FINAL PACKAGE INSERT

SCHEDULING STATUS

S3

PROPRIETARY NAME (and dosage form)

BELAIR 10 mg (film-coated tablet)

COMPOSITION

BELAIR 10 mg: Each film-coated tablet contains 10,0 mg montelukast.

Contains lactose.

Other ingredients:

Microcrystalline cellulose (Type PH 112), croscarmellose sodium, low-substituded hydroxypropyl cellulose (Type LH-11), magnesium stearate, Opadry Orange (03B23378).

PHARMACOLOGICAL CLASSIFICATION

A.10.2.2 Other anti-asthmatics

Leukotriene receptor antagonist

PHARMACOLOGICAL ACTION

Pharmacodynamics:

Montelukast causes potent inhibition of airway cysteinyl leukotriene receptors as demonstrated by the ability to inhibit bronchoconstriction due to inhaled LTD_4 in asthmatic patients. Doses as low as 5 mg cause substantial blockage of LTD_4-

induced bronchoconstriction.

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. In asthma, leukotriene-mediated effects include a number of airway actions, including bronchoconstriction, mucous secretion, vascular permeability, and eosinophil recruitment.

Montelukast binds with high affinity and selectivity to the $CysLT_1$ receptor (in preference to other pharmacologically important airway receptors such as the prostanoid, cholinergic, or beta-adrenergic receptors). Montelukast inhibits physiological actions of LTC_4, LTD_4, and LTE_4 at the $CysLT_1$ receptor without agonist activity.

Pharmacokinetics

Absorption:

Montelukast is absorbed following oral administration. For the 10 mg film-coated tablet, the mean peak plasma concentration (C_{max}) is achieved 3 hours (T_{max}) after administration in adults in the fasted state. The mean oral bioavailability is 64 %. The oral bioavailability and C_{max} are not influenced by a standard meal.

Distribution:

Montelukast is more than 99 % bound to plasma proteins. The steady-state volume of distribution of montelukast averages 8 to 11 litres. 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 the liver. In studies with therapeutic doses, plasma concentrations of metabolites of montelukast are undetectable at steady-state in adults and paediatric patients.

In vitro studies using human liver microsomes indicate that cytochrome P450 3A4 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 cytochrome P450 isoenzymes 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 less than 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 is nearly linear for oral doses up to 50 mg. No difference in pharmacokinetics was noted between dosing in the morning or in the evening. During once-daily dosing with 10 mg montelukast, there is little accumulation of the parent drug in plasma (approximately 14 %).

Special populations

Hepatic Insufficiency:

Patients with mild-to-moderate hepatic insufficiency and clinical evidence of cirrhosis had evidence of decreased metabolism of montelukast resulting in approximately 41 % higher mean montelukast area under the plasma concentration curve (AUC) following a single 10 mg dose. 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 greater than 9).

Renal Insufficiency:

Since montelukast and its metabolites are not excreted in the urine, the pharmacokinetics of montelukast was not evaluated in patients with renal insufficiency. No dosage adjustment is recommended in these patients.

Elderly

The pharmacokinetic profile and the oral bioavailability of a single 10 mg oral dose of montelukast are similar in elderly and younger adults. The plasma half-life of montelukast is slightly longer in the elderly. No dosage adjustment in the elderly is required. In clinical studies, there were no age-related differences in the efficacy or safety profiles of **BELAIR 10 mg**.

INDICATIONS

BELAIR 10 mg is indicated in adults and children 15 years of age and older for the prophylaxis and chronic treatment of atopic asthma.

CONTRAINDICATIONS

· Hypersensitivity to any component of this product.

· Pregnancy and lactation (see PREGNANCY AND LACTATION).

· **BELAIR 10 mg** is contraindicated in children under the age of 15 years, as safety and efficacy have not been demonstrated.

WARNINGS

BELAIR 10 mg is not indicated in the reversal of bronchospasm in acute asthma attacks, including status asthmaticus (see SPECIAL PRECAUTIONS).

The efficacy of **BELAIR 10 mg** has not been established for the treatment of acute asthma attacks.

INTERACTIONS

BELAIR 10 mg may be administered together with other therapies used in the prophylaxis and chronic treatment of asthma. In 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 oestradiol/norethindrone 35 µg/1 mg), digoxin and warfarin.

The area under the plasma concentration curve (AUC) for montelukast was decreased approximately 40 % in subjects with co-administration of phenobarbital. No dosage adjustment for **BELAIR 10 mg** is recommended. However, clinical monitoring is recommended when potent hepatic enzyme inducers such as phenytoin, phenobarbital, or rifampicin are given with montelukast.

PREGNANCY AND LACTATION

The safety of **BELAIR 10 mg** in pregnant and lactating woman has not been established.

Since there are no controlled studies in pregnant or nursing woman, montelukast should not be used during pregnancy or by nursing mothers. It is not known if **BELAIR 10 mg** is excreted in human milk.

DOSAGE AND DIRECTIONS FOR USE

BELAIR 10 mg should be taken once daily in the evening.

Adults and children 15 Years of age and older with atopic asthma:

The dosage for adults 15 years of age and older is one 10 mg film-coated tablet daily. There is no additional clinical benefit to montelukast doses above 10 mg once daily, in adults and children 15 years of age and older.

General Recommendations:

A therapeutic effect of **BELAIR 10 mg** on parameters of asthma control occurs within one day. **BELAIR 10 mg** may be taken with or without food. Patients should be advised to continue taking **BELAIR 10 mg** while their asthma is controlled, as well as during periods of worsening asthma.

No dosage adjustment is necessary for the elderly, for patients with renal insufficiency (see SPECIAL PRECAUTIONS), or mild-to-moderate hepatic impairment, or for patients of either gender.

Therapy with BELAIR 10 mg in Relation to Other Treatments for Asthma:

BELAIR 10 mg can be added to a patient's existing treatment regimen.

SIDE EFFECTS AND SPECIAL PRECAUTIONS

SIDE EFFECTS

Blood and the lymphatic system disorders:

Less frequent: Agranulocytosis, increased bleeding tendency, bruising

Immune system disorders:

Less frequent: Eosinophilia

Psychiatric disorders:

Frequent: Insomnia

Less frequent: Dream abnormalities, hallucinations, irritability, agitation including, aggressive behaviour, hostility, restlessness, suicidal thinking and behaviour.

Nervous system disorders:

Frequent: Headache, dizziness

Less frequent: Drowsiness, paraesthesia/hypoesthesia, seizure.

Cardiac disorders:

Less frequent: Palpitations

Respiratory, thoracic and mediastinal disorders:

Frequent: Congestion (nasal), cough, influenza, epistaxis, respiratory tract infection (in the elderly)

Gastrointestinal disorders:

Frequent: Dyspepsia, gastroenteritis (infectious), pain (dental), diarrhoea, thirst, dry mouth

Less frequent: Nausea, vomiting

Hepato- biliary disorders:

Frequent: ALT increased, AST increased, hyperbilirubinaemia.

Less frequent: cholestatic hepatitis

Skin and subcutaneous tissue disorders:

Frequent: Rash, urticaria, pruritus, erythema nodosum, bruising

Musculoskeletal, connective tissue and bone disorders:

Less frequent: Arthralgia, myalgia including muscle cramps

Renal and urinary disorders:

Frequent: pyuria

General disorders and administrative site conditions:

Frequent: Asthenia/fatigue, fever, abdominal pain, trauma.

Less frequent: Oedema, hypersensitivity reactions including anaphylaxis, angioedema, hepatic eosinophilic infiltration, generalised pain

SPECIAL PRECAUTIONS:

The efficacy of oral **BELAIR 10 mg** for the treatment of acute asthma attacks has not been established.

BELAIR 10 mg should not be used as monotherapy for the treatment and management of exercise-induced bronchospasm. Patients who have exacerbations of asthma after exercise should continue to use their usual regimen of inhaled beta-agonists as prophylaxis and have available for rescue a short-acting inhaled beta-agonist.

BELAIR 10 mg 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 **BELAIR 10 mg** can be continued during acute exacerbations of asthma (see WARNINGS).

While the dose of inhaled corticosteroid may be reduced gradually under medical supervision, **BELAIR 10 mg** should not be abruptly substituted for inhaled or oral corticosteroids. To ensure safe and appropriate use, patients should be advised to read the precautions section of the patient information leaflet.

Patients should be advised to take **BELAIR 10 mg** daily as prescribed, even when they are asymptomatic, as well as during periods of worsening asthma, and to contact their physicians if their asthma is not well controlled.

Patients should be advised that oral tablets of **BELAIR 10 mg** is not for the treatment of acute asthma attacks. They should have appropriate short-acting inhaled beta-agonist medication available to treat asthma exacerbations (see WARNINGS).

Patients should be advised that, while using **BELAIR 10 mg**, medical attention should be sought if short-acting inhaled bronchodilators are needed more often than usual, or if more than the maximum number of inhalations of short-acting bronchodilator treatment prescribed for 24-hour period is needed.

Patients receiving **BELAIR 10 mg** should be instructed not to decrease the dose or stop taking any other anti-asthma medications unless instructed by a doctor.

Patients who have exacerbations of asthma after exercise should be instructed to continue to use their usual regimen of inhaled beta-agonists as prophylaxis unless otherwise instructed by their doctor. All patients should have available for rescue a short-acting inhaled beta-agonist.

Eosinophilic Conditions:

In less frequent cases, patients on therapy with **BELAIR 10 mg** 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 usually, but not always, have been associated with the reduction of oral corticosteroid therapy. Cases of Churg-Strauss syndrome have been described in patients on leukotrienes who were on comitant corticosteroid therapy, suggesting there is a casual link. Doctors should be on the alert for patients presenting with eosinophilia, vasculitic rash, worsening pulmonary symptoms, cardiac complications, and/or neuropathy. **BELAIR 10 mg** should be withdrawn in these patients (see SIDE EFFECTS).

Neuropsychiatric Events:

Neuropsychiatric events have been reported in some patients taking **BELAIR 10 mg**. 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 inform their healthcare professionals if these events occur. Healthcare professionals should carefully evaluate the risks and benefits of continuing treatment with **BELAIR 10 mg** if such events occur.

Hypersensitivity to Aspirin:

Patients with a known hypersensitivity to aspirin should continue avoidance of aspirin or non-steroidal anti-inflammatory agents (NSAIDs such as ibuprofen) while taking **BELAIR 10 mg**. Although **BELAIR 10 mg** 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.

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 is not available in patients with severe hepatic function impairment.

Galactose Intolerence:

BELAIR 10 mg contains lactose. Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicine.

Effects on ability to drive and use machines:

BELAIR 10 mg may cause side-effects such as drowsiness and dizziness which may affect the ability to drive or operate machines safely. Patients should therefore be advised not to drive or operate machinery until their individual susceptibility is known.

KNOWN SYMPTOMS OF OVERDOSE AND PARTICULARS OF ITS TREATMENT

No specific information is available on the treatment of over dosage with **BELAIR 10 mg**. The most frequent adverse experience observed where thirst, somnolence, mydriasis, hyperkinesia, and abdominal pain.

It is not known whether montelukast is dialysable by peritoneal or hemodialysis. Treatment is symptomatic and supportive.

IDENTIFICATION

BELAIR 10 mg: A beige, square shape, biconvex film-coated tablets, marked ***MOK10*** on one face and ***PHD471*** on the other face.

PRESENTATION

The tablets are blister packed in Opaque PA-AL-PVC/Alu foil blisters, one side bright and the other side dull. Each pack contains 28 or 30 tablets, containing 2 blister strips of 14 tablets or 3 blister strips containing 10 tablets.

Not all pack sizes are necessarily marketed.

STORAGE INSTRUCTIONS

Store at or below 25 °C, protected from moisture and light.

Keep the blisters in the outer carton until required for use.

KEEP OUT OF REACH OF CHILDREN

REGISTRATION NUMBER

44/10.2.2 /0431

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

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DATE OF PUBLICATION OF THE PACKAGE INSERT

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