**PROFESSIONAL INFORMATION**

## SCHEDULING STATUS

S3

## 1. NAME OF THE MEDICINE

LEUKOBLOK 4 mg (chewable tablets)

LEUKOBLOK 5 mg (chewable tablets)

LEUKOBLOK 10 mg (film-coated tablets)

## 2. QUALITATIVE AND QUANTITATIVE COMPOSITION

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

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

LEUKOBLOK 10 mg: Each film-coated tablet contains 10 mg montelukast as montelukast sodium.

**Excipient with known effect:**

LEUKOBLOK 4 mg contains 0,6 mg aspartame and 124.44 mg mannitol per tablet.

LEUKOBLOK 5 mg contains 0,743 mg aspartame and 154.068 mg mannitol per tablet.

LEUKOBLOK 10 mg contains 1,5 mg aspartame and 163.1 mg mannitol per tablet.

For the full list of excipients, see section 6.1.

## 3. PHARMACEUTICAL FORM

LEUKOBLOK 4 mg chewable tablets: Pink, flat round, tablets with bevelled edges, marked with ‘4’ on one side and plain on the other.

LEUKOBLOK 5 mg chewable tablets: Pink, flat round, tablets with bevelled edges.

LEUKOBLOK 10 mg film-coated tablets: Beige, round, biconvex film-coated tablets.

## 4. CLINICAL PARTICULARS

### 4.1 Therapeutic indications

LEUKOBLOK is indicated for the prophylaxis and chronic treatment of atopic asthma as follows:.

- LEUKOBLOK 4 mg chewable tablets in paediatric patients 2 to 5 years of age.
- LEUKOBLOK 5 mg chewable tablets in paediatric patients over 6 years of age.
- LEUKOBLOK 10 mg film-coated tablets in adults and children 15 years of age and older.

In those adult asthmatic patients, in whom LEUKOBLOK is indicated in asthma, LEUKOBLOK may also provide some symptomatic relief of seasonal allergic rhinitis.

### 4.2 Posology and method of administration

**Posology:**

LEUKOBLOK should be taken once daily in the evening.

*Paediatric patients 2 to 5 years of age with atopic asthma:* The dosage for paediatric patients 2 to 5 years of age is one 4 mg chewable tablet in the evening.

*Paediatric patients 6 to 14 years of age with atopic asthma:* The dosage for paediatric patients 6 to 14 years of age is one 5 mg chewable tablet in the evening.

LEUKOBLOK 4 mg and LEUKOBLOK 5 mg have not been studied in seasonal allergic rhinitis in children with asthma.

*Adults and children 15 years of age and older with atopic asthma with or without seasonal allergic rhinitis:* The dosage for adults 15 years of age and older is one 10 mg film-coated tablet to be taken in the evening.

Clinical studies in adults and children 15 years of age and older did not demonstrate additional clinical benefit to montelukast, as in LEUKOBLOK at doses above 10 mg daily.

**General recommendations:**

- LEUKOBLOK can be taken with or without food.
- A therapeutic effect of LEUKOBLOK on parameters of asthma control occurs within one day.
- Patients are advised to continue taking LEUKOBLOK while their asthma is controlled, as well as during periods of worsening asthma.
- Patients receiving LEUKOBLOK should be instructed not to decrease the dose or stop taking any other anti-asthma medicines unless instructed by a doctor.
- No dosage adjustment is necessary for the elderly, for patients with renal insufficiency, or mild-to-moderate hepatic impairment.
- The dosage is the same for male or female patients.

**Therapy with LEUKOBLOK in relation to other treatments for asthma:**

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

A gradual reduction of the dose of inhaled corticosteroids may be possible under medical supervision.

***Reduction in Concomitant Therapy:***

One randomized, placebo-controlled, parallel-group trial (n=266) enrolled stable asthmatic adults with a mean FEV1 of approximately 84 % of predicted, who were previously maintained on various inhaled corticosteroids. The pre-study inhaled corticosteroid requirements were reduced by approximately 37 % during a 5- to 7-week placebo run-in period designed to titrate patients toward their lowest effective inhaled corticosteroid dose. Treatment with montelukast resulted in a further 47 % reduction in mean inhaled corticosteroid dose compared with a mean reduction of 30 % in the placebo group over the

12-week active treatment period (p less than or equal to 0,05). Approximately 40 % of the montelukast treated patients and 29 % of the placebo-treated patients could be tapered off inhaled corticosteroids and remained off inhaled corticosteroids at the conclusion of the study (p=NS). It is not known whether the results of this study are generalisable to asthmatics who require higher doses of inhaled corticosteroids or systemic corticosteroids.

Safety and efficacy for more than 12 (twelve) weeks have not been established in controlled clinical trials.

**Method of administration:**

Oral use.

The chewable tablets are to be chewed before swallowing.

### 4.3 Contraindications

Hypersensitivity to montelukast or to any of the excipients listed in section 6.1.

LEUKOBLOK 4 mg should not be used in children under the age of 2 years as safety and efficacy have not been demonstrated.

### 4.4 Special warnings and precautions for use

**General:**

Patients should be advised never to use oral tablets of LEUKOBLOK to treat acute asthma attacks. They should have appropriate short-acting inhaled beta-agonist medication available as rescue medicine to treat an acute asthma attack.

Patients should be advised that, while using LEUKOBLOK, 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 are needed.

LEUKOBLOK 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 the usual regimen of inhaled beta-agonist as prophylaxis and have available for rescue a short-acting inhaled beta-agonist.

LEUKOBLOK 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. During acute exacerbations of asthma, therapy with LEUKOBLOK can be continued.

LEUKOBLOK should not be abruptly substituted for inhaled or oral corticosteroids. If appropriate, the dose of inhaled corticosteroid could be tapered gradually under medical supervision.
There are no data demonstrating that oral corticosteroids can be reduced when LEUKOBLOK is given concomitantly.

Patients on therapy with LEUKOBLOK 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. Medical doctors should be alerted to eosinophilia, vasculitic rash, worsening pulmonary symptoms, cardiac complications, and/or neuropathy presenting in their patients. Patients who develop these symptoms should be reassessed and their treatment regimens evaluated.

Patients with a known hypersensitivity to aspirin should continue avoiding aspirin and non-steroidal anti-inflammatory drugs (NSAIDs) while taking LEUKOBLOK. Although

montelukast, as in LEUKOBLOK 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 in aspirin-sensitive asthmatic patients.

Neuropsychiatric events have been reported in adults, adolescents, and children taking LEUKOBLOK (see section 4.8). Patients and physicians should be alert for neuropsychiatric events. Patients and/or caregivers should be instructed to notify their physician if these changes occur. Prescribers should carefully the continuation of treatment with LEUKOBLOK if such events occur.

LEUKOBLOK contains aspartame which is metabolised to phenylalanine (0,6 mg per 4 mg chewable tablet, 0,743 mg per 5 mg chewable tablet and 1,5 mg per 10 mg film-coated tablet respectively).
LEUKOBLOK should be used with caution in patients with phenylketonuria.

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

Use in elderly: there are no age-related differences in the efficacy or safety profiles of LEUKOBLOK.

**4.5 Interactions with other medicinal products and other forms of interactions**

LEUKOBLOK may be administered with other therapies routinely used in the prophylaxis and chronic treatment of asthma, and in adults also for seasonal allergic rhinitis. In medicine interactions studies, the recommended clinical dose of montelukast did not have clinically important effects on the pharmacokinetics of the following medicines: theophylline,

prednisone, prednisolone, oral contraceptives (ethinyl oestradiol/norethindrone 35/1), terfenadine, digoxin and warfarin.

The area under the plasma concentration time curve (AUC) for montelukast was decreased approximately 40 % in subjects with co-administration of phenobarbital.

Since montelukast is metabolised by CYP 3A4, 2C8, and 2C9, caution should be exercised, particularly in children, when LEUKOBLOK 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 medicine-medicine interaction study involving montelukast and rosiglitazone (a probe substrate representative of medicinal products primarily metabolized by CYP 2C8) demonstrated that montelukast does not inhibit CYP 2C8 *in vivo*. Therefore, LEUKOBLOK is not anticipated to markedly alter the metabolism of medicines metabolised 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 medicine 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 LEUKOBLOK is required upon co-administration with gemfibrozil or other potent inhibitors of CYP 2C8, but the doctor should be aware of the potential for an increase in adverse reactions.

Based on *in vitro* data, clinically important medicine interactions with less potent inhibitors of CYP 2C8 (e.g. trimethoprim) are not anticipated. Co-administration of LEUKOBLOK with

itraconazole, a strong inhibitor of CYP 3A4, resulted in no significant increase in the systemic exposure of montelukast.

### 4.6 Fertility, pregnancy and lactation

The safety of LEUKOBLOK in pregnancy and lactating woman has not been established, and therefore the use thereof in pregnancy and lactation is not recommended. It is not known if montelukast is excreted in human milk.

During worldwide marketing experience, congenital limb defects have been reported in the offspring of women being treated with montelukast during pregnancy. A casual relationship between these events and montelukast has not been established.
Studies in rats have shown that montelukast is excreted in milk.

### 4.7 Effects on ability to drive and use machines

LEUKOBLOK has no or negligible influence on the ability to drive and use of machines. However, individuals have reported drowsiness or dizziness.

### 4.8 Undesirable effects

**Summary of the safety profile**

Side effects generally did not require discontinuation of therapy.
In clinical studies the most frequently reported medicine-related adverse reaction in all population groups was headache and abdominal pain in adult and adolescent patients 15 years and older. The most frequent adverse reaction reported in children was thirst. The safety profile did not change with prolonged treatment in all patient groups.

**Listing of side effects:**

**Infections and infestations**

*Frequent:* Upper respiratory infection

**Blood and lymphatic system disorders**

*Less frequent:* Increased bleeding tendency, thrombocytopenia

**Immune system disorders**

*Less frequent:* Hypersensitivity reactions including anaphylaxis, hepatic eosinophilic infiltration

**Psychiatric disorders**

*Less frequent:* Dream abnormalities including nightmares, insomnia, somnambulism, anxiety, agitation including aggressive behaviour or hostility, depression, psychomotor hyperactivity (including irritability, restlessness, tremor), disturbance in attention, memory impairment, tics, hallucinations, disorientation, suicidal thinking and behaviour (suicidality), obsessive-compulsive symptoms, dysphemia

**Nervous system disorders**

*Less frequent:* Dizziness, drowsiness, paraesthesia/hypoesthesia, seizure

**Cardiac disorders**

*Less frequent:* Palpitations

**Respiratory, thoracic and mediastinal disorders**

*Less frequent:* Epistaxis, Churg-Strauss Syndrome (see section 4.4), pulmonary eosinophilia

**Gastrointestinal disorders**

*Frequent:* Diarrhoea, nausea, vomiting

*Less frequent:* Dry mouth, dyspepsia

**Hepato-biliary disorders**

*Frequent:* Elevated levels of serum transaminases (ALT, AST)

*Less frequent:* Hepatitis (including cholestatic, hepatocellular and mixed-pattern liver injury)

**Skin and subcutaneous tissue disorders**

*Frequent:* Rash

*Less frequent:* Bruising, urticaria, pruritus, angioedema, erythema nodosum, erythema multiforme

**Musculoskeletal and connective tissue disorders**

*Less frequent:* Arthralgia, myalgia including muscle cramps

**Renal and urinary disorders**

*Less frequent*: Enuresis in children

**General disorders and administration site conditions**

*Frequent:* Pyrexia

*Less frequent:* Asthenia/fatigue, malaise, oedema

**Description of selected adverse reactions**

Patients on therapy with LEUKOBLOK 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. Doctors 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 (see Section 4.4).

**Reporting of suspected adverse reactions:**

Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Healthcare providers are asked to report any suspected adverse reactions to SAHPRA via the "6.04 Adverse Drug Reactions Reporting Form" found online under SAHPRA's publications:

http://www.sahpra.org.za/Publications/Index/8

### 4.9 Overdose

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. The clinical and laboratory findings observed were consistent with the safety profile in adults and older paediatric patients. There were no adverse experiences reported in the majority of overdose reports.

**Symptoms of overdose:**

The most frequently occurring adverse experiences observed were consistent with safety profile of montelukast and included abdominal pain, somnolence, thirst, headache, vomiting and psychomotor hyperactivity.

**Management of overdose:**

No specific information is available on the treatment of overdose with LEUKOBLOK.

It is not known whether montelukast is dialysable by peritoneal dialysis or haemodialysis.

## 5. PHARMACOLOGICAL PROPERTIES

### 5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Leukotriene receptor antagonist

ATC code: RO3D CO3

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 ($CysLT_1$) 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). CysLTs have been correlated with the pathophysiology of asthma and allergic

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

Montelukast is an orally active compound which 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 receptor). Montelukast inhibits physiological actions of $LTC_4$, $LTD_4$ and $LTE_4$ at the $CysLT_1$ receptor without agonist activity.

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.

**5.2 Pharmacokinetic properties**

**Absorption**

Montelukast is rapidly absorbed following oral administration. Peak plasma concentrations of montelukast are achieved in 2 hours with the 4 mg and 5 mg tablets and 3 hours after oral doses of the 10 mg tablet. The mean oral bioavailability is 64 % and 73 % for the 10 mg and the 5 mg tablets respectively. Food does not have a clinically important influence with chronic administration.

**Distribution**

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

**Metabolism**

Montelukast is extensively metabolised in the liver by cytochrome P450 isoenzymes 3A4 and 2C9. In studies with therapeutic doses, plasma concentrations of metabolites of montelukast are undetectable at steady state in adults and paediatric patients.

Therapeutic plasma concentrations of montelukast do not inhibit cytochromes P450 3A4, 2C9, 1A2, 2A6, 2C19 or 2D6.

**Elimination**

Elimination data are not available for children 2 to 5 years of age. The mean plasma half-life of montelukast ranged from 2,7 to 5,5 hours in healthy young adults. Plasma clearance of montelukast averages 45 ml/min in healthy adults. It is mainly excreted in the faeces via the bile (86 %).

The pharmacokinetics of montelukast are 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**

No dosage adjustment is necessary for the elderly or mild to moderate hepatic insufficiency. Studies in patients with renal impairment have not been undertaken. No dose adjustment is anticipated to be necessary in patients with renal impairment, since montelukast and its metabolites are eliminated by the biliary route.

There are no data on the pharmacokinetics of montelukast in patients with severe hepatic insufficiency (Child-Pugh score > 9).

With high doses of montelukast (20- and 60-fold the recommended adult dose), a decrease in plasma theophylline concentration was observed. This effect was not seen at the recommended dose of 10 mg once daily.

## 6. PHARMACEUTICAL PARTICULARS

### 6.1 List of excipients

LEUKOBLOK 4 mg and LEUKOBLOK 5 mg: Mannitol spray dried, croscarmellose sodium, aspartame, banana flavour, microcrystalline cellulose, low-substituted hydroxypropyl cellulose, iron oxide red (E172) and magnesium stearate.

LEUKOBLOK 10 mg: Mannitol spray dried, croscarmellose sodium, aspartame, cherry flavour, microcrystalline cellulose, low-substituted hydroxypropyl cellulose, iron oxide red (E172) and magnesium stearate. Film-coating: Hypromellose 3cP, hydroxypropylcellulose, talc, titanium oxide (E 171), iron oxide yellow (E172), iron oxide red (E172).

### 6.2 Incompatibilities

Not applicable.

### 6.3 Shelf-life

24 months

### 6.4 Special precautions for storage

Store at or below 30 °C in the original packaging to protect from light and moisture.

### 6.5 Nature and contents of container

LEUKOBLOK 4 mg is available in aluminium/aluminium blister packs of 28 or 30.

LEUKOBLOK 5 mg is available in aluminium/aluminium blister packs of 28 or 30.

LEUKOBLOK 10 mg is available in aluminium/aluminium blister packs of 28 or 30.

Not all pack sizes may be marketed.

### 6.6 Special precautions for disposal

No special requirements.

## 7. HOLDER OF CERTIFICATE OF REGISTRATION

Smart Pharmaceuticals (Pty) Ltd

247 Voortrekker Road

Kraaifontein, Cape Town

7570

## 8. REGISTRATION NUMBERS

LEUKOBLOK 4 mg: 47/10.2.2/0412

LEUKOBLOK 5 mg: 47/10.2.2/0413

LEUKOBLOK 10 mg: 47/10.2.2/0414

## 9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

17 August 2021

## 10. DATE OF REVISION OF THE TEXT

17 August 2021

LEU/C/PI/A