HCR: LHC Pharmaceuticals (Pty) Ltd
Product Name: Antaluko10
Dosage form and strength: Film-coated Tablets, Montelukast 10mg
Date Approved: 31 January 2024

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SCHEDULING STATUS

S3

1. NAME OF THE MEDICINE

Antaluko10 mg Film Coated Tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each film-coated tablet contains 10 mg montelukast equivalent to 10.4 mg montelukast sodium.

Contains sugar: lactose monohydrate *81, 94 mg.*

For full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Film-coated tablet.

Round, slightly biconvex, apricot film-coated tablets with bevelled edges.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

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Antaluko 10 mg film-coated tablets are indicated in 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 **Antaluko** tablets are indicated in asthma, **Antaluko** tablets may also provide some symptomatic relief of seasonal allergic rhinitis.

4.2 Posology and method of administration

Posology

The recommended dose for adults and adolescents 15 years of age and older with atopic asthma, or with asthma and concomitant seasonal allergic rhinitis, is one 10 mg tablet daily to be taken in the evening with or without food. Clinical studies in adults 15 years of age and older demonstrated there is no additional clinical benefit to montelukast doses above 10 mg once daily.

The therapeutic effect of **Antaluko** on parameters of asthma control occurs within one day. Patients should be advised to continue taking **Antaluko** even if their asthma is under control, as well as during periods of worsening asthma.

Hepatic impairment

The metabolism of montelukast may be decreased in patients with mild to moderate hepatic impairment and clinical evidence of cirrhosis. The half-life may be slightly prolonged; however, dosage adjustment is not necessary. No data are available for patients with severe hepatic impairment. 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 renal insufficiency (See Sec 4.4).

Renal impairment

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 (See Sec 5.2).

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 (See Sec 5.2).

Children

Antaluko10 is not recommended to children under the age of 15 years, as safety and efficacy have not been demonstrated (See Sec 4.3).

Therapy with Antaluko in relation to other treatments for asthma

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

Reduction in Concomitant Therapy

Bronchodilator Treatments: **Antaluko** can be added to the treatment regimen of patients who are not adequately controlled on bronchodilator alone. When a clinical response is evident (usually after the first dose), the patient’s bronchodilator therapy may be reduced as tolerated.

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Inhaled Corticosteroids: A reduction in the corticosteroid dose can be made as tolerated. The dose should be reduced gradually with medical supervision. **Antaluko** should not be abruptly substituted for inhaled corticosteroids.

Method of administration

Oral use

4.3 Contraindications

- Hypersensitivity to montelukast or any component of **Antaluko** tablets.
- Children under the age of 15 years, as safety and efficacy of **Antaluko 10** have not been demonstrated.

4.4. Special warnings and precautions for use

Antaluko is not indicated in the reversal of bronchospasm in acute asthma attacks, including status asthmaticus as the efficacy of **Antaluko** 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 **Antaluko** can be continued.

Eosinophilic Conditions:

Patients on therapy with **Antaluko** 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. Medical practitioners should be on the alert to eosinophillia, vasculitic rash, worsening

pulmonary symptoms, cardiac complications, and/or neuropathy presenting in their patients. In such patients **Antaluko** tablets should be withdrawn.

Neuropsychiatric events:

Neuropsychiatric events have been reported in adults, adolescents, and children taking **Antaluko**. Post-marketing reports with **Antaluko** use include agitation, aggressive behaviour or hostility, anxiousness, depression, disorientation, disturbance in attention, abnormal dreams, hallucinations, insomnia, irritability, memory impairment, restlessness, somnambulism, suicidal ideation and behaviour (including suicide), tic and tremor.
Patients and medical practitioners should be alert for neuropsychiatric events. Patients should be instructed to notify their medical practitioners if these changes occur. Medical practitioners should carefully evaluate the risks and benefits of continuing treatment with **Antaluko** if such events occur.

Hypersensitivity to aspirin

Patients with a known aspirin sensitivity should be advised to avoid taking aspirin or non-steroidal anti-inflammatory agents while taking **Antaluko** tablets**.** Although **Antaluko** is effective in improving airway function in asthmatics, it has not been demonstrated to reduce the bronco-constrictor response to aspirin or other NSAIDs in aspirin-sensitive asthmatic patients.

Hepatic impairment

The metabolism of montelukast may be decreased in patients with mild to moderate hepatic impairment and clinical evidence of cirrhosis. The half-life may be slightly prolonged; however, dosage adjustment is not necessary. No data are available for patients with severe hepatic impairment.

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General:

- Patients should be advised to take **Antaluko** tablets daily as prescribed, even when they are asymptomatic, as well as during periods of worsening asthma and to contact their medical practitioners if their asthma is not well controlled.
- Patients should be advised that oral tablets of **Antaluko** 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.
- Patients should be advised that, while using **Antaluko** 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 **Antaluko** tablets should be instructed not to decrease the dose or stop taking any other anti-asthma medication unless instructed by 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 practitioner. All patients should have available for rescue a short-acting inhaled beta-agonist.

To ensure safe and appropriate use, patients should be advised to read the section on "Warnings and precautions" in the Patient Information Leaflet.

Effects on ability to drive and use machines:

Antaluko 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.

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Lactose intolerance:

Antaluko10 tablets contains lactose monohydrate. Patients with a rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take **Antaluko10** tablets.

Sodium:

Antaluko10 contains less than 1 mmol sodium (23 mg) per capsule, that is to say essentially 'sodium-free'.

4.5 Interaction with other medicines and other forms of interaction

Antaluko tablets may be administered with other therapies routinely used in the prophylaxis and chronic treatment of atopic asthma and seasonal allergic rhinitis. 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 **Antaluko** tablets is recommended. Clinical monitoring is recommended when potent hepatic enzyme inducers (such as ritonavir, phenytoin, phenobarbitone, rifampicin, or *St John's wort* are given concurrently with **Antaluko**.

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 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 **Antaluko** 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, co-administration of montelukast with itraconazole alone resulted in no significant increase in the systemic exposure of montelukast.

4.6 Fertility, pregnancy and lactation

The safety of **Antaluko** tablets in pregnant and breastfeeding women has not been established.

Available data from published prospective and retrospective cohort studies with montelukast use in pregnant women evaluating major birth defects have not established a drug-associated risk. Available studies have methodologic limitations, including small sample size, in some cases retrospective data

collection, and inconsistent comparator groups.

It is not known if **Antaluko** is excreted in human milk. Women using **Antaluko** should not breastfeed their infants.

The effect of **Antaluko** on fertility has not been established.

4.7 Effects on ability to drive and use machines:

Antaluko 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**
Blood and lymphatic system disorders		Churg-Strauss Syndrome (see sec 4.4).	Increased bleeding tendency and thrombocytopenia.
Immune system disorders		Hypersensitivity reactions including allergy, anaphylaxis, angiodema, hepatic oesinophilic, rashes and urticaria.	
Endocrine disorders			Pancreatitis
Psychiatric disorders			Abnormal dreams, hallucinations, agitation including aggressive, behavior/hostility, restlessness, anxiousness, depression,

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			irritability, suicidality, tic,obsessive-compulsive symptoms,dysphemia and tremor.
Nervous system disorders	Dizziness, Headache and Insomnia.		Drowsiness, paraesthesia, hypoaesthesia and seizure.
Cardiac disorders			Palpitations
Respiratory, thoracic and mediastinal disorders:		Nasal congestion, epistaxis cough, influenza, asthma, pulmonary eosinophilia, Churg-Strauss syndrome, and increased incident of respiratory tract infections.	
Gastrointestinal disorders	Abdominal pains	Dyspepsia and gastroenteritis.	Nausea, vomiting and diarrhoea.
Hepato-biliary disorders		Elevated hepatic enzymes (AST,ALT), symptomatic hepatitis or hyperbilirubinaemia.	Cholestatic hepatitis.
Skin and subcutaneous tissue disorders		Skin rash and acne.	Angioedema, erythema multiforme, erythema nodosum, bruising, pruritus, and urticaria.
Musculoskeletal and connective tissue disorders			Arthralgia and myalgia including muscle cramps.
Renal and urinary disorders			Pyuria and enuresis in children.
General disorders and administration site disorders		Asthenia, fatigue, dental pain, and fever.	Oedema, generalised pain, and fatalities.

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. Health care provders 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

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4.9 Overdose

Treatment is symptomatic and supportive.

No specific information is available on the treatment of overdosage with **Antaluko** tablets.

The most frequent adverse experience observed were abdominal pain, somnolence, thirst, headache, vomiting and psychomotor hyperactivity. It is not known whether montelukast is dialysable by peritoneal or haemodialysis.

5. PHARMACOLOGICAL PROPERTIES

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

Pharmacotherapeutic group: Other systemic drugs for obstructive airway diseases, Leukotriene receptor antagonists.

ATC code: R03DC03.

5.1 Pharmacodynamic properties

Montelukast is a leukotriene receptor antagonist. Montelukast inhibits airway cysteinyl leukotriene receptors, as demonstrated by it's ability to inhibit bronchoconstriction due to inhaled LTD4 in asthmatic patients. Montelukast binds with high affinity and selectivity to the CysLT1 receptor. Montelukast inhibits physiological actions of LTC4, LTD4, and LTE4 at the CysLT1 receptor without agonist activity.

5.2 Pharmacokinetic properties

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Absorption:

Montelukast is absorbed following oral administration.

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

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 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 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 %).

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 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).

Elderly

The pharmacokinetic profile and the oral bioavailability of a single 10 mg oral dose of montelukast are similar in elderly an younger adults. The plasma half-life of montelukast is slightly longer in the elderly. No dosage adjustment in the elderly is required.

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6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Tablet core:

Lactose monohydrate

Cellulose, powdered (E460)

Cellulose, microcrystalline (E460)

Croscarmellose sodium (E468)

Magnesium stearate (E470b)

Film coating:

Hypromellose (E464)

Titanium dioxide (E171)

Talc (E553b)

Propylene glycol (E1520)

Iron oxide, red (E172)

Iron oxide, yellow (E172)

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 years

6.4 Special precautions for storage

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

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 and contents of container

Box of 30 film-coated tablets in blister packs of foil and OPA/Al/PVC.

6.6 Special precautions for disposal and other handling

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

45/10.2.2/0460

9. DATE OF FIRST AUTHORISATION

01 August 2019

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10. DATE OF REVISION OF THE TEXT

31 January 2024