Proprietary name:	MONTELUKAST ALKEM
Dosage form:	Film-coated tablets
Active Ingredient:	Montelukast Sodium equivalent to Montelukast
Strength per dosage unit:	10 mg per tablet

1.3.1.1 PROFESSIONAL INFORMATION

SCHEDULING STATUS

S3

1. NAME OF THE MEDICINE

Montelukast Alkem Film-coated Tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each **Montelukast Alkem** film-coated tablet contains montelukast sodium equivalent to 10 mg of montelukast.

Excipient(s) with known effect:

Each film-coated tablet contains 89.000 mg of lactose monohydrate.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Beige coloured, square shaped, biconvex, film coated tablets plain on both sides.

4.1 Therapeutic indications

INDICATIONS:

Montelukast Alkem is indicated for the prophylaxis and chronic treatment of atopic asthma, in adults and children 15 years of age and older.

Montelukast Alkem can provide symptomatic relief of seasonal allergic rhinitis in those adult asthmatic patients using **Montelukast Alkem.**

4.2 Posology and method of administration

Posology:

Montelukast Alkem should be taken once daily in the evening.

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

One tablet daily. Clinical studies in adults 15 years of age or older have demonstrated that there is no additional clinical benefit to montelukast doses above 10 mg once daily.

General Recommendations:

A therapeutic effect of **Montelukast Alkem** on parameters of asthma control occurs within one day. **Montelukast Alkem** tablets can be taken with or without food. Patients should be advised to continue taking **Montelukast Alkem** while their asthma is controlled, as well as during periods of worsening asthma.

*Therapy with **Montelukast Alkem** in Relation to Other Treatments for Asthma:*

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

Reduction in Concomitant Therapy:

Bronchodilator Treatments: **Montelukast Alkem** 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.

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

Special population:

No dosage adjustment is necessary for patients with mild to moderate hepatic impairment, renal impairment, the elderly, children 6 to 14 years or patients of either gender.

Method of Administration:

Montelukast Alkem is for oral administration and must be administered as a once daily dose in the evening.

4.3 Contraindications

- Hypersensitivity to montelukast or to any of the excipients in **Montelukast Alkem,** as listed in section 6.1.
- Safety and efficacy have not been established in children under the age of 15 years.

4.4 Special warnings and precautions for use

Use in Acute Asthma:

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

Montelukast Alkem is 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. During acute exacerbations of asthma, therapy can be continued with **Montelukast Alkem.**

Concomitant corticosteroid use:

Montelukast Alkem should not be used as monotherapy 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 have exacerbations of asthma after exercise.

Montelukast Alkem should not be substituted abruptly for inhaled or oral corticosteroids. The dose of the corticosteroid may be tapered gradually under medical supervision.

Aspirin sensitivity:

Patients with known aspirin sensitivity should continue avoidance of aspirin or non-steroidal anti-inflammatory medicines while taking **Montelukast Alkem**.

Although **Montelukast Alkem**. is effective in improving airway function in asthmatics with documented aspirin sensitivity; it has not been shown to truncate bronchoconstrictor response to aspirin and other non-steroidal anti-inflammatory medicines 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 **Montelukast Alkem** 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 alert to eosinophilia, vasculitic rash, worsening pulmonary symptoms, cardiac complications, and/or neuropathy presenting in their patients. **Montelukast Alkem** treatment should be withdrawn in patients presenting with this condition.

Neuropsychiatric events:

Neuropsychiatric events have been reported in some patients taking montelukast as in **Montelukast Alkem**. These include agitation, aggression, anxiousness, dream abnormalities, hallucinations, depression, insomnia, irritability, restlessness, suicidal thinking and behaviour (including suicide), and tremor **(see Side Effects)**. Patients and healthcare professionals should be aware of the potential for neuropsychiatric events.

Patients should be instructed to notify their healthcare professionals if these events occur. Healthcare professionals should carefully evaluate continuing treatment with **Montelukast Alkem** if such events occur.

Information for patients:

- Patients should be advised to continue taking **Montelukast Alkem** as prescribed, on a daily basis, even when they are asymptomatic and also during periods of worsening asthma. Patients should be advised to contact their medical practitioners if their asthma is not well controlled.
- Advise patients that **Montelukast Alkem** should not be used for the treatment of acute asthma attacks. They should have appropriate short acting inhaled beta-agonist bronchodilators available to treat asthma exacerbations.

  Patients should be advised to seek medical attention if short acting beta-agonist inhaled bronchodilators are needed more often than usual, or if more than the recommended dose of the short acting beta-agonist inhaled bronchodilators is needed in 24 hours.
- Patients should be instructed not to decrease the dose or stop taking any other anti-asthma medications, unless instructed by a medical practitioner to do so.
- For patients who have exacerbations of asthma after exercise: instruct them to use their usual regimen of inhaled beta-agonists as prophylaxis, unless otherwise instructed by a medical practitioner. All patients should have available for rescue, a short acting beta-agonist inhalant.

- Patients should be instructed to notify their medical practitioner if neuropsychiatric events occur while using **Montelukast Alkem**.
- Advise patients with known aspirin-sensitivity to continue avoidance of aspirin or non-steroidal anti-inflammatory medicines while taking **Montelukast Alkem**.

Lactose:

Montelukast Alkem film-coated tablets contain lactose. Patients with rare hereditary problems of galactose intolerance, total lactase deficiency or glucose-galactose malabsorption should not take **Montelukast Alkem**.

4.5 Interaction with other medicines and other forms of interaction

Montelukast Alkem may be administered with other therapies routinely used in the prophylaxis and the treatment of asthma, seasonal allergic rhinitis. In drug-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 estradiol/ norethindrone 35/1), terfenadine, digoxin and warfarin.

The area under the plasma concentration-time curve (AUC) for montelukast was decreased approximately 40 % in subjects with co-administration with phenobarbital.

Monitoring is recommended during concurrent use with potent cytochrome P_{450} enzyme inducers, such as phenytoin, phenobarbital and rifampicin, due to the potential for interactions.

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 as in **Montelukast Alkem** 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 experiences were not observed. Therefore, no dosage adjustment of montelukast as in **Montelukast Alkem** 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

Pregnancy:

The safety of **Montelukast Alkem** in pregnancy and lactation 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.

Breastfeeding:

It is not known if montelukast as in **Montelukast Alkem** is excreted in human milk. Women using **Montelukast Alkem** should not breastfeed their infants.

Fertility data

No fertility data is available.

4.7 Effects on ability to drive and use machines

Montelukast Alkem may cause side effects such as dizziness or drowsiness, which may affect the ability to drive or operate machines safely.

4.8 Undesirable effects

The frequencies of adverse events are ranked according to the following frequency classification: *Frequent, less frequent, and frequency unknown.*

Infection and infestation:

Frequent: upper respiratory tract infections.

Immune system disorders:

Less frequent: hypersensitivity reactions, including anaphylaxis and hepatic eosinophilic infiltration.

Blood and lymphatic system disorders:

Less frequent: systemic eosinophilia consistent with Churg-Strauss syndrome, agranulocytosis, increased bleeding tendencies and thrombocytopenia.

Nervous system disorders:

Frequent: headache

Less frequent: dizziness, drowsiness, paraesthesia/ hypoaesthesia and seizure.

Psychiatric disorders:

Less frequent: sleep disorders, primarily insomnia; agitation including aggressive behaviour or hostility, anxiousness, somnambulism, restlessness; vertigo, anxiety; abnormal dreams; hallucinations, malaise, depression; irritability, nightmares; sedation; suicidality and suicide, tremor, disturbance in attention, memory attention, obsessive compulsive disorder and dysphemia.

Cardiovascular disorders:

Less frequent: palpitations.

Respiratory, thoracic and mediastinal disorders:

Less frequent: Churg-Strauss syndrome, chest pain, epistaxis and pulmonary eosiniphilia.

Gastro-intestinal disorders:

Frequent: diarrhoea, nausea and vomiting.

Less frequent: abdominal or stomach pain; dyspepsia (heartburn); dry mouth, thirst and gastro-intestinal disturbances.

Hepato-biliary disorders:

Frequent: elevations in liver enzyme values, increased alanine aminotransferase (ALT) and aspartate aminotransferase (AST).

Less frequent: hepatitis (including cholestatic, hepatocellular and mixed pattern liver injury).

Skin and subcutaneous tissue disorders:

Frequent: rash

Less frequent: increased sweating, erythema nodosum pruritis, erythema multiforme, angioedema, bruising, pruritis and urticaria.

Musculoskeletal and connective tissue disorders:

Less frequent: arthralgia, myalgia including muscle cramps.

General disorders and administration sites:

Frequent: fever

Less frequent: asthenia, fatigue, malaise and oedema

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 professionals 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

Alternatively all adverse events can be reported to Ascend Laboratories via the e-mail: pharmacist.rsa@Alkem.com

4.9 Overdose

Symptoms:

The frequently occurring adverse reaction are abdominal pain; thirst, headache, somnolence, vomitting and some psychomotor hyperactivity.

Treatment:

Treatment is symptomatic and supportive. It is not known if montelukast can be removed by peritoneal dialysis or haemodialysis.

5.1 Pharmacodynamic properties

Category and Class: A 10.2.2 Other anti-asthmatics.

Pharmacotherapeutic group: Leukotriene receptor antagonist

ATC code: R03D C03

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

Absorption:

Montelukast is absorbed rapidly following oral administration, with mean oral bioavailability of 64 %. Peak plasma concentrations of montelukast are achieved in 3 hours (T_{max}) after administration in adults in the fasted state. The oral bioavailability and peak plasma concentration, $C_{max,}$ are not affected by administration with a standard meal.

Distribution:

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

Metabolism:

Montelukast is extensively metabolised in the liver by cytochrome P_{450} isoenzymes CYP3A4, CYP2A6 and CYP2C9.

Elimination:

The half-life of montelukast is approximately 2.7 to 5.5 hours in healthy young adults. Montelukast is excreted principally in the faeces via the bile, with less than 0,2 % eliminated in urine.

Hepatic and renal impairment:

Metabolism was reduced and the elimination half-life slightly prolonged in patients with mild to moderate hepatic impairment and those with clinical evidence of cirrhosis, compared to healthy adults. No clinical data is available in patients with severe hepatic insufficiency (Child-Pugh score greater than 9).

No dosage adjustment is required in patients with mild to moderate hepatic insufficiency.

No dosage adjustment is expected to be necessary in patients with renal impairment, since biliary excretion is the primary route of elimination of montelukast.

Elderly Population:

The pharmacokinetics and oral bioavailability of montelukast are similar in elderly and younger adults. The plasma half-life is slightly longer in the elderly, but no dosage adjustment is necessary.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Croscarmellose sodium, hydroxypropyl cellulose; lactose monohydrate, magnesium stearate, microcrystalline cellulose and coating solution, Opadry yellow 03B52874 (hydroxypropyl methylcellulose, iron oxide red, iron oxide yellow and polyethylene glycol.

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

2 years.

6.4 Special precautions for storage

Store below or at 25 °C.

Keep the blisters in the outer cartons until required for use.

KEEP OUT OF REACH OF CHILDREN.

6.5 Nature and contents of container

Packs of 14 tablets made of aluminium and aluminium blister strips of 7 tablets per strip. 2 strips are packed into an outer carton.

Pack sizes: 14.

6.6 Special precautions for disposal

No special requirements.

7 MARKETING AUTHORISATION HOLDER

Ascend Laboratories (Pty) Ltd.

R21 Corporate Park

121 Sovereign Drive, Block A, Office 202

Irene Ext.30, Centurion, 0157

8 MARKETING AUTHORISATION NUMBER(S)

To be allocated by authority.

9 DATE OF REVISION OF THE TEXT

To be allocated by authority.