PROFESSIONAL INFORMATION

SCHEDULING STATUS: S3

1 NAME OF THE MEDICINE

Montelukast Oral Granules Unicorn

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each sachet of MONTELUKAST ORAL GRANULES UNICORN contains 4,15 mg of montelukast sodium equivalent to 4,00 mg of montelukast.

MONTELUKAST ORAL GRANULES UNICORN contains sweetener (mannitol (484,70 mg per sachet)).

For full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Oral granules.

White to off white granules.

4 CLINICAL PARTICULARS

4.1. Therapeutic indications

MONTELUKAST ORAL GRANULES UNICORN is indicated in paediatric patients 2 to 5 years of age for the prophylaxis and chronic treatment of atopic asthma.

4.2. Posology and method of administration

Posology

This medicine is to be given to a child under adult supervision. The recommended dose for paediatric patients 2 to 5 years of age is one sachet of 4 mg oral granules daily to be taken in the evening.

Administration of MONTELUKAST ORAL GRANULES UNICORN

MONTELUKAST ORAL GRANULES UNICORN can be administered either directly in the mouth or mixed with a spoonful of cold or room temperature soft food (e.g., applesauce, ice cream, carrots and rice). The sachet should not be opened until ready to use. After opening the sachet, the full dose of MONTELUKAST ORAL GRANULES UNICORN must be administered immediately (within 15 minutes). If mixed with food, MONTELUKAST ORAL GRANULES UNICORN must not be stored for future use. MONTELUKAST ORAL GRANULES UNICORN are not intended to be dissolved in liquid for administration. However, liquids may be taken subsequent to administration. MONTELUKAST ORAL GRANULES UNICORN can be administered without regard to the timing of food ingestion.

General recommendations

The therapeutic effect of MONTELUKAST ORAL GRANULES UNICORN on parameters of asthma control occurs within one day. Patients should be advised to continue taking MONTELUKAST ORAL GRANULES UNICORN even if their asthma is under control, as well as during periods of worsening asthma.

No dosage adjustment is necessary for patients with renal insufficiency, or mild to moderate hepatic impairment.

There are no data on patients with severe hepatic impairment. The dosage is the same for both male and female patients.

Therapy with MONTELUKAST ORAL GRANULES UNICORN in relation to other treatments for asthma

MONTELUKAST ORAL GRANULES UNICORN can be added to a patient's existing treatment regimen.

Method of administration

Oral use as described above.

4.3 Contraindications

- Known sensitivity to montelukast or to any of the excipients in MONTELUKAST ORAL GRANULES UNICORN (see sections 2 and 6.1).
- Children under the age of 2 years, as safety and efficacy of MONTELUKAST ORAL GRANULES UNICORN have not been demonstrated.

4.4. Special warnings and precautions for use

Patients should be advised never to use oral montelukast to treat acute asthma attacks, including status asthmaticus and to keep their usual appropriate rescue medication for this purpose readily available. MONTELUKAST ORAL GRANULES UNICORN is not indicated for use in the reversal of bronchospasm in acute asthma attacks. 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.

MONTELUKAST ORAL GRANULES UNICORN 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 β -agonists as prophylaxis and have available for rescue a short-acting inhaled β agonist.

Montelukast should not be abruptly substituted for inhaled or oral corticosteroids.
There are no data demonstrating that oral corticosteroids can be reduced when MONTELUKAST ORAL GRANULES UNICORN is given concomitantly.

Renal Insufficiency

Since MONTELUKAST ORAL GRANULES UNICORN and its metabolites are not excreted in the urine, the pharmacokinetics of MONTELUKAST ORAL GRANULES UNICORN were not evaluated in patients with renal insufficiency. No dosage adjustment is recommended in these patients.
Patients on therapy with anti-asthma medicines including MONTELUKAST ORAL GRANULES UNICORN 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, medical practitioners 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.
Treatment with montelukast does not alter the need for patients with aspirin-sensitive asthma to avoid taking aspirin and other non-steroidal anti-inflammatory medicines.

Neuropsychiatric events have been reported in adults, adolescents, and children taking MONTELUKAST ORAL GRANULES UNICORN (see section 4.8). Patients and medical practitioners should be alert for neuropsychiatric events. Patients and/or caregivers should be instructed to notify their medical practitioners if these changes occur. Prescribers should carefully evaluate the risks and benefits of continuing treatment with MONTELUKAST ORAL GRANULES UNICORN if such events occur.

MONTELUKAST ORAL GRANULES UNICORN as an alternative treatment option to low-dose inhaled corticosteroids for mild, persistent asthma

Montelukast is not recommended as monotherapy in patients with moderate persistent asthma. The use of montelukast as an alternative treatment option to low-dose inhaled corticosteroids for

children 2 to 5 years old with mild persistent asthma should only be considered for patients who do not have a recent history of serious asthma attacks that required oral corticosteroid use and who have demonstrated that they are not capable of using inhaled corticosteroids (see section 4.1). Mild persistent asthma is defined as asthma symptoms more than once a week but less than once a day, nocturnal symptoms more than twice a month but less than once a week, normal lung function between episodes. If satisfactory control of asthma is not achieved at follow-up (usually within one month), the need for an additional or different anti-inflammatory therapy based on the step system for asthma therapy should be evaluated. Patients should be periodically evaluated for their asthma control.

Information for Patients:

- Patients should be advised to take MONTELUKAST ORAL GRANULES UNICORN 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 MONTELUKAST ORAL GRANULES UNICORN are not for the treatment of acute asthma attacks. They should have appropriate short-acting inhaled β -agonist medication available to treat asthma exacerbations.
- Patients should be advised that, while using MONTELUKAST ORAL GRANULES UNICORN, 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 a 24-hour period are needed.
- Patients receiving MONTELUKAST ORAL GRANULES UNICORN should be instructed not to decrease the dose or stop taking any other anti-asthma medications unless instructed by a physician.
- Patients who have exacerbations of asthma after exercise should be instructed to continue to use their usual regimen of inhaled β -agonists as prophylaxis unless otherwise instructed

by their medical practitioner. All patients should have available for rescue a short-acting inhaled β -agonist.

- Patients with known aspirin sensitivity should be advised to continue avoidance of aspirin or non-steroidal anti-inflammatory agents while taking MONTELUKAST ORAL GRANULES UNICORN.

4.5. Interaction with other medicinal products and other forms of interaction

Montelukast may be administered with other therapies routinely used in the prophylaxis and chronic treatment of asthma. In medicine-interactions studies, the recommended clinical dose of montelukast did not have clinically important effects on the pharmacokinetics of the following medicinal products: theophylline, prednisone, prednisolone, oral contraceptives (ethinyl estradiol/norethindrone 35/1), 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 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 medicine interaction study involving montelukast and rosiglitazone (a probe substrate representative of medicinal products primarily metabolised 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 medical practitioner 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 montelukast 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

Pregnancy

The safety of montelukast in pregnant and lactating women has not been established.
MONTELUKAST ORAL GRANULES UNICORN should not be used during pregnancy.
During worldwide marketing experience, congenital limb defects have been reported in offspring of women treated with MONTELUKAST ORAL GRANULES UNICORN during pregnancy. A causal relationship between these events and MONTELUKAST ORAL GRANULES UNICORN has not been established.

Lactation

Studies in rats have shown that montelukast is excreted in milk (see section 5.3). It is unknown whether montelukast/metabolites are excreted in human milk. MONTELUKAST ORAL GRANULES UNICORN should not be used in breastfeeding mothers.

4.7. Effects on ability to drive and use machines

MONTELUKAST ORAL GRANULES UNICORN has no or negligible influence on the ability to drive and use machines. However, individuals have reported drowsiness or dizziness.

4.8. Undesirable effects

Tabulated list of Adverse Reactions:

System organ class	Adverse reactions	Frequency category
Infections and infestations	Upper respiratory infection	Frequent
Blood and lymphatic system Disorders	Increased bleeding tendency, thrombocytopenia	Less frequent
Immune system disorders	Hypersensitivity reactions including anaphylaxis, hepatic eosinophilic infiltration	Less frequent
Psychiatric disorders	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	Less frequent
Nervous system disorders	Headache, hyperkinesia	Frequent
	Dizziness, drowsiness, paraesthesia/hypoesthesia, seizure	Less frequent
Cardiac disorders	Palpitations	Less frequent

Respiratory, thoracic and mediastinal disorders	Epistaxis, Churg-Strauss Syndrome (CSS) (see section 4.4), pulmonary eosinophilia	Less frequent
Gastro-intestinal disorders	Diarrhoea, nausea, vomiting, abdominal pain	Frequent
	Dry mouth, dyspepsia	Less frequent
Hepatobiliary disorders	Elevated levels of serum transaminases (ALT, AST)	Frequent
	Hepatitis (including cholestatic, hepatocellular, and mixed-pattern liver injury).	Less frequent
Skin and subcutaneous tissue Disorders	Rash	Frequent
	Bruising, urticaria, pruritus, angioedema, erythema nodosum, erythema multiforme, eczematous, dermatitis, rash	Less frequent
Musculoskeletal and connective tissue disorders	Arthralgia, myalgia including muscle cramps	Less frequent
Renal and urinary disorders	Enuresis in children	Less frequent
General disorders and administration site conditions	Pyrexia, thirst	Frequent
	Asthenia/fatigue, malaise, oedema	Less frequent

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. 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 HCR via Patientsafety.sacg@novartis.com.

4.9 Overdose

No specific information is available on the treatment of overdosage with MONTELUKAST ORAL GRANULES UNICORN.

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 1000 mg. 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 haemo-dialysis.

5. PHARMACOLOGICAL PROPERTIES

5.1. Pharmacodynamic 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 receptors (CysLT) found in the human airway and cause airway actions, including bronchoconstriction, mucous secretion, vascular permeability, and eosinophil recruitment.

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). In adult and paediatric patients 2 to 14 years of age, montelukast, compared with placebo, decreased peripheral blood eosinophils 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. After administration of the 4 mg chewable tablet to paediatric patients 2 to 5 years of age in the fasted state, C_{max} is achieved 2 hours after administration. The mean C_{max} is 66 % higher while mean C_{min} is lower than in adults receiving a 10 mg tablet.
The 4 mg granule formulation is bioequivalent to the 4 mg chewable tablet when administered to adults in the fasted state. In paediatric patients 6 months to 2 years of age, C_{max} is achieved 2 hours after administration of the 4 mg granules formulation. C_{max} is nearly 2-fold greater than in adults receiving a 10 mg tablet. The co-administration of applesauce or a high-fat standard meal with the granule formulation did not have a clinically meaningful effect on the pharmacokinetics of montelukast as determined by AUC.

Distribution

Montelukast is more than 99 % bound to plasma proteins. The steady-state volume of distribution of montelukast averages 8 to11 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.

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, 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.

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. Because montelukast and its metabolites are eliminated by the biliary route, no dose adjustment is anticipated to be necessary in patients with renal impairment. 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

Hydroxypropyl cellulose (klucel LF), mannitol (Pearlitol DC300) and magnesium stearate.

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 in order to protect from light and moisture.

Do not use after the expiry date stated on the sachet / carton.

6.5. Nature and contents of container

Pouch laminate sachet (PET/Aluminium foil/PE).

The sachets are packed in an outer cardboard carton.

Packs sizes of 7, 10, 14, 20, 28, 30 and 100 sachets.

Not all pack sizes may be marketed.

6.6. Special precautions for disposal and other handling

No special requirements.

7. HOLDER OF CERTIFICATE OF REGISTRATION

Sandoz SA (Pty) Ltd[1]

Waterfall 5-Ir,

Magwa Crescent West

Waterfall City

Jukskei View

2090

Marketed by **UNICORN PHARMACEUTICALS (PTY) LTD**

8. REGISTRATION NUMBER

47/10.3/0742

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

08 March 2022

10. DATE OF REVISION OF THE TEXT

Not applicable.

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