SCHEDULING STATUS

S3

1 NAME OF THE MEDICINE

MONTELUKAST CHEW BIOTECH 4 Chewable tablets

MONTELUKAST CHEW BIOTECH 5 Chewable tablets

MONTELUKAST BIOTECH 10 Film-coated tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

MONTELUKAST CHEW BIOTECH 4: Each chewable tablet contains 4,0 mg montelukast.

MONTELUKAST CHEW BIOTECH 5: Each chewable tablet contains 5,0 mg montelukast.

MONTELUKAST BIOTECH 10: Each film-coated tablet contains 10,0 mg montelukast.

Excipients with known effect:

Each MONTELUKAST CHEW BIOTECH 4 tablet contains:

Sweetener: Aspartame 2,40 mg

Sugar: Mannitol 179,76 mg

Each MONTELUKAST CHEW BIOTECH 5 tablet contains:

Sweetener: Aspartame 3,00 mg

Sugar: Mannitol 224,71 mg

Each MONTELUKAST BIOTECH 10 tablet contains:

Sugar: lactose monohydrate 85,81 mg

Lecithin (soya) contained in film-coating.

For full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Chewable tablets

MONTELUKAST CHEW BIOTECH 4: A pink, oval, biconvex tablet with "4" debossed in one side.

MONTELUKAST CHEW BIOTECH 5: A pink, round, biconvex tablet with "5" debossed in one side.

Film-coated tablets

MONTELUKAST BIOTECH 10: A pale orange round, biconvex tablet.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

MONTELUKAST CHEW BIOTECH 4 Tablets are indicated in paediatric patients 2 – 5 years of age for the prophylaxis and chronic treatment of atopic asthma.

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

MONTELUKAST BIOTECH 10 Film-coated tablets are indicated for adults and children 15 years of age and older for the prophylaxis and chronic treatment of atopic asthma.

In those adult asthmatic patients, in whom MONTELUKAST BIOTECH is indicated for asthma, MONTELUKAST BIOTECH may also provide some symptomatic relief of seasonal allergic rhinitis.

4.2 Posology and method of administration

Posology

MONTELUKAST BIOTECH should be taken once daily in the evening.

MONTELUKAST CHEW BIOTECH 4:

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 MONTELUKAST CHEW BIOTECH 4 chewable tablet daily.

MONTELUKAST CHEW BIOTECH 5:

Paediatric patients 6 to 14 years of age with atopic asthma:

The dosage for paediatric patients 6 to 14 years of age is one 5 mg MONTELUKAST CHEW BIOTECH 5 chewable tablet daily. MONTELUKAST CHEW BIOTECH 5 has not been studied in seasonal allergic rhinitis in children with asthma.

MONTELUKAST BIOTECH 10 Film-Coated Tablet:

Adults and children 15 years of age and older with atopic asthma with or without seasonal allergic rhinitis:

The dosage for adults 15 years of age and older is one 10 mg MONTELUKAST BIOTECH 10 film-coated tablet daily.

The 10 mg MONTELUKAST BIOTECH 10 film-coated tablet should be swallowed whole.

Therapy with MONTELUKAST BIOTECH in relation to other treatments for asthma:

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

Patients should be advised to take MONTELUKAST BIOTECH every day even while their asthma is controlled, as well as during periods of worsening asthma.

Special populations

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

Method of administration

For oral use.

MONTELUKAST BIOTECH can be taken with or without food.

4.3 Contraindications

- Hypersensitivity to montelukast or to any of the excipients of MONTELUKAST BIOTECH listed in section 6.1.
- MONTELUKAST CHEW BIOTECH 4 is contraindicated in children under the age of 2 years as safety and efficacy of the 4 mg tablets have not been demonstrated.
- MONTELUKAST CHEW BIOTECH 5 is contraindicated in children under the age of 6 years, as safety and efficacy of 5 mg tablets have not been demonstrated.
- MONTELUKAST BIOTECH 10 is contraindicated in children under the age of 15 years.
- Pregnancy and lactation.
- MONTELUKAST BIOTECH 10 contains soy lecithin (E-322) (peanut oil). If you are allergic to peanut or soya, do not use MONTELUKAST BIOTECH 10.

4.4 Special warnings and precautions for use

MONTELUKAST BIOTECH is not indicated in the reversal of bronchospasm in acute asthma attacks, including status asthmaticus.

MONTELUKAST BIOTECH should not be used for the treatment of acute asthma attacks as efficacy has not been established.

Eosinophilic conditions

Patients on therapy with MONTELUKAST BIOTECH 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 usually, but not always, 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.

Neuropsychiatric events

Neuropsychiatric events have been reported in adult, adolescent and paediatric patients taking MONTELUKAST BIOTECH.

These include agitation, aggression, hostility, anxiousness, dream abnormalities, hallucinations, depression, disorientation, disturbance in attention, insomnia, irritability, memory impairment, restlessness, somnambulism, suicidal thinking and behaviour (including suicide), tic and tremor.

Patients and medical practitioners should be aware of the potential for neuropsychiatric events. Patients should be instructed to inform their medical practitioners if these events occur.

Medical practitioners should carefully evaluate the risks and benefits of continuing treatment with MONTELUKAST BIOTECH if such events occur.

Hypersensitivity to aspirin

Patients with a known hypersensitivity to aspirin should continue avoiding aspirin and NSAIDs while taking MONTELUKAST BIOTECH. Although MONTELUKAST BIOTECH is effective in improving airway function in asthmatics, it has not been shown to reduce the bronchoconstrictor response to aspirin and other non-steroidal anti-inflammatory drugs (NSAIDs) in aspirin-sensitive asthmatic patients.

Hepatic 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 function impairment.

General

MONTELUKAST BIOTECH is not indicated for use in the reversal of bronchospasms in acute asthma attacks, including status asthmaticus. Patients should be instructed to always have appropriate rescue medication available. Therapy with MONTELUKAST BIOTECH can however be continued during acute exacerbations of asthma.

Patients should be advised to take MONTELUKAST BIOTECH daily as prescribed, even if they are asymptomatic, as well as during periods of worsening 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, are needed.

MONTELUKAST BIOTECH should not be used as monotherapy in the treatment and management of exercise-induced bronchospasm. Patients should rather be advised to continue with their usual regimen of an inhaled beta-agonist as prophylaxis and to have a short-acting inhaled beta-agonist available for rescue treatment, if they have exacerbations of asthma after exercise.

Corticosteroid therapy should not be abruptly substituted with MONTELUKAST BIOTECH. Under medical supervision the dose of inhaled or oral corticosteroids should be tapered gradually, if appropriate. To ensure safe and appropriate use, patients should be advised to read the precautions section in the patient information leaflet.

MONTELUKAST CHEW BIOTECH contains aspartame

MONTELUKAST CHEW BIOTECH 4 and MONTELUKAST CHEW BIOTECH 5 contain aspartame. Aspartame is hydrolysed in the gastrointestinal tract when orally ingested. One of the major hydrolysis products is phenylalanine.

It may be harmful to patients with phenylketonuria (PKU).

MONTELUKAST BIOTECH 10 contains lactose monohydrate and lecithin (soya)

Lactose:

MONTELUKAST BIOTECH 10 contains lactose. Patients with rare hereditary problems of galactose intolerance, total lactase deficiency or glucose-galactose malabsorption, should not take MONTELUKAST BIOTECH 10.

Lecithin (soya):

MONTELUKAST BIOTECH 10 contains lecithin (soya) in the film-coating. Soy lecithin (E-322) can contain soy protein, and it can therefore result in allergic reactions in people who are sensitive to peanuts or soya (see section 4.3).

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

4.5 Interaction with other medicines and other forms of interaction

MONTELUKAST BIOTECH may be administered with other therapies routinely used in the prophylaxis and chronic treatment of asthma, and seasonal allergic rhinitis.

In medicine interaction 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 mcg /1 mg), digoxin and warfarin.

Patients sensitive to aspirin should avoid the use of aspirin or non-steroidal anti-inflammatory drugs (NSAIDs) while using MONTELUKAST BIOTECH (see section 4.4).

Clinical monitoring is recommended during co-administration of MONTELUKAST BIOTECH with potent cytochrome P450 enzyme inducers, such as ritonavir, rifampicin, phenytoin and phenobarbital

(phenobarbitone) or *St John's wort*.

Phenobarbital (phenobarbitone) induces the hepatic metabolism of MONTELUKAST BIOTECH resulting in significant decreases of approximately 40 % in the area under the curve (AUC) for MONTELUKAST BIOTECH. No dosage adjustment for MONTELUKAST BIOTECH is recommended.

MONTELUKAST BIOTECH may potentiate sodium and fluid retention caused by prednisone which could result in severe peripheral oedema.

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

In vitro studies have shown that montelukast is a substrate of CYP2C8, CYP2C9, and CYP3A4. Data from an interaction study involving montelukast and gemfibrozil (an inhibitor of both CYP2C8 and CYP2C9) demonstrated that gemfibrozil increased the systemic exposure of montelukast by 4,4-fold. Co-administration of itraconazole, a strong CYP3A4 inhibitor, with gemfibrozil and montelukast did not further increase the systemic exposure of montelukast. The effect of gemfibrozil on systemic exposure of montelukast is not considered to be clinically meaningful based on clinical safety data with doses greater than the 10 mg approved dose in adults (e.g., 200 mg/day to adult patients for 22 weeks, and up to 900 mg/day to patients for approximately one week) where clinically important adverse experiences were not observed. Therefore, no dosage adjustment of MONTELUKAST BIOTECH is required upon co-administration with gemfibrozil.

Based on *in vitro* data, important interactions with other known inhibitors of CYP2C8 (e.g., trimethoprim) are not anticipated. In addition, coadministration of montelukast with itraconazole alone resulted in no significant increase in the systemic exposure of montelukast.

4.6 Fertility, pregnancy and lactation

Pregnancy

The safety of MONTELUKAST BIOTECH in pregnant and lactating women has not been established.

MONTELUKAST BIOTECH should not be used during pregnancy (see section 4.3).

Breastfeeding

MONTELUKAST BIOTECH should not be used during breastfeeding (see section 4.3).

It is not known if MONTELUKAST BIOTECH is excreted in human breastmilk.

Fertility

No data available.

4.7 Effects on ability to drive and use machines

MONTELUKAST BIOTECH 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

Infections and infestations	Frequent	Upper respiratory infection
Blood and lymphatic system disorders	Less frequent	Increased bleeding tendency, agranulocytosis, thrombocytopenia, systemic eosinophilia, vasculitis consistent with Churg-Strauss syndrome (see section 4.4), porphyria.

Immune system disorders	Less frequent	Hypersensitivity reactions including anaphylaxis, angioedema, hepatic eosinophilic infiltration, decreased immune responsiveness.
Psychiatric disorders	Less frequent	Abnormal dreams including nightmares, and insomnia, somnambulism, hallucinations, agitation including aggressive behaviour or hostility, anxiousness, depression, psychomotor hyperactivity (including irritability, restlessness, tremor) suicidal thinking and behaviour (suicidality), disturbance in attention, memory impairment, tic, disorientation, obsessive-compulsive symptoms, dysphemia
Nervous system disorders	Frequent	Headache, dizziness.
	Less frequent	Drowsiness, paraesthesia/ hypoesthesia, seizure
Cardiac disorders	Less frequent	Palpitations, chest pain
Eye disorders	Less frequent	Blepharospasm, mydriasis
Respiratory, thoracic and mediastinal disorders	Less frequent	Congestion (nasal), cough, influenza, epistaxis, pulmonary eosinophilia.
Gastrointestinal disorders	Frequent	Dyspepsia, gastroenteritis (infectious), pain (dental), diarrhoea, thirst, abdominal pain
	Less frequent	Nausea, vomiting, bowel movement irregularity, dry mouth, flatulence, salivary hypersecretion
Hepato-biliary disorders	Less frequent	Hepatitis (including cholestatic, hepatocellular, and mixed-pattern liver injury), increased alanine aminotransferase (ALT) and aspartate aminotransferase (AST)

Skin and subcutaneous tissue disorders	Frequent	Rash
	Less frequent	Pruritus, urticaria, erythema nodosum, bruising, erythema multiforme
Musculoskeletal, connective tissue and bone disorders	Less frequent	Arthralgia, myalgia, including muscle cramps
Renal and urinary disorders	Less frequent	Enuresis in children
General disorders and administration site conditions	Frequent	Asthenia/fatigue, trauma
	Less frequent	Oedema, pyrexia and increased sweating
Ear and labyrinth disorders	Frequent	Vertigo
Investigations	Less frequent	Alanine aminotransferase increased, Aspartate aminotransferase increased, white blood cell count decreased, eosinophil count increased, haematocrit decreased, haemoglobin decreased

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. 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.

4.9 Overdose

Symptoms

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

No specific information is available on the treatment of overdosage with MONTELUKAST BIOTECH.

Treatment may include removal of unabsorbed material from the gastro-intestinal tract, clinical monitoring and supportive therapy if required.

It is not known whether montelukast is dialysable by peritoneal or haemodialysis.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Category and class: A. 10.2.2 Other anti-asthmatics, Leukotriene receptor antagonist

Pharmacotherapeutic group: Leukotriene receptor antagonist

ATC-code: R03D C03

Montelukast binds with high affinity and selectivity to the cysteinyl leukotriene (Cys-LT1) receptor. Montelukast inhibits physiological actions of cysteinyl leukotriene LTC4, LTD4 and LTE4 at the Cys-LT1 receptor without agonist activity.

The cysteinylleukotrienes (cys-LTs) which include LTC4, LTD4 and LTE4 are potent inflammatory eicosanoids released from various cells including mast cells and eosinophils. These important pro-asthmatic mediators bind to cysteinyl leukotriene (cys-LTs) receptors in the human airway. cys-LTs have been correlated with the pathophysiology of asthma and allergic rhinitis. In asthma, leukotriene-mediated effects include a number of airway actions, including 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 LTD4, in asthmatic patients. Doses as low as 5 mg cause substantial blockage of LTD4-induced bronchoconstriction.

5.2 Pharmacokinetic properties

Absorption

Montelukast is rapidly absorbed following oral administration.

For the 10 mg film-coated tablet, the peak plasma concentration (C_{max}) is achieved in 3 hours after oral doses in the fasted state. Bioavailability of about 64 % is unaffected by co-administration of a standard meal in the morning.

For the 5 mg chewable tablet, the peak plasma concentration is achieved in 2 hours after oral doses in the fasted state. Bioavailability of about 73 % is achieved and is not clinically been influenced by food with chronic administration.

For the 4 mg chewable 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.

Distribution

Montelukast is highly protein bound with more than 99 %. The steady-state volume of distribution of montelukast averages 8 to 11 litres.

Biotransformation

Montelukast is extensively metabolised in the liver by cytochrome P450 isozymes CYP3A4 and CYP2C9.

Elimination

The plasma clearance of montelukast averages 45 ml/min in healthy adults.

Montelukast is excreted primarily in the faeces via the bile. The duration of action is 24 hours and the half-life ranges between 2,7 to 5,5 hours in healthy young adults. The pharmacokinetics of montelukast is nearly linear for oral doses up to 50 mg.

Characteristics in specific groups of subjects or patients

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 adjustments are required for 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 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.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

MONTELUKAST CHEW BIOTECH 4 & 5:

Aspartame

Croscarmellose sodium

Hydroxypropylcellulose

Magnesium stearate

Mannitol

Microcrystalline cellulose

Red iron oxide

Strawberry flavour

MONTELUKAST BIOTECH 10:

Croscarmellose sodium

Hydroxypropylcellulose

Lactose monohydrate

Magnesium stearate

Microcrystalline cellulose

Opadry AMB Rosa 80W34307 consisting of: Lecithin (soya), iron oxide red, iron oxide yellow, polyvinyl alcohol, talc, titanium dioxide and xanthum gum.

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 years

6.4 Special precautions for storage

Store at room temperature at or below 25 °C, protected from moisture and light.

Keep blister in outer carton until required for use. Tablets should not be removed from blisters until required for use, to protect it from moisture.

6.5 Nature and contents of container

MONTELUKAST BIOTECH: is available in silver polyamide/Alu/PVC and silver aluminium blister packs of 28 and 30.

6.6 Special precautions for disposal and other handling

No special requirements.

7 HOLDER OF CERTIFICATE OF REGISTRATION

Biotech Laboratories (Pty) Ltd

Block K West, Central Park

400 16th Road, Halfway House

Midrand, 1685

8 REGISTRATION NUMBER(S)

MONTELUKAST CHEW BIOTECH 4: 45/10.2.2/0475

MONTELUKAST CHEW BIOTECH 5: 45/10.2.2/0476

MONTELUKAST BIOTECH 10: 45/10.2.2/0477

9 DATE OF FIRST AUTHORISATION/ RENEWAL OF THE AUTHORISATION

Date of registration: 19 April 2013

10 DATE OF REVISION OF THE TEXT

22 October 2024.