PROFESSIONAL INFORMATION

SCHEDULING STATUS

S3

1. NAME OF THE MEDICINE

SINTAIR 4 mg chewable tablets

SINTAIR 5 mg chewable tablets

SINTAIR 10 mg tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

SINTAIR 4 mg: Each chewable tablet contains montelukast sodium, equivalent to 4 mg montelukast.

SINTAIR 5 mg: Each chewable tablet contains montelukast sodium, equivalent to 5 mg montelukast.

SINTAIR 10 mg: Each tablet contains montelukast sodium, equivalent to 10 mg montelukast.

SINTAIR tablets contain a form of sugar (mannitol).

For each strength of tablet, the quantity of mannitol is: SINTAIR 4 mg (75 mg), SINTAIR 5 mg (94 mg) and SINTAIR 10 mg (188 mg).

SINTAIR tablets contain sweetener (aspartame). For each strength of tablet the quantity of aspartame is: SINTAIR 4 mg (0,300 mg), SINTAIR 5 mg (0,375 mg) and SINTAIR 10 mg (0,750 mg).

For the full list of excipients, see section 6.1

3. PHARMACEUTICAL FORM

Chewable tablet 4 and 5 mg.

SINTAIR 4 mg: Pink coloured, oval biconvex shaped, uncoated tablets, with a break-line on both sides.

SINTAIR 5 mg: Pink coloured, round shaped, uncoated tablets, with a break-line on both sides.

Tablet - 10 mg.

SINTAIR 10 mg: Light brown coloured, round biconvex shaped, uncoated tablets, with a break-line on both sides.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

- SINTAIR 4 mg chewable tablets are indicated in paediatric patients 2 to 5 years of age for the prophylaxis and chronic treatment of atopic asthma.
- SINTAIR 5 mg chewable tablets are indicated in paediatric patients from 6 years of age for the prophylaxis and chronic treatment of atopic asthma.
- SINTAIR 10 mg tablets are indicated in adults and children 15 years of age and older for the prophylaxis and chronic treatment of atopic asthma.
- In asthmatic adults in whom SINTAIR is indicated, SINTAIR may provide some symptomatic relief of seasonal allergic rhinitis.

4.2 Posology and method of administration

- SINTAIR 4 mg / 5 mg are chewable tablets.
- SINTAIR should be taken once daily in the evening.
- SINTAIR tablets may be taken with or without food.
- Patients should be advised to continue taking SINTAIR while their asthma is controlled, as well as during periods of worsening asthma.

Treatment for atopic asthma:

Paediatric patients 2 to 5 years: One SINTAIR 4 mg chewable tablet daily.

Paediatric patients 6 to 14 years: One SINTAIR 5 mg chewable tablet daily.

Adults and children 15 years of age and older: One SINTAIR 10 mg tablet daily.

Treatment of patients with both atopic asthma and seasonal allergic rhinitis:

Adults and children 15 years of age and older: One SINTAIR 10 mg tablet, daily. In chronic asthma the dose is given in the evening.

SINTAIR has not been studied in children with both of these conditions.

Treatment for asthma:

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

Special populations

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

Missed dose

Doctors should advise patients who forget to take SINTAIR to take a dose as soon as possible and then continue with the normal dose. Patients should not take a double dose to compensate for the missed dose.

4.3 Contraindications

- Hypersensitivity to montelukast or to any of the ingredients of SINTAIR
- Pregnancy and lactation (see section 4.6)
- SINTAIR 4 mg: Safety and efficacy have not been established in children under the age of 2 years.
- SINTAIR 5 mg: Safety and efficacy have not been established in children under the age of 6 years.
- SINTAIR 10 mg: Safety and efficacy have not been established in children under the age of 15 years.

4.4 Special warnings and precautions for use

SINTAIR is not indicated for use in the reversal of bronchospasm in acute asthma attacks, including status asthmaticus. The efficacy of SINTAIR has not been established for the treatment of acute asthma attacks. Patients should be advised to have appropriate rescue medication available. During acute exacerbations of asthma, therapy with SINTAIR can be continued.

Eosinophilic conditions:

Patients on therapy with SINTAIR may present with 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 have been associated with the reduction of oral corticosteroid therapy. Medical practitioners should be on the alert for patients presenting with eosinophilia, vasculitic rash, worsening of pulmonary symptoms, cardiac complications, and/or neuropathy. Patients who develop these symptoms should be reassessed and their treatment regimens evaluated.

Neuropsychiatric events:

Neuropsychiatric events have been reported in some patients taking SINTAIR. These include agitation, aggression, anxiousness, hostility, dream abnormalities, hallucinations, depression, insomnia, irritability, restlessness, suicidal ideation and behaviour (including suicide), and tremor. Patients and health care professionals should be aware of the potential for neuropsychiatric events. Patients should be instructed to inform their health care

professionals if these events occur. Health care professionals should carefully evaluate the risks and benefits of continuing treatment with SINTAIR if such events occur.

Hypersensitivity to aspirin:

Patients with a known hypersensitivity to aspirin should continue avoiding aspirin and NSAIDs while taking SINTAIR. Although SINTAIR 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 (NSAIDs) 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 are not available in patients with severe hepatic impairment.

Patients should be advised to take SINTAIR daily as prescribed, even if they are asymptomatic, as well as during periods of worsening of asthma, and to contact their medical practitioners if their asthma is not well controlled. Medical attention should be sought if more than the prescribed maximum number of inhalations of short-acting bronchodilator treatment for a 24-hour period is needed.

SINTAIR should not be used as mono-therapy for the management and treatment of exercise-induced bronchospasm. Patients should continue with their usual inhaled beta-agonists as

prophylaxis and have a short-acting inhaled beta-agonist available for rescue, if they experience exacerbations of asthma after exercise.

SINTAIR should not be substituted abruptly for inhaled or oral corticosteroids. The dose of the corticosteroid may be tapered gradually under medical supervision. To ensure safe and appropriate use, patients should be advised to read [~~the precautions section in~~] the patient information leaflet.

Porphyria:

SINTAIR is considered to be unsafe in patients with porphyria because montelukast is considered to be probably porphyrinogenic.

Information on excipients of SINTAIR:

SINTAIR tablets contain mannitol and may have a laxative effect.

SINTAIR tablets contain aspartame as a sweetener, which is metabolised to phenylalanine, and may be hazardous to patients with phenylketonuria.

4.5 Interaction with other medicines and other forms of interaction

SINTAIR may routinely be used together with medicines used in the prophylaxis and chronic treatment of asthma.

Montelukast, as in SINTAIR, 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 SINTAIR and phenobarbitone results in significant decreases (approximately 40 %) in the area under the curve for montelukast, as a result of induction of hepatic metabolism. No dosage adjustment is necessary. However, clinical monitoring is recommended when potent hepatic enzyme inducers (such as ritonavir, phenytoin, phenobarbitone or rifampicin) or potent hepatic enzyme inhibitors (such as ketoconazole, itraconazole or voriconazole) are used with SINTAIR.

In vitro studies have shown that SINTAIR is a potent inhibitor of CYP 2C8. However, data from an interaction study involving montelukast and rosiglitazone (a probe substrate representative of medicines primarily metabolised by CYP2C8) demonstrated that montelukast did not significantly inhibit CYP2C8 *in vivo*.
Therefore, SINTAIR is not anticipated to alter the metabolism of medicines metabolised by this enzyme (e.g. paclitaxel, rosiglitazone and repaglinide).

In vitro studies have shown that montelukast, as in SINTAIR, is a substrate of CYP2C8, and to a less significant extent, of 2C9, and 3A4. In a medicine-medicine interaction study involving montelukast and gemfibrozil (an inhibitor of both CYP2C8 and 2C9) gemfibrozil increased the systemic exposure of montelukast by 4,4-fold. No routine dosage adjustment of SINTAIR 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, as contained in SINTAIR.

4.6 Fertility, pregnancy and lactation

SINTAIR should not be used during pregnancy or lactation (see section 4.3).

Pregnancy

Congenital limb defects have been reported in the babies of women treated with montelukast, as in SINTAIR, during pregnancy.

4.7 Effects on ability to drive and use machines

SINTAIR may cause side effects such as dizziness or drowsiness, which may affect the ability to drive. Patients should therefore be advised not to drive or operate machinery until their individual susceptibility is known.

4.8 Undesirable effects

Tabulated summary of adverse reactions

System Organ Class	**Frequency**	**Side effects**
Infections and Infestations	Frequent	Upper respiratory infection
Blood and lymphatic system disorders	Less frequent	Increased bleeding tendency, agranulocytosis, systemic eosinophilia, vasculitis consistent with Churg-Strauss syndrome, porphyria
Immune system disorders	Less frequent	Hypersensitivity reactions including anaphylaxis, angioedema

Metabolism and nutrition disorders	Less frequent	Pancreatitis
Psychiatric disorders	Less frequent	Abnormal dreams, hallucinations, agitation including aggressive behaviour, anxiousness, depression, insomnia, irritability, restlessness, disturbance in attention, memory impairment, disorientation, nervousness, [~~hyperventilation~~], malaise, somnambulism, suicidal thinking and behaviour (suicidality), tremor
Nervous system disorders	Frequent Less frequent	Headache, dizziness Paraesthesia, hypoesthesia, drowsiness, seizure
Ear and labyrinth disorders	Frequent	Vertigo
Cardiac disorders	Less frequent	Palpitations, chest pain
Respiratory, thoracic and mediastinal disorders	Frequent Less frequent	Congestion (nasal), cough, influenza Epistaxis, shortness of breath, hyperventilation
Gastrointestinal disorders	Frequent Less frequent	Dyspepsia, gastroenteritis (infectious), pain (dental), diarrhoea, thirst, abdominal pain, nausea, vomiting Dry mouth

Hepatobiliary disorders	Frequent Less frequent	Elevated hepatic enzymes; alanine aminotransferase (ALT) and aspartate aminotransferase (AST) Hepatitis (including cholestatic, hepatocellular, and mixed-pattern liver injury), hepatic eosinophilic infiltration
Skin and subcutaneous tissue disorders	Frequent Less frequent	Rash Pruritus, urticaria, bruising, angioedema, erythema nodosum, erythema multiforme
Musculoskeletal, connective tissue and bone disorders	Less frequent	Arthralgia, myalgia, muscle cramps (spasm)
Renal and urinary disorders	Less frequent	Pyuria
General disorders and administrative site conditions	Frequent Less frequent	Pyrexia, oedema Asthenia, fatigue, trauma

<u>Reporting of suspected adverse reactions</u>

Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Health care providers are asked to report any suspected adverse reactions to SAHPRA via the online service for adverse drug reaction reporting by following the link: https://www.sahpra.org.za/Publications/Index/8. An email can be sent directly to the company, pharmacovigilance@pharmadynamics.co.za to ensure safety of the product.

4.9 Overdose

Signs and symptoms:

Headache, vomiting, abdominal pain, hyperkinesia, mydriasis, somnolence and thirst.

Management of overdose:

It is not known whether Montelukast, as in SINTAIR, is dialysable by pertinoneal or haemodialysis.

Treatment is symptomatic and supportive.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Leukotriene receptor antagonists

ATC code: R03D C03

Pharmacological classification: A.10.2.2 Other anti-asthmatics (Leukotriene receptor antagonist).

Mechanism of action

Montelukast is a selective leukotriene receptor antagonist of the cysteinyl leukotriene CysLT1 receptor. The cysteinyl leukotrienes (LTC4, LTD4, LTE4) are products of arachidonic acid metabolism that are released from various cells including mast cells and eosinophils. They bind to cysteinyl leukotriene receptors (CysLT) found in the human airway. All the cysteinyl leukotrienes are potent constrictors of the bronchial smooth muscle. On a molar basis LTD4 is approximately 1 000 times more potent than histamine as a bronchoconstrictor. The receptor

responsible for the bronchoconstrictor effect of leukotrienes is the CysLT1 receptor. Although each of the cysteinyl leukotrienes is an antagonist at the CysLT1 receptor, LTE4 is less potent than either LCT4 or LTD4. Montelukast is a selective, high affinity competitive antagonist of the CysLT1 receptor.

5.2 Pharmacokinetic properties

Absorption:

4 mg montelukast:

Montelukast is rapidly absorbed following oral administration. The mean peak plasma concentration (C_{max}) for the 4 mg chewable tablet is achieved 2 hours after administration in paediatric patients 2 to 5 years of age in fasted state. Safety and efficacy were demonstrated in clinical studies where the 4 mg chewable tablet was administered without regard to the timing of food ingestion.

5 mg montelukast:

The mean peak plasma concentration (C_{max}), for the 5 mg chewable tablet is achieved 2 hours after administration in adults in the fasted state. The mean oral bioavailability is 73 %. Food does not have a clinically important influence with chronic administration.

10 mg montelukast:

The mean peak plasma concentration (C_{max}), for the 10 mg tablet is achieved 3 hours (T_{max}), after administration in adults in the fasted state. The mean oral bioavailability is 64 %. A standard meal does not influence the oral bioavailability and C_{max}.

Distribution:

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

Biotransformation:

Montelukast is extensively metabolised 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 cytochromes P450, 3A4, 2C9, 1A2, 2A6, 2C19, or 2D6.

Elimination:

Elimination data are not available for children 2 to 5 years of age, however, 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 faecal collections and less than 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.

The mean plasma half-life of montelukast ranged from 2,7 to 5,5 hours in healthy young adults. Montelukast pharmacokinetics 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 there is little accumulation of the parent substance in plasma (approximately 14 %).

Pharmacokinetics in special patient groups

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.

5.3 Preclinical safety data

Not applicable.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

SINTAIR 4 mg and SINTAIR 5 mg:

Aspartame (sweetener)

Cherry flavour

Croscarmellose sodium

Ferric oxide red (colourant)

Magnesium stearate

Mannitol

Microcrystalline cellulose.

SINTAIR 10 mg:

Aspartame (sweetener)

Cherry flavour

Croscarmellose sodium

Ferric oxide red (colourant)

Ferric oxide yellow (colourant)

Magnesium stearate

Mannitol

Microcrystalline cellulose.

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

36 months

6.4 Special precautions for storage

Store at or below 25 °C.

Keep in outer carton until required for use. Protect from moisture and light.

6.5 Nature and contents of container

Aluminium / aluminium silver coloured blister strips of 10 tablets each. Three blister strips per outer carton.

6.6 Special precautions for disposal

No special precautions.

7. HOLDER OF THE CERTIFICATE OF REGISTRATION

Pharma Dynamics (Pty) Ltd

1st Floor, Grapevine House, Steenberg Office Park

Silverwood Close

Westlake, Cape Town

7945, South Africa

8. REGISTRATION NUMBER(S)

SINTAIR 4 mg: A44/10.2.2/0829

SINTAIR 5 mg: A44/10.2.2/0830

SINTAIR 10 mg: A44/10.2.2/0831

9. DATE OF FIRST AUTHORISATION

26 October 2012

10. DATE OF REVISION OF THE TEXT

17 August 2022

NAMIBIA:

Sintair 4 mg: NAM NS2 13/10.2.2/0214

Sintair 5 mg: NAM NS2 13/10.2.2/0215

Sintair 10 mg: NAM NS2 13/10.2.2/0216