PROFESSIONAL INFORMATION

SCHEDULING STATUS: **S3**

1. NAME OF THE MEDICINE

MONTELUKAST UNICORN 10 (film-coated tablets)

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each **MONTELUKAST UNICORN 10** film-coated tablet contains montelukast sodium equivalent to 10 mg montelukast.

Contains sugar (lactose monohydrate 89,10 mg per tablet).

3. PHARMACEUTICAL FORM

A beige, round, biconvex, coated tablet, that is plain on both sides.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

MONTELUKAST UNICORN 10 film-coated tablets are indicated in adults and children 15 years of age and older for the:

- Prophylaxis and chronic treatment of atopic asthma.

4.2 Posology and method of administration

MONTELUKAST UNICORN 10 film-coated tablets should only be used in adults and children 15 years of age and older.

Prophylaxis and treatment of atopic asthma*:*

1 tablet (10 mg) to be taken daily in the evening.

MONTELUKAST UNICORN 10 tablets may be taken with or without food.

Patients should be advised to continue taking **MONTELUKAST UNICORN 10** while their asthma is controlled, as well as during periods of worsening asthma.

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

4.3 Contraindications

- Hypersensitivity to montelukast or any other component of **MONTELUKAST UNICORN 10** listed in section 6.1.
- Pregnancy and lactation.
- Safety and efficacy of **MONTELUKAST UNICORN 10** film-coated tablets have not been established in children under the age of 15 years.

4.4 Special warnings and precautions for use

Patients should be advised never to use oral montelukast to treat acute asthma attacks and to keep their usual appropriate rescue medication for this purpose readily available. If an acute attack occurs, a short-acting inhaled β-agonist should be used. Patients should seek their doctors' advice as soon as possible if they need more inhalations of short-acting β-agonists than usual.

Patients should be advised to take **MONTELUKAST UNICORN 10** exactly as prescribed, even if they are asymptomatic. **MONTELUKAST UNICORN 10** should also be used during periods of worsening asthma and patients should contact their healthcare practitioner if their asthma is not well controlled.

MONTELUKAST UNICORN 10 should not be abruptly substituted for inhaled or oral corticosteroids. If appropriate, the dose of corticosteroids should be tapered gradually under medical supervision.

Eosinophilic conditions:

In rare cases, patients on therapy with anti-asthma agents including 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 cases

have been sometimes associated with the reduction or withdrawal of oral corticosteroid therapy. Although a causal relationship with leukotriene receptor antagonism has not been established, physicians should be alert 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.

MONTELUKAST UNICORN 10 should not be used as monotherapy for the treatment or management of exercise-induced bronchospasm. Patients should be advised to continue with the usual regimen of an inhaled beta-agonist for prophylaxis of exercise-induced bronchospasm and to have a short-acting inhaled beta-agonist available for rescue treatment.

While using **MONTELUKAST UNICORN 10**, patients must seek medical attention if short-acting bronchodilators are needed more often than usual, or if more than the maximum number of inhalations of short-acting bronchodilator treatment prescribed for a 24-hour period is needed.

Patients with known hypersensitivity to aspirin should be advised to continue avoiding the use of aspirin or NSAIDs (non-steroidal anti-inflammatory agents) while taking **MONTELUKAST UNICORN 10.**

Neuropsychiatric events have been reported in adults, adolescents, and children taking **MONTELUKAST UNICORN 10** (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 evaluate the risks and benefits of continuing treatment with **MONTELUKAST UNICORN 10** if such events occur.

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.

Lactose*:*

MONTELUKAST UNICORN 10 contains lactose monohydrate. Patients with the rare hereditary conditions of galactose intolerance e.g. galactosaemia, Lapp lactase deficiency, glucose-galactose malabsorption or fructose intolerance should not take **MONTELUKAST UNICORN 10.**

MONTELUKAST UNICORN 10 contains lactose monohydrate which may have an effect on the glycaemic control of patients with diabetes mellitus.

4.5 Interaction with other medicines and other forms of interaction

MONTELUKAST UNICORN 10 may be used together with other medicines used in the prophylaxis and chronic treatment of asthma. Montelukast does not significantly change the pharmacokinetics of theophylline, warfarin, digoxin, fexofenadine, oral contraceptives (containing 1 mg norethindrone and 35 µg ethinyl estradiol), prednisone or prednisolone.

Concurrent use of **MONTELUKAST UNICORN 10** and phenobarbital results in significant decreases (approximately 40 %) in the area under the curve (AUC) for montelukast, as a result of induction of hepatic metabolism. No dosage adjustment is necessary. However, clinical monitoring is required when potent hepatic enzyme inducers such as phenytoin, phenobarbital or rifampicin are given with montelukast. Since montelukast is metabolised 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 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, montelukast is not anticipated to markedly alter the metabolism of medicinal products 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 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.

4.6 Pregnancy and lactation

The safety of the use of **MONTELUKAST UNICORN 10** in pregnant and lactating women has not yet been established.

It is not known if **MONTELUKAST UNICORN 10** is excreted in human milk.

MONTELUKAST UNICORN 10 should not be used in pregnancy and lactation (see section 4.3).

4.7 Effects on ability to drive and use machines

MONTELUKAST UNICORN 10 may cause side effects such as drowsiness and dizziness which may affect the ability to drive and operate machines safely.

4.8 Undesirable effects

Infections and infestations:

***Frequent*:** Upper respiratory infection†.

Blood and lymphatic system disorders:

***Less frequent*:** Increased bleeding tendency, thrombocytopenia.

The following has been reported but frequency is unknown:

Bruising, agranulocytosis.

Immune system disorders:

Less frequent: Anaphylaxis, angioedema, allergy, hypersensitivity reactions including rashes and urticaria, hepatic eosinophilic infiltration.

Endocrine disorders:

The following has been reported but frequency is unknown:

Pancreatitis.

Psychiatric disorders*:*

Less frequent: Aggressive behaviour or hostility, agitation, hallucinations, dream abnormalities including nightmares, insomnia, drowsiness, irritability, restlessness, depression, suicidal thinking and behaviour (suicidality), somnambulism, anxiety, psychomotor hyperactivity (including irritability, restlessness, tremor[§]), disturbance in attention, memory impairment, tic, obsessive-compulsive symptoms, dysphemia.

Nervous system disorders:

Frequent: Headache.

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

Cardiac disorders:

Less frequent: Palpitations.

Respiratory, thoracic and mediastinal disorders:

Less frequent: Churg-Strauss Syndrome (see section 4.4), nasal congestion, cough, influenza, increased incidence of respiratory tract infections, epistaxis, pulmonary eosinophilia.

Gastrointestinal disorders*:*

Frequent: Abdominal pain, diarrhoea‡, nausea‡, vomiting‡.

Less frequent: Dyspepsia, gastroenteritis, dry mouth.

Hepato-biliary disorders*:*

Frequent: Elevated levels of serum transaminases (AST, ALT), symptomatic hepatitis.

Less frequent: Elevated hepatic enzymes (AST, ALT), symptomatic hepatitis (including cholestatic, hepatocellular, and mixed-pattern liver injury) or hyperbilirubinaemia.

Skin and subcutaneous tissue disorders:

Frequent: Skin rash‡.

Less frequent: Pruritus, urticaria, bruising, angioedema, erythema nodosum, erythema multiforme.

Musculoskeletal, connective tissue and bone disorders:

Less frequent: Arthralgia, myalgia including muscle cramps.

Renal and urinary disorders:

The following has been reported but frequency is unknown: Pyuria.

Less frequent: Enuresis in children.

General disorders and administration site conditions:

Less frequent: Asthenia, fatigue, dental pain, pyrexia‡, malaise, oedema.

The following has been reported but frequency is unknown:

Generalised pain, fatalities.

†This adverse experience, reported as Very Common in the patients who received montelukast, was also reported as Very Common in the patients who received placebo in clinical trials.

‡This adverse experience, reported as Common in the patients who received montelukast, was also reported as Common in the patients who received placebo in clinical trials.

§ Frequency Category: Rare

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

Suspected adverse reactions can also be reported directly to the Holder of the Certificate of Registration (HCR) via Patientsafety.sacg@novartis.com.

4.9 Overdose

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.

Management of overdose:

No specific information is available on the treatment of overdose with montelukast. It is not known whether montelukast is dialysable by peritoneal- or haemodialysis.

5. PHARMACOLOGICAL PROPERTIES

Pharmacological classification: A.10.3 Others (Medicines acting on respiratory systems), ATC-code: R03D C03.

Mechanism of action

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.

5.1 Pharmacodynamic properties

Montelukast is an orally active compound which binds with high affinity and selectivity to the $CysLT_1$ receptor. In clinical studies, montelukast inhibits bronchoconstriction due to inhaled LTD_4 at doses as low as 5 mg.

Bronchodilation was observed within 2 hours of oral administration. The bronchodilation effect caused by a β-agonist was additive to that caused by montelukast. Treatment with montelukast inhibited both early- and late-phase bronchoconstriction due to antigen challenge. Montelukast, compared with placebo, decreased peripheral blood eosinophils in adult and paediatric patients. In a separate study,

treatment with montelukast significantly decreased eosinophils in the airways (as measured in sputum) and in peripheral blood while improving clinical asthma control.

5.2 Pharmacokinetic properties

***Absorption**:*

Montelukast is rapidly 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. Safety and efficacy were demonstrated in clinical trials where the 10 mg film-coated tablet was administered without regard to the timing of food ingestion.

For the 5 mg chewable tablet, the C_{max} is achieved in 2 hours after administration in adults in the fasted state. The mean oral bioavailability is 73 % and is decreased to 63 % 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 radiolabelled montelukast indicate minimal distribution across the blood-brain barrier. In addition, concentrations of radiolabelled material at 24 hours post-dose were minimal in all other tissues.

***Metabolism**:*

Biotransformation:

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. Additionally, CYP 3A4 and 2C9 may have a minor contribution, although itraconazole, an inhibitor of CYP 3A4, was shown not to change pharmacokinetic variables of montelukast in healthy subjects that received 10 mg montelukast daily. Based on *in vitro* results in human liver microsomes, therapeutic plasma

concentrations of montelukast do not inhibit cytochromes P450 3A4, 2C9, 1A2, 239 2A6, 2C19, or 2D6. The contribution of metabolites to the therapeutic effect of montelukast is minimal.

Elimination:

It is mainly excreted in the faeces via the bile. 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.

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 adjustments are 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).

Elderly:

The pharmacokinetic profile and the oral bioavailability of a single 10 mg 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.

6. PHARMACEUTICAL PARTICULARS

6.1. List of excipients

Tablet core: cellulose microcrystalline, croscarmellose sodium, hydroxypropylcellulose, lactose monohydrate and magnesium stearate.

Film-coating layer: opadry beige (II) composed of ferric oxide red (E172), ferric oxide yellow (E172), macrogol 400, polyvinyl alcohol, talc and titanium dioxide (E171).

6.2. Incompatibilities

Not applicable.

6.3. Shelf life

24 months

6.4. Special precautions for storage

Store at or below 25 °C. Store in the original package. The product is sensitive to light and moisture.

Container: Keep the bottle tightly closed.

6.5. Nature and contents of container

MONTELUKAST UNICORN 10 film-coated tablets are packed as 10, 14, 20, 28, 30, 35 or 50 tablets in: OPA/Al/PVC/Aluminium blisters or white, opaque polyethylene containers and tamper evident polypropylene closures with desiccant insert.

Not all packs may be marketed.

7. HOLDER OF CERTIFICATE OF REGISTRATION

Sandoz SA (Pty) Ltd[1]

Magwa Crescent West

Waterfall City

Jukskei View

Midrand

2090

Marketed by: Unicorn Pharmaceuticals (Pty) Ltd

Corner of Searle and Pontac Streets, Woodstock, Cape Town, 8001

8. REGISTRATION NUMBER

44/10.2.2/0204

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

18 May 2012

10. DATE OF REVISION OF THE TEXT

31 August 2022

[1]Company Reg. No.: 1990/001979/07