CLEAN PROPOSED PI FOR MONTELUKAST UNICORN 4 AND MONTELUKAST UNICORN 5

PROFESSIONAL INFORMATION

SCHEDULING STATUS S3

1. NAME OF THE MEDICINE

MONTELUKAST UNICORN 4 (chewable tablets)

MONTELUKAST UNICORN 5 (chewable tablets)

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each MONTELUKAST UNICORN 4 chewable tablet contains 4,16 mg of montelukast sodium equivalent to 4 mg montelukast.

Each MONTELUKAST UNICORN 5 chewable tablet contains 5,20 mg of montelukast sodium equivalent to 5 mg montelukast.

Contains sugar

Each MONTELUKAST UNICORN 4 chewable tablet contains sweetener (aspartame 0,96 mg) and mannitol 155,92 mg.

Each MONTELUKAST UNICORN 5 chewable tablet contains sweetener (aspartame 1,20 mg) and mannitol 194,90 mg.

3. PHARMACEUTICAL FORM

MONTELUKAST UNICORN 4: Oval pink to slightly speckled pink tablet with odour of cherry, encoded “4” on one side.

MONTELUKAST UNICORN 5: Round pink to slightly speckled pink tablet with odour of cherry, encoded “5” on one side.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

MONTELUKAST UNICORN 4 chewable tablets are indicated in paediatric patients 2 to 5 years of age for the prophylaxis and chronic treatment of atopic asthma.

MONTELUKAST UNICORN 5 chewable tablets are indicated in paediatric patients from 6 years of age for the prophylaxis and chronic treatment of atopic asthma.

4.2 Posology and method of administration

This medicinal product is to be given to a child under adult supervision.
MONTELUKAST UNICORN 4: The dosage for paediatric patients 2 to 5 years of age is one 4 mg chewable tablet daily to be taken in the evening.
MONTELUKAST UNICORN 5: The dosage for paediatric patients 6 to 14 years of age is one 5 mg tablet daily to be taken in the evening.
MONTELUKAST UNICORN may be taken with or without food.
MONTELUKAST UNICORN can be added to a patient’s existing treatment regimen.
No dosage adjustment is necessary for the elderly, patients with renal insufficiency or mild to moderate hepatic impairment.

4.3 Contraindications

- Hypersensitivity to montelukast or any other component of MONTELUKAST UNICORN listed in section 6.1.
- MONTELUKAST UNICORN 4: Safety and efficacy have not been established in children under the age of 2 years.
- MONTELUKAST UNICORN 5: Safety and efficacy have not been established in children under the age of 6 years.
- Pregnancy and lactation.

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.

MONTELUKAST UNICORN should be taken once daily in the evening. Patients should be advised to take MONTELUKAST UNICORN exactly as prescribed, even if they are asymptomatic. MONTELUKAST UNICORN 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 should not be abruptly substituted for inhaled or oral corticosteroids. If appropriate, the dose of corticosteroids should be tapered gradually under medical supervision.

There are no data demonstrating that oral corticosteroids can be reduced when montelukast is given concomitantly.

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 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, 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.

Precautions relating to excipients:

MONTELUKAST UNICORN 4 and 5 chewable tablets contain aspartame, which is metabolised to phenylalanine.

MONTELUKAST UNICORN should be used with caution in patients with phenylketonuria.

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

Neuropsychiatric events have been reported in adults, adolescents, and children taking MONTELUKAST UNICORN (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 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.

4.5 Interaction with other medicines and other forms of interaction

MONTELUKAST UNICORN may be administered together with other medicines used for the prophylaxis and chronic treatment of asthma. MONTELUKAST UNICORN 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 and phenobarbital results in significant decreases (approximately 40 %) in the area under the curve (AUC) for MONTELUKAST UNICORN, 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 and 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 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 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 in pregnant and lactating women has not yet been established. It is not known if MONTELUKAST UNICORN is excreted in human milk. MONTELUKAST UNICORN should not be used in pregnant and lactating women (see “CONTRAINDICATIONS”).

4.7 Effects on ability to drive and use machines

MONTELUKAST UNICORN may cause side effects such as drowsiness and dizziness which may affect your ability to drive or operate machinery.

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, hepatic eosinophilic infiltration.

Endocrine disorders*:*

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

Psychiatric disorders:

The following has been reported but frequency is unknown: Aggressive behaviour or hostility, agitation, hallucinations, disorientation, 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).

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

The following has been reported but frequency is unknown: Cholestatic hepatitis, symptomatic hepatitis, 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:

Less frequent: enuresis in children

The following has been reported but frequency is unknown: pyuria

General disorders and administration site conditions:

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

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

4.9 Overdose

KNOWN SYMPTOMS OF OVERDOSAGE AND PARTICULARS OF ITS TREATMENT:

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 haemo-dialysis.

5. PHARMACOLOGICAL PROPERTIES

Pharmacological classification: A 10.3 Medicines acting on respiratory system – others

(Leukotriene receptor antagonist)

ATC-code: R03D C03

a. Pharmacodynamic properties

Mechanism of action

The cysteinyl leukotrienes (LTC4, LTD4, LTE4) 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.

b. Pharmacodynamic effects

Montelukast is an orally active compound which binds with high affinity and selectivity to the CysLT1 receptor. In clinical studies, montelukast inhibits bronchoconstriction due to inhaled LTD4 at doses Gas 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 (Cmax) is achieved 3 hours (Tmax) after administration in adults in the fasted state. The mean oral bioavailability is 64%. The oral bioavailability and Cmax 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 Cmax 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, Cmax is achieved 2 hours after administration. The mean Cmax is 66% higher while mean Cmin is lower than in adults receiving a 10 mg tablet.

Distribution*:*

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

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:

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 necessary for mild to moderate hepatic insufficiency. There are no clinical data in patients with severe hepatic insufficiency (Child-Pugh score > 9).

Elderly:

The plasma half-life of montelukast is slightly longer in the elderly.

No dosage adjustment is necessary for the elderly.

6. PHARMACEUTICAL PARTICULARS

6.1. List of excipients

Aspartame, cherry flavour, cellulose microcrystalline, croscarmellose sodium, hydroxypropylcellulose, type EXF, magnesium stearate, mannitol and red ferric oxide (E172).

6.2. Incompatibilities

Not applicable.

6.3. Shelf life

24 months

6.4. Special precautions for storage

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

Keep the container tightly closed.

KEEP OUT OF THE REACH OF CHILDREN.

6.5. Nature and contents of container

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]

Waterfall 5-lr

Magwa Crescent West

Waterfall City

Jukskei View

2090

Marketed by sanofi aventis south africa (pty) ltd.

8. REGISTRATION NUMBERS

MONTELUKAST UNICORN 4: 44/10.2.2/0487

MONTELUKAST UNICORN 5: 44/10.2.2/0488

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

18 May 2012

10. DATE OF REVISION OF THE TEXT

05 October 2022

Additional country registration details:

Country	*Product name*	*Scheduling status (or Category of distribution)*	*Registration number*
Botswana	MONTELUKAST UNICORN 4	S2	BOT1602876/A
	MONTELUKAST UNICORN 5	S2	BOT1602877/A
Namibia	MONTELUKAST UNICORN 4	NS2	13/10.2.2/0118
	MONTELUKAST UNICORN 5	NS2	13/10.2.2/0117
Zimbabwe	MONTELUKAST UNICORN 4	P.P	2017/22.1.1/5458
	MONTELUKAST UNICORN 5	P.P	2017/22.1.1/5459

ATC Code: R03DC03 – Leukotriene receptor antagonists

Pharmacological classification: 22.1.1 – Systemic bronchodilator

(Zimbabwe)

Name and address of manufacturer:

Genveon Ilac Sanayi ve Ticaret A.S.

Inönü Mah. Gebze Plastikciler

Organize Sanayi Bölgesi

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414000 Gebze-Kocaeli,

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or

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95-010 Strykow

Poland

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

References:

Ref. No	Description	Module
1	Current UK approved innovator SmPC: Singulair 4, 26 May 2020	1.3.1.2
2	Current UK approved innovator SmPC: Singulair 5, 26 May 2020	1.3.1.2