CLEAN PROPOSED PROFESSIONAL INFORMATION

SCHEDULING STATUS

S3

1. NAME OF THE MEDICINE

MONTELUKAST 4 LHC Chewable Tablets

MONTELUKAST 5 LHC Chewable Tablets

2. QUALITATIVE AND QUANTITAVE COMPOSITION

MONTELUKAST 4 LHC: Each chewable tablet contains montelukast sodium equal to 4 mg montelukast.

MONTELUKAST 5 LHC: Each chewable tablet contains montelukast sodium equal to 5 mg montelukast.

MONTELUKAST LHC chewable tablets contains sweetener:

Aspartame 1.20 mg (4 mg tablet)

Aspartame 1.50 mg (5 mg tablet)

MONTELUKAST LHC chewable tablets contains sugar alcohol:

Mannitol 168.84 mg (4 mg tablet)

Mannitol 211.05 mg (5 mg tablet)

For full list of excipients, see **section 6.1**

3. PHARMACEUTICAL FORM

Chewable tablets

MONTELUKAST 4 LHC: Pink, marbled, round, slightly biconvex tablet with bevel edges and inscription '4' on one side and plain on the other side.

MONTELUKAST 5 LHC: Pink, marbled, round, slightly biconvex tablet with bevel edges and inscription

'5' on one side and plain on the other side.

4. CLINICAL PARTICULARS

4.1 Therapeutic Indications

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

MONTELUKAST 5 LHC are indicated in paediatric patients over 6 years of age for the prophylaxis and chronic treatment of atopic asthma.

4.2 Posology and method of administration

Posology

MONTELUKAST 4 LHC

***Paediatric patients 2 to 5 years of age with atopic asthma*:**

The dosage for paediatric patients 2 to 5 years of age is one 4 mg chewable tablet daily to be taken at bedtime.

MONTELUKAST 5 LHC

Paediatric patients 6 to14 years of age with atopic asthma:

The dosage for paediatric patients 6 to 14 years of age is one 5 mg chewable tablet daily to be taken at bedtime.

General Recommendations:

A therapeutic effect of **MONTELUKAST LHC** on parameters of asthma control occurs within one day. Patients should be advised to continue taking **MONTELUKAST LHC** while their asthma is controlled, as well as during periods of worsening asthma.

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

CLEAN PROPOSED PROFESSIONAL INFORMATION

Safety and efficacy for more than 12 (twelve) weeks has not been established in controlled clinical trials.

*Therapy with **MONTELUKAST LHC** in Relation to Other Treatments for Asthma:*

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

MONTELUKAST LHC chewable tablets have not been studied in seasonal allergic rhinitis in children with asthma.

Method of administration

Oral use

The chewable tablets should be given to a child under adult supervision.

MONTELUKAST LHC chewable tablets should be given at bedtime. If given in connection with food it should be1 hour before or 2 hours after food in the evening.

4.3 Contraindications

- Hypersensitivity to montelukast or any component of **MONTELUKAST LHC** chewable tablets listed in section 6.1
- **MONTELUKAST 4 LHC:** Children under the age of 2 years, as safety and efficacy have not been demonstrated.
- **MONTELUKAST 5 LHC:** Children under the age of 6 years, as safety and efficacy have not been demonstrated.
- Pregnancy and lactation (see **section 4.6**).

4.4 Special warnings and precautions for use

General:

The efficacy of oral **MONTELUKAST LHC** chewable tablets for the treatment of acute asthma attacks has not been established.

CLEAN PROPOSED PROFESSIONAL INFORMATION

MONTELUKAST LHC chewable tablets 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 beta-agonists as prophylaxis and have available for rescue a short-acting inhaled beta-agonist.

MONTELUKAST LHC chewable tablets are not indicated for use in the reversal of broncho-spasm in acute asthma attacks, including status asthmaticus. Patients should be advised to have appropriate rescue medication available. Therapy with **MONTELUKAST LHC** chewable tablets can be continued during acute exacerbations of asthma.

While the dose of inhaled corticosteroid may be reduced gradually under medical supervision, **MONTELUKAST LHC** chewable tablets should not be abruptly substituted for inhaled or oral corticosteroids.

Patients with known aspirin sensitivity should continue avoidance of aspirin or non-steroidal anti-inflammatory agents while taking **MONTELUKAST LHC** chewable tablets. Although **MONTELUKAST LHC** chewable tablets are affective in improving airway function in asthmatics with document aspirin sensitivity, it has not been shown to truncate bronchoconstrictor response to aspirin and other non-steroidal anti-inflammatory drugs in aspirin-sensitive asthmatic patients.

Renal Insufficiency:

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

Eosinophilic Conditions:

Patients on therapy with **MONTELUKAST LHC** chewable tablets 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 events usually, but not always, have been associated with the reduction of oral corticosteroid therapy. The possibility that leukotriene receptor antagonists may be associated with emergence of Churg-Strauss syndrome can neither be excluded nor established. Medical practitioners should be alert to eosinophillia, vasculitic rash, worsening pulmonary symptoms, cardiac complications, and/or neuropathy presenting in their patients. In such patients **MONTELUKAST LHC** chewable tablets should be withdrawn

Neuropsychiatric events

Neuropsychiatric events have been reported in patients taking montelukast (see **Section 4.8**).
Patients and doctors should be alert for neuropsychiatric events. Patients and/or caregivers should be instructed to notify their healthcare professional if these changes occur.
Healthcare professionals should carefully consider continuation of treatment with **MONTELUKAST LHC** if such events occur.

Other:

Treatment with **MONTELUKAST LHC** does not alter the need for patients with aspirin-sensitive asthma to avoid taking aspirin and other non-steroidal anti-inflammatory medicines.

Information for the patients:

- Patients should be advised to take **MONTELUKAST LHC** chewable tablets daily as prescribed, even when they are asymptomatic, as well as during periods of worsening asthma and to contact their physician if their asthma is not well controlled.
- Patients should be advised that oral tablets of **MONTELUKAST LHC** chewable tablets are not for the treatment of acute asthma attacks. They should have appropriate short-acting inhaled beta-agonist medication available to treat asthma exacerbations.

CLEAN PROPOSED PROFESSIONAL INFORMATION

- Patients should be advised that, while using **MONTELUKAST LHC** chewable tablets, 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 24 hour period are needed.
- Patients receiving **MONTELUKAST LHC** chewable tablets should be instructed not to decrease the dose or stop taking any other anti-asthma medication unless instructed by a medical practitioner.
- Patients who have exacerbations of asthma after exercise should be instructed to continue to use their usual regime of inhaled beta-agonist as prophylaxis unless otherwise instructed by their medical practitioners. All patients should have available for rescue a short-acting inhaled beta-agonist.
- Patients with a known aspirin sensitivity should be advised to avoid taking aspirin or non-steroidal anti-inflammatory medicines while taking **MONTELUKAST LHC** chewable tablets**.**

Phenylalanine:

MONTELUKAST LHC contains aspartame, which is a source of phenylalanine which may be harmful for patients with phenylketonuria.

4.5 Interaction with other medicines and other forms of interaction

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

The area under the plasma concentration time curve (AUC) for montelukast was decreased

approximately 40 % in subjects with co-administration of phenobarbital. No dosage adjustment for **MONTELUKAST LHC** chewable tablets is recommended.

Since montelukast is metabolised by CYP 3A4, 2C8, and 2C9, caution should be exercised, particularly in children, when **MONTELUKAST LHC** 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 an inhibitor of CYP2C8. However, data from a clinical interaction study involving montelukast and rosiglitazone (a probe substrate representative of medicines primarily metabolised by CYP2C8) demonstrated that montelukast does not inhibit CYP2C8 *in vivo.* Therefore 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 is a substrate of CYP 2C8, and to a less significant extent, of 2C9, and 3A4. In a clinical medicines 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 LHC** is required upon co-administration with gemfibrozil or other potent inhibitors of CYP 2C8, but the doctor 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 LHC** chewable tablets in pregnant women has not been established (see

CLEAN PROPOSED PROFESSIONAL INFORMATION

section 4.3).

Since there are no controlled studies in pregnant women, **MONTELUKAST LHC** chewable tablets should not be used during pregnancy.

Breastfeeding

The safety of **MONTELUKAST LHC** chewable tablets in breastfeeding women has not been established (see **section 4.3**).

Since there are no controlled studies in breastfeeding women, **MONTELUKAST LHC** chewable tablets should not be used by breastfeeding mothers. It is not known if **MONTELUKAST LHC** chewable tablets are excreted in human milk.

Fertility

Congenital limb defects have been reported in offspring of women treated with Montelukast as contained in MONTELUKAST LHC chewable tablets during pregnancy. A causal relationship between these events and montelukast has not been established.

4.7 Effects on ability to drive and use machines

MONTELUKAST LHC chewable tablets may cause adverse effects such as dizziness and drowsiness which may affect ability to drive and operate machines safely. Patients should therefore be advised not to drive or operate machinery until their individual susceptibility is known.

4.8 Undesirable effects

Body System Class	**Frequency**		
	Frequent	**Less Frequent**	**Unknown**

CLEAN PROPOSED PROFESSIONAL INFORMATION

Infections and infestations	Upper respiratory infection		
Blood and lymphatic system disorders		Churg-Strauss Syndrome, Eosinophilic Conditions.	Increased bleeding tendency, agranulocytosis, thrombocytopenia.
Immune system disorders		Hypersensitivity reactions including allergy, anaphylaxis, angiodema, hepatic oesinophilic, rashes and urticaria.	Hepatic eosinophilic infiltration
Endocrine disorders			Pancreatitis
Psychiatric disorders		Dream abnormalities including nightmares, somnambulism, anxiety, agitation including aggressive behaviour or hostility, depression, psychomotor hyperactivity (including irritability, restlessness, tremor).	Hallucinations, suicidality, disturbance in attention, memory impairment, tic, disorientation, obsessive-compulsive symptoms, dysphemia.
Nervous system disorders	Dizziness, headache, insomnia.	Drowsiness, paraesthesia/ hypoesthesia, seizure.	
Cardiac disorders			Palpitations
Respiratory, thoracic and mediastinal disorders:		Nasal congestion, epistaxis cough, influenza, increased incident of respiratory tract infections.	Pulmonary eosinophilia
Gastrointestinal disorders	Abdominal pains, diarrhoea, nausea, vomiting.	Dyspepsia, gastroenteritis. dry mouth.	
Hepato-biliary disorders	Elevated levels of serum transaminases (ALT, AST).	symptomatic hepatitis or hyperbilirubinaemia.	Hepatitis (including cholestatic, hepatocellular, and mixed-pattern liver injury)
Skin and subcutaneous tissue disorders	Rash	Bruising, urticaria, pruritus.	Erythema nodosum, erythema multiforme.

CLEAN PROPOSED PROFESSIONAL INFORMATION

Musculoskeletal and connective tissue disorders		Arthralgia, myalgia including muscle cramps.	
Renal and urinary disorders		Enuresis in children.	Pyuria
General disorders and administration site disorders	Pyrexia	Asthenia, fatigue, dental pain, fever, malaise, oedema.	Generalized pain

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 medicine. Healthcare professionals are asked to report any suspected adverse reactions to SAHPRA via The '6.04 Adverse Drug Reactions Reporting Form'. Found under SAHPRA's publications: https://www/sahpra.org.za/Publications/Index/8.

4.9 Overdose

Symptoms

The most frequent adverse experience observed were abdominal pain, somnolence, thirst, headache, vomiting and psychomotor hyperactivity.

Treatment

Treatment is symptomatic and supportive.

No specific information is available on the treatment of overdosage with **MONTELUKAST LHC** chewable tablets. It is not known whether montelukast is dialysable by peritoneal or haemodialysis.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group:

CLEAN PROPOSED PROFESSIONAL INFORMATION

A 10.2.2 Other anti-asthmatics, Leukotriene receptor antagonists.

ATC Code: R03DC03

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 a number of airway actions, including bronchoconstriction, mucous secretion, vascular permeability, and eosinophil recruitment.

Montelukast 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-adrenegic receptor). Montelukast inhibits physiological actions of LTC_4, LTD_4, and LTE_4 at the $CysLT_1$ receptor without agonist activity.

Montelukast causes potent inhibition of airway cysteinyl leukotriene receptors as demonstrated by the ability to inhibit bronchoconstriction due to inhaled LTD4 in asthmatic patients. Doses as low as 5 mg cause substantial blockage of LTD4 – induced bronchoconstriction.

5.2 Pharmacokinetic properties

Absorption

Montelukast is absorbed following oral administration.

For the 4 mg tablet, C_{max} is achieved 2 hours after administration in paediatric patients 2 to 5 years of age in the 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.

For the 5 mg tablet, C_{max} 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.

Distribution

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

Metabolism

Montelukast is extensively metabolised in the liver. In studies with therapeutic doses, plasma concentrations of metabolites of montelukast are undetectable at 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 radiolabelled 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 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. The pharmacokinetics of montelukast are nearly linear for oral doses up to 50 mg. No differences in pharmacokinetics was noted between dosing in the morning or the evening. During once daily dosing with 10 mg montelukast, there is little accumulation of the parent drug in plasma (approximately 14 %).

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). 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

In animal toxicity studies, minor serum biochemical alterations in ALT, glucose, phosphorus and triglycerides were observed which were transient in nature. The signs of toxicity in animals were increased excretion of saliva, gastrointestinal symptoms, loose stools and ion imbalance. These occurred at dosages which provided > 17 -fold the exposure seen at the clinical dosage. In monkeys, the adverse effects appeared at doses from 150 mg/kg/day (> 232-fold the systemic exposure seen at the clinical dose).

In animal studies, montelukast did not affect fertility or reproductive performance at systemic exposure exceeding the clinical systemic exposure by greater than 24-fold. A slight decrease in pup body weight was noted in the female fertility study in rats at 200 mg/kg/day (> 69 fold the clinical systemic exposure). In studies in rabbits, a higher incidence of incomplete ossification, compared with concurrent control animals, was seen at systemic exposure> 24-fold the clinical systemic exposure seen at the clinic dose. No abnormalities were seen in rats. Montelukast has been shown to cross the placenta barrier and is excreted in breast milk of animals.

No death occurred following a single oral administration of montelukast sodium at doses up to 5,000

CLEAN PROPOSED PROFESSIONAL INFORMATION

mg/kg in mice and rats (15,000 mg/m^2 and 30,000mg/m^2 in mice and rats, respectively), the maximum dose tested. This dose is equivalent to 25, 000 times the recommended daily adult human dose (based on an adult patient weight of 50kg).

Montelukast was determined not to be phototoxic in mice for UVA, UVB or visible light spectra at doses up to 500 mg/kg/day (approximately>200-fold based on systemic exposure)
Montelukast was neither mutagenic in *in vitro and in vivo* tests nor tumorigenic in rodent species.

6.PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Mannitol

Microcrystalline cellulose

Croscarmellose sodium

Hydroxypropyl cellulose

Aspartame

Iron oxide red E172

Flavour cherry black

Magnesium stearate.

6.2 Incompatibilities

Not applicable

6.3 Shelf Life

3 years

6.4 Special precautions for storage

Store at or below 30 °C, protected from light.

CLEAN PROPOSED PROFESSIONAL INFORMATION

The blisters must be kept in the outer carton until required for use.

Do not remove tablets from blister until required for use.

6.5 Nature of contents of container

MONTELUKAST LHC Chewable Tablets are packed in blister packs of Foil and OPA/Al/PVC.

MONTELUKAST LHC Chewable Tablets are available in pack sizes of 30's.

Blisters are kept in an outer carton.

6.6 SPECIAL PRECAUTIONS FOR DISPOSAL

No special requirements

Any unused product or waste material should be disposed of in accordance with local requirements.

7. HOLDER OF CERTIFICATE OF REGISTRATION

LHC Pharmaceuticals (Pty) Ltd

N4 Gate Way Industrial Park

553 Willow Park Manor

33 Ghaap Street

PRETORIA

8. REGISTRATION NUMBER (S)

TBA

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

TBA

10 DATE OF REVISION OF THE TEXT