PROFESSIONAL INFORMATION

MONTASH

SCHEDULING STATUS

S3

1. NAME OF THE MEDICINE

MONTASH CHEW 4 (4 mg montelukast) chewable tablets.

MONTASH CHEW 5 (5 mg montelukast) chewable tablets.

MONTASH 10 (10 mg montelukast) film-coated tablets.

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Active ingredients:

Each chewable tablet of **MONTASH CHEW 4** contains 4,2 mg montelukast sodium, which is equivalent to 4 mg montelukast.

MONTASH CHEW 4 is sugar free.

Excipients with known effect:

This medicine contains 0,6 mg aspartame per tablet.

This medicine contains less than 1 mmol sodium (23 mg) per tablet, that is to say essentially 'sodium-free'.

Each chewable tablet of **MONTASH CHEW 5** contains 5,2 mg montelukast sodium, which is equivalent to 5 mg montelukast.

MONTASH CHEW 5 is sugar free.

Excipients with known effect:

This medicine contains 0,743 mg aspartame per tablet.

This medicine contains less than 1 mmol sodium (23 mg) per tablet, that is to say essentially 'sodium-free'.

Each film-coated tablet of **MONTASH 10** contains montelukast sodium 10,4 mg equivalent to 10 mg montelukast.

MONTASH 10 is sugar free.

Excipients with known effect:

This medicine contains 1,5 mg aspartame per tablet.

This medicine contains less than 1 mmol sodium (23 mg) per tablet, that is to say essentially 'sodium-free'.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

MONTASH CHEW 4: Chewable tablets.

MONTASH CHEW 5: Chewable tablets.

MONTASH 10: Film-coated tablets.

MONTASH CHEW 4: Pink, flat round tablets with beveled edges, marked with “4” on one side and plain on the other side.

MONTASH CHEW 5: Pink, flat round tablets with beveled edges.

MONTASH 10: Beige, round, biconvex, film-coated tablets.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

MONTASH CHEW 4 is indicated in paediatric patients 2 - 5 years of age for the prophylaxis and chronic treatment of atopic asthma.

MONTASH CHEW 5 is indicated in paediatric patients over 6 years of age for the prophylaxis and chronic treatment of atopic asthma.

MONTASH 10 is indicated in adults and children 15 years of age and older for the prophylaxis

and chronic treatment of atopic asthma.

MONTASH 10 may also provide some symptomatic relief of seasonal allergic rhinitis when used in those adult asthmatic patients (when indicated in asthma).

4.2 Posology and method of administration

Posology

MONTASH CHEW 4:

Atopic asthma:

The dosage for paediatric patients 2 - 5 years of age is one **MONTASH CHEW 4** chewable tablet daily at bedtime.

The dosage for paediatric patients 6 - 14 years of age is one **MONTASH CHEW 5** chewable tablet daily at bedtime.

***MONTASH CHEW 5** has not been studied in seasonal allergic rhinitis in children with asthma.*

Atopic Asthma with or without Seasonal Allergic Rhinitis:

The dosage for adults 15 years of age and older is one **MONTASH 10** film-coated tablet daily. Based on data from clinical studies in adults 15 years of age and older, there is no additional clinical benefit to montelukast doses above 10 mg once daily.

Therapy with MONTASH in Relation to Other Treatments for Asthma

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

Reduction in Concomitant Therapy:

Based on one randomized, placebo-controlled, parallel-group trial (n=226) which enrolled stable asthmatic adults, with a mean FEV_1 of approximately 84 % of predicted, who were previously maintained on various inhaled corticosteroids. During a 5- to 7-week placebo run-in period designed to titrate patients toward their lowest effective inhaled corticosteroid dose, the pre-study inhaled corticosteroid requirements were reduced by approximately 37 %. 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 subjects and 29 % of the placebo-treated subjects could be tapered off inhaled corticosteroids and remained off inhaled corticosteroids at the end of the study (p=NS).

It is not known whether the results of this study are generalizable to asthmatics that require higher doses of inhaled corticosteroids or systemic corticosteroids.

General recommendation

Within one day, the therapeutic effect of **MONTASH** should control the parameters of asthma. Even if the asthma is under control or during worsening periods of asthma, patients should be advised to keep taking **MONTASH.**

For the paediatric patients, elderly, patients with renal insufficiency or mild to moderate hepatic impairment, no dose adjustment is required. Both male and female patients may take the same dosage.

No safety and efficacy data has been established for therapy of more than 12 (twelve) weeks.

Paediatric population:

The safety and efficacy have not been demonstrated in children under the age of 2 years.

MONTASH CHEW 4 is indicated for children between 2 and 5 years of age.

MONTASH CHEW 5 is indicated for children between 6 - 14 years of age.

MONTASH 10 is indicated for children over the age of 15 years.

Method of administration:

Oral.

MONTASH should be taken once daily in the evening.

4.3 Contraindications:

- Hypersensitivity to montelukast sodium or any of the inactive excipients listed in section 6.1.
- **MONTASH CHEW 4:** The safety and efficacy have not been demonstrated in children under the age of 2 years.
- **MONTASH CHEW 5** and **MONTASH 10**: The safety and efficacy have not been demonstrated in children under the age of 6 years.

4.4 Special warnings and precautions for use

The efficacy of oral **MONTASH** for the treatment of acute asthma attacks has not been established.

MONTASH should not be used as monotherapy for the treatment and management of exercise-induced bronchospasm.

MONTASH 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 medicine readily available to treat acute asthma attacks, as oral montelukast is not advised for this. A short-acting β-agonist inhaler should be used for acute attacks. If more inhalations than usual are required of a short-acting β-inhaler, patients should be advised to consult their medical practitioner.

MONTASH should not be used abruptly as a substitute for inhaled or oral corticosteroids.
No data is available to indicate that oral corticosteroids can be reduced when given in combination with montelukast.

Patients on therapy with anti-asthma medicines including montelukast, may in rare cases, present with systematic eosinophilia, sometimes presenting clinical features of vasculitis consistent with Churg-Strauss syndrome, a condition which is often treated with systematic

corticosteroid therapy. Reduction or withdrawal of oral corticosteroids therapy has sometimes been associated with these cases. 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 should be reassessed, and their treatment regimens evaluated.

In patients with aspirin-sensitive asthma, the use of **MONTASH** does not alter the need to avoid aspirin or other non-steroidal anti-inflammatory medicine. Although montelukast is effective in improving airway function in asthmatics with documented aspirin sensitivity, it has not been demonstrated to shorten bronchoconstrictor response to aspirin and other non-steroidal anti-inflammatory drugs in aspirin-sensitive asthmatic patients.

There have been reports of neuropsychiatric events in children, adolescents and adults using montelukast. Patients and medical practitioners should be alert for these neuropsychiatric events. Patients and/or caregivers should be instructed to contact their medical practitioners if these changes occur. If such events occur, carefully evaluate the risks and benefits before continuing therapy with **MONTASH**.

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

Excipients

MONTASH contains aspartame, a source of phenylalanine. This should be taken into account in patients with phenylketonuria.

MONTASH CHEW 4 contains 0,6 mg aspartame per tablet.

MONTASH CHEW 5 contains 0,743 mg aspartame per tablet.

MONTASH 10 contains 1,5 mg aspartame per tablet.

4.5 Interaction with other medicinal products and other forms of interaction

MONTASH may be used concomitantly with other therapies used routinely in the prophylaxis and chronic treatment of asthma. The recommended clinical dose of montelukast did not have clinically important effects in drug-interactions studies, on the pharmacokinetics of the following medicines: theophylline, prednisone, prednisolone, oral contraceptives (ethinyl oestradiol/norethindrone 35/1), terfenadine, digoxin and warfarin.

The co-administration of phenobarbital and montelukast resulted in approximately 40 % decrease of the area under the plasma concentration curve (AUC) for montelukast. When montelukast is co-administered with inducers of CYP 3A4, 2C8 and 2C9 such as phenytoin, phenobarbital and rifampicin, caution should be exercised, especially in children, since montelukast is metabolised by CYP 3A4, 2C8, and 2C9.

Montelukast is a potent inhibitor of CYP 2C8 as shown in *in vitro* studies. Montelukast does not inhibit CYP 2C8 in *in vivo* studies, as demonstrated from data from a clinical interaction study involving montelukast and rosiglitazone (a probe substrate representative of medicines primarily metabolised by CYP 2C8). This concludes that **MONTASH** is not anticipated to markedly alter the metabolism of medicines metabolised by this enzyme, such as paclitaxel, rosiglitazone, and repaglinide.

Montelukast is a substrate of CYP 2C8, and to a less significant extent, of 2C9, and 3A4 as shown in *in vitro* studies.
The systematic exposure of montelukast by 4,4-fold was increased in a clinical interaction study involving montelukast and gemfibrozil (an inhibitor of both CYP 2C8 and 2C9). Co-administration of montelukast with gemfibrozil or other potent inhibitors of CYP 2C8 requires no routine dose adjustment of montelukast, however the medical practitioner should be made aware of the potential for an increase in adverse reactions.

Clinically important medicine interactions, with less potent inhibitors of CYP 2C8 (for example, trimethropin) are not anticipated based on *in vitro* studies. No significant increase in the systematic exposure of montelukast resulted from the co-administration of montelukast with itraconazole, a strong inhibitor of CYP 3A4.

4.6 Fertility, pregnancy and lactation

Pregnancy

The safety of **MONTASH** in pregnant women has not been established. During worldwide marketing experience, congenital limb defects have been reported in offspring of women treated with montelukast during pregnancy. A causal relationship between these events and montelukast has not been established.

Lactation

The safety of **MONTASH** in breastfeeding women has not been established.

There are no controlled studies in breastfeeding women, **MONTASH** should not be used by breastfeeding mothers. It is unknown if **MONTASH** is excreted in human milk.

Fertility

No data is available to indicate how **MONTASH** affects male and female fertility.

4.7 Effects on ability to drive and operate machinery

MONTASH has no or little influence on the ability to drive or use machinery. There have been reports of drowsiness and dizziness in individuals. Therefore it is advised that patients do not drive, operate complex machinery or engage in other potentially hazardous activities until it is known whether **MONTASH** affects their ability to perform such activities.

4.8 Undesirable effects

The following frequent side effects are from available clinical data for the use of montelukast:

- Montelukast 10 mg film coated tablets (4 000 adult and adolescent patients 15 years of age and older): abdominal pain and headaches.
- Montelukast 5 mg chewable tablets (1 750 paediatric patients 6 to 14 years of age): headache
- Montelukast 4 mg chewable tablets (851 paediatric patients 2 to 5 years of age): abdominal pain and thirst

Tabulated list of Adverse Reactions

Body System Class	**Frequency**	**Adverse Reactions**
Infections and infestations	*Frequent*	Upper respiratory infections
Blood and lymphatic system disorders	*Less frequent*	Increased bleeding tendency, thrombocytopenia
Immune system disorder	*Less frequent*	Hypersensitivity reactions including anaphylaxis, hepatic eosinophilic infiltration, angioedema
Psychiatric disorders	*Less frequent*	Abnormal dreams including nightmares, insomnia, somnambulism, anxiety, agitation including aggressive behaviour or hostility, depression, psychomotor hyperactivity (including irritability, restlessness, tremor), disturbance in attention, memory impairment, tic, hallucinations, disorientation, suicidal thinking and behaviour (suicidality), obsessive-compulsive symptoms, dysphemia
Nervous system	*Less frequent*	Dizziness, drowsiness,

Body System Class	Frequency	Adverse Reactions
disorders		paraesthesia/hypoesthesia, seizure
Cardiac disorders	*Less frequent*	Palpitations
Respiratory, thoracic and mediastinal disorders	*Less frequent*	Epistaxis, Churg-Strauss Syndrome (CSS) (see section 4.4), pulmonary eosinophilia
Gastrointestinal disorders	*Frequent:*	Diarrhoea, nausea, vomiting
	Less frequent	Dry mouth, dyspepsia
Hepatobiliary 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, erythema multiforma, erythema nodosum, pruritus, rash, urticaria
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

Reporting of suspected adverse reactions

If you get side effects, talk to your doctor or, pharmacist or nurse. You can also report side effects to SAHPRA via the "**6.04 Adverse Drug Reaction Reporting Form**", found online under

SAHPRA's publications: https://www.sahpra.org.za/Publications/Index/8.

Report all side effects to Unicorn Pharmaceuticals (Pty) Ltd to enquiries@unicornpharma.co.za

4.9 Overdose

No clinically important adverse experiences were reported in chronic asthma studies when montelukast was administered at doses of up to 200 mg/day to adult patients for 22 weeks and in short-term studies when montelukast was administered at doses of up to 900 mg/per for approximately one week.

Post-marketing experience and clinical studies with montelukast have reported acute overdoses. These reports included adults and children with a dose as high as 1 000 mg (approximately 61 mg/kg in a 42 month old child). These observations from clinical and laboratory findings were consistent with the safety profile in adults and children.

No adverse findings were reported in the majority of the overdose reports.

Symptoms:

Frequent adverse reactions included abdominal pain, headache, psychomotor hyperactivity, somnolence, thirst and vomiting.

Management of overdose

No specific data is available on the treatment of montelukast, as in **MONTASH**, overdose. It is not known whether montelukast is dialysable by peritoneal- or haemo-dialysis.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamics properties:

Pharmacological Class: A.10.2.2 Other anti-asthmatics

Pharmacotherapeutic group: Leukotriene receptor antagonist

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). CysLT type-1 ($CystLT_1$) which 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), causing airway actions, such as bronchoconstriction, mucous secretion, vascular permeability and eosinophil recruitment. 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.

Pharmacodynamic effects

Oral montelukast is an 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. In clinical studies, montelukast inhibits bronchoconstriction due to inhaled LTD_4 at doses as low as 5 mg. Bronchodilation was observed within 2 hours following oral administration. The bronchodilation effect caused by a β-agonist was additive to that caused by montelukast.

Due to antigen challenge, treatment with montelukast inhibited both early- and late-phase bronchoconstriction.
In adult and paediatric patients, montelukast has shown to decrease peripheral blood eosinophils, when compared to placebo.

In a separate study, treatment with montelukast significantly decreased eosinophils in the airways (as measured in sputum). In adult and paediatric patients (2 - 14 years of age), montelukast decreased peripheral blood eosinophils while improving clinical asthma control, when compared with placebo.

5.2 Pharmacokinetic Properties

Absorption:

Following oral administration, montelukast is rapidly absorbed. The mean peak plasma concentration (C_{max}) is achieved 3 hours (T_{max}) after administering the 10 mg film-coated tablet in adults in the fasted state. The mean oral bioavailability is 64 %. A standard mean does not influence the oral bioavailability and C_{max}. In clinical trials where the 10 mg film-coated tablet was administered, safety and efficacy were demonstrated regardless of the timing of food ingestion. In adults in the fasted state, the C_{max} is achieved in 2 hours after administration of the 5 mg chewable tablet. The mean oral bioavailability is 73 % and following a standard meal, is decreased by 63 %.

C_{max} is achieved 2 hours after administering the 4 mg chewable tablet to paediatric patients aged 2 – 5 in the fasted state. The mean C_{max} is 66 % higher while mean C_{min} is lower than in adults receiving a 10 mg tablet. Safety and efficacy were demonstrated in clinical studies where the 4 mg chewable tablet was administered without regard to the timing of food ingestion.

Distribution

Montelukast is more than 99 % bound to plasma proteins. The steady-state volume of distribution of montelukast averages 8 - 11 litres. Minimal distribution across the blood-brain barrier where indicated in studies in rats with radiolabelled montelukast. Minimal concentrations of radiolabelled material at 24 hours post-dose were in all other tissues.

Biotransformation

Montelukast is extensively metabolised in the liver. The plasma concentrations of montelukast are undetectable at steady state in adults and children in studies with therapeutic doses.

In the metabolism of montelukast, cytochrome P450 2C8 is the major enzyme. CYP 3A4 and 2C9

may have a minor contribution, although in healthy subjects, itraconazole, an inhibitor of CYP 3A4, have shown not to change pharmacokinetic variables of montelukast after receiving 10 mg montelukast daily. Therapeutic plasma concentrations of montelukast do not inhibit cytochromes P450 3A4, 2C9, 1A2, 2A6, 2C19, or 2D6 based on *in vitro* results in human liver microsomes. The contribution of metabolites to the therapeutic effect of montelukast is minimal.

Elimination

Elimination data are not available for children 2 to 5 years of age. In healthy adults, the plasma clearance of montelukast averages 45 ml/min. Following an oral dose of radiolabelled montelukast, 86 % of the radioactivity was recovered in a 5-day faecal collection and < 0,2 % was recovered in the urine. Therefore, montelukast and its metabolites are excreted almost exclusively in the bile together with estimates of montelukast oral bioavailability.

Several studies have demonstrated the mean plasma half-life of montelukast ranged from 2,7 to 5,5 hours in healthy young adults, with nearly linear pharmacokinetics 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 %).

Pharmacokinetics in Special Patient Groups:

Elderly (over 65 years of age)

No dose adjustments are required in the elderly.

Renal impairment

No studies have been undertaken in patients with renal impairment. No dose adjustment should be necessary in patients with renal impairment because montelukast and its metabolites are eliminated by the biliary route.

Hepatic impairment

Evidence demonstrates that patients with mild-to-moderate hepatic insufficiency and clinical evidence of cirrhosis had 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.

No dosage adjustment is necessary for mild to moderate hepatic insufficiency. In patients with severe hepatic insuffiency (Child-Pugh score >9), no data is available on the pharmacokinetics of montelukast.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Inactive ingredients of **MONTASH** include: Aspartame, croscarmellose sodium, iron oxide red (E 172), low-substituted hydroxypropyl cellulose, magnesium stearate, microcrystalline cellulose and spray dried mannitol.

MONTASH CHEW 4 & 5: cherry flavour (containing arabic gum E414, flavouring substances, maltodextrin and propylene glycol E1520).

MONTASH 10: banana flavour (containing flavouring substances, maltodextrin, modified starch E1450, propylene glycol E1520) and Opadry yellow 20A33251 (containing hypromellose 3cP, hydroxypropylcellulose, talc, titanium dioxide, iron oxide yellow (E172), iron oxide red (E172)).

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

2 years.

6.4 Special precautions for storage

Store at or below 25 °C.

Store in the original packaging.

Protect from moisture.

KEEP OUT OF REACH OF CHILDREN.

6.5 Nature and contents of container

MONTASH CHEW 4 & 5 chewable tablets are packed in Aluminium/Aluminium blisters, which are subsequently packed into cartons.

MONTASH 10 film-coated tablets are packed in Aluminium/Aluminium blisters, which are subsequently packed into cartons.

Pack sizes:

MONTASH CHEW 4: 7, 10, 14, 20, 28, 30, 50, 56, 98, 100, 140 and 200 tablets

MONTASH CHEW 5: 7, 10, 14, 20, 28, 30, 50, 56, 84, 90, 98, 100, 140 and 200 tablets

MONTASH 10: 7, 10, 14, 20, 28, 30, 50, 56, 84, 90, 98, 100, 140 and 200 tablets

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

Unicorn Pharmaceuticals (Pty) Ltd

Cnr. Searle & Pontac Streets

Cape Town, 8001

South Africa

Montash 10	Each film-coated tablet contains montelukast sodium equivalent to 10 mg montelukast
Montash Chew 4/5	Each chewable tablet contains montelukast sodium equivalent to 4/5 mg montelukast

8 REGISTRATION NUMBER(S)

MONTASH CHEW 4: TBA

MONTASH CHEW 5: TBA

MONTASH 10: 55/10.2.2/0914

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

MONTASH CHEW 4: TBA

MONTASH CHEW 5: TBA

MONTASH 10: 17 October 2023

10 DATE OF REVISION OF THE TEXT

Not applicable