be slightly prolonged; however, dosage adjustment is not necessary. Data are not available in patients with severe hepatic function impairment.

General

BelAIR is not indicated in the reversal of bronchospasm in acute asthma attacks, including status asthmaticus.

Patients should be advised to have appropriate rescue medication available. During acute exacerbations of asthma, therapy with **BelAIR** can be continued. See WARNINGS.

Patients should be advised to take **BelAIR** daily as prescribed, even if they are asymptomatic, as well as during periods of worsening of asthma, and to contact their medical practitioners if their asthma is not well controlled. Medical attention should be sought if more than the prescribed maximum number of inhalations of short-acting bronchodilator treatment for a 24-hour period are needed.

BelAIR should not be used as mono-therapy for the management and treatment of exercised-induced bronchospasm. Patients should continue with their usual inhaled beta-agonists as prophylaxis and have a short-acting inhaled beta-agonist available for rescue, if they have exacerbations of asthma after exercise.

BelAIR should not be substituted abruptly for inhaled or oral corticosteroids. The dose of the corticosteroid may be tapered gradually under medical supervision. To ensure safe and appropriate use, patients should be advised to read the precautions section in the patient information leaflet.

Phenylalanine

BelAIR 4 & 5 chewable tablets contain aspartame, which is a source of phenylalanine. It

may be harmful for people with phenylketonuria.

Effects on the Ability to Drive or Operate Machinery

BelAIR may cause side-effects such as dizziness or drowsiness, which may affect the ability to drive. Patients should therefore be advised not to drive or operate machinery until their individual susceptibility is known.

KNOWN SYMPTOMS OF OVER-DOSAGE AND PARTICULARS OF ITS TREATMENT

Symptoms

Abdominal pain; hyperkinesia; mydriasis; increased sensitivity; somnolence; thirst.

Treatment

Treatment may include removal of unabsorbed material from the gastro-intestinal tract, clinical monitoring, and supportive therapy if required.

It is not known if montelukast can be removed by peritoneal dialysis or haemodialysis.

Patients in whom intentional overdose is confirmed or suspected should be referred for psychiatric evaluation.

IDENTIFICATION

BELAIR 4: Pink, flat round tablets with bevelled edges, marked with '4' on one side and plain on the other, with a diameter of ± 7, 1 mm.

BELAIR 5: Pink, flat round tablets with bevelled edges, with a diameter of ± 8, 1 mm.

PRESENTATION

BelAIR tablets are packed in packs of 28 (2 strips of 14 tablets or 4 strips of 7 tablets) or 30 (3 strips of 10 tablets) in blisters made of oPA/Al/PVC foil and Aluminium push through foil, in a cardboard carton.

STORAGE INSTRUCTIONS:

Store in the original packaging. Keep blister packs in the carton until required for use.

Store at or below 25 °C.

KEEP THIS MEDICINE OUT OF THE REACH OF CHILDREN.

REGISTRATION NUMBERS

BELAIR 4: 45/10.2.2/0744

BELAIR 5: 45/10.2.2/0745

NAME AND BUSINESS ADDRESS OF THE HOLDER OF THE CERTIFICATES OF REGISTRATION

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