SCHEDULING STATUS

S3

PROPRIETARY NAME (AND DOSAGE FORM):
MONTEFLO 4 (Chewable Tablets)
MONTEFLO 5 (Chewable Tablets)
MONTEFLO 10 (Tablets)

COMPOSITION
MONTEFLO 4: Each chewable tablet contains montelukast sodium equivalent to 4 mg montelukast.
MONTEFLO 5: Each chewable tablet contains montelukast sodium equivalent to 5 mg montelukast.
MONTEFLO 4 and **MONTEFLO** 5 also contain the following inactive ingredients: Mannitol, cellulose microcrystalline, croscarmellose sodium, aspartame, cherry flavour, ferric oxide red, magnesium stearate.
MONTEFLO 10: Each tablet contains montelukast sodium equivalent to 10 mg montelukast.
MONTEFLO 10 also contains the following inactive ingredients: Mannitol, cellulose microcrystalline, croscarmellose sodium, aspartame, cherry flavour, ferric oxide red and ferric oxide yellow, magnesium stearate.

PHARMACOLOGICAL CLASSIFICATION
A.10.2.2 Other anti-asthmatics, Leukotriene receptor antagonist

PHARMACOLOGICAL ACTION

Pharmacodynamics:
Montelukast causes potent inhibition of airway cysteinyl leukotriene receptors.
The cysteinyl leukotrienes (LTC_4, LTD_4, LTE_4) are potent inflammatory eicosanoids which are released from various cells including mast cells and eosinophils. These important pro-asthmatic mediators bind to cysteinyl leukotriene (CysLT) receptors. The CysLT type-1 ($CysLT_1$) receptor 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). CysLTs have been correlated with the pathophysiology of asthma. In asthma, leukotriene-mediated effects include a number of airway actions, including bronchoconstriction, mucus secretion, vascular permeability, and eosinophil recruitment. Montelukast binds with high affinity and selectivity to the $CysLT_1$ receptor. Montelukast inhibits physiological actions of LTC_4, LTD_4, and LTE_4 at the $CysLT_1$ receptor without agonist activity. Doses as low as 5 mg cause substantial blockage of LTD_4 induced bronchoconstriction.

PHARMACOKINETICS:
Absorption
Montelukast is rapidly absorbed following oral administration. The mean peak plasma concentration (C_{max}) for the 4 mg chewable tablet 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. The mean peak plasma concentration (C_{max}) for the 5 mg chewable tablet 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. The mean peak plasma concentration (C_{max}), for the 10 mg tablet is achieved 3 hours (T_{max}), after administration in adults in the fasted state. The mean oral bioavailability is 64 %. A standard meal does not influence the oral bioavailability and C_{max}.
Distribution
Binding is more than 99 % to plasma proteins. The steady-state volume of distribution of montelukast averages 8 to 11 litres.
Metabolism
Montelukast is extensively metabolised in the liver.
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. Montelukast pharmacokinetics are nearly linear 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 there is little accumulation of the parent compound 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.

INDICATIONS
MONTEFLO tablets are indicated for prophylaxis and chronic treatment of atopic asthma.
MONTEFLO 4 chewable tablets are indicated for paediatric patients 2 to 5 years of age.
MONTEFLO 5 chewable tablets are indicated for paediatric patients over 6 years of age.
MONTEFLO 10 tablets are indicated in adults and children 15 years of age and older.

CONTRA-INDICATIONS
Hypersensitivity to any components of this product. Pregnancy and lactation
- **MONTEFLO** 5 and 10 should not be used in children under the age of 6 years, as safety and efficacy have not been demonstrated.
- **MONTEFLO** 4 should not be used in children under the age of 2 years, as safety and efficacy have not been demonstrated.
- **MONTEFLO** 10 should not be used in children under the age of 15 years, as safety and efficacy have not been demonstrated.

WARNINGS AND SPECIAL PRECAUTIONS
General The efficacy of oral **MONTEFLO** for the treatment of acute asthma attacks has not been established. **MONTEFLO** 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. **MONTEFLO** 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 medication available. Therapy with **MONTEFLO** can be continued during acute exacerbations of asthma. While the dose of inhaled corticosteroid may be reduced gradually under medical supervision, **MONTEFLO** 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 **MONTEFLO**. Although **MONTEFLO** is effective in improving airway function in asthmatics with documented aspirin sensitivity, it has not been shown to reduce 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.
Use in Elderly There are no age-related differences in the efficacy or safety profiles of **MONTEFLO**.
Eosinophilic Conditions
Patients on therapy with **MONTEFLO** 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. Doctors should be alert to eosinophilia, vasculitic rash, worsening pulmonary symptoms, cardiac complications and/or neuropathy presenting in their patients. **MONTEFLO** should be withdrawn in these patients (see **SIDE EFFECTS**).
Neuropsychiatric events
Neuropsychiatric events have been reported in some patients taking **MONTEFLO**. These include agitation, aggression, anxiousness, dream abnormalities, hallucinations, depression, insomnia, irritability, restlessness, suicidal thinking and behaviour (including suicide), and tremor. Patients and healthcare professionals should be aware of the potential for neuropsychiatric events. Patients should be instructed to inform their healthcare professionals if these events occur. Healthcare professionals should carefully evaluate the risks and benefits of continuing treatment with **MONTEFLO** if such events occur.
Hepatic function impairment The metabolism of montelukast may be decreased in patients with mild to moderate hepatic function and 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. Due to the side effects such as dizziness or drowsiness, caution should be taken when driving and operating heavy machinery. Patients should therefore be advised not to drive or operate machinery until their individual susceptibility is known.
Information for patients:
Patients should be advised to take **MONTEFLO** daily as prescribed, even when they are asymptomatic, as well as during periods of worsening asthma, and to contact their doctor if their asthma is not well-controlled.
Patients should be advised that **MONTEFLO** is 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 **MONTEFLO**, 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 a 24-hour period are needed. Patients receiving **MONTEFLO** should be instructed not to decrease the dose or stop taking any other anti-asthma medicine unless instructed to do so by their doctor. **MONTEFLO** should not be used as monotherapy for the management and treatment of exercise induced bronchospasm. Patients who have exacerbations of asthma after exercise should be instructed to continue to use their usual regimen of inhaled beta-agonists as prophylaxis, unless otherwise instructed by their doctor. All patients should have a short-acting inhaled beta-agonist available for rescue treatment. Patients with known aspirin sensitivity should be advised to continue avoidance of aspirin or non steroidal anti-inflammatory agents while taking **MONTEFLO**. Although **MONTEFLO** is effective in improving airway function in asthmatics, it has not been shown to reduce the bronchoconstrictor response to aspirin or other non-steroidal anti-inflammatory drugs (NSAIDs) in aspirin-sensitive asthmatic patients.
MONTEFLO 4 and 5 mg chewable tablets and 10 mg tablets:
Phenylketonuric patients should be informed that **MONTEFLO** 4 and 5 mg chewable tablets and 10 mg tablets contain aspartame which has a phenylalanine component.

INTERACTIONS
MONTEFLO may be administered together with other therapies used in the prophylaxis and chronic treatment of asthma. 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 (ethinyloestradiol-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 **MONTEFLO** is recommended. However, clinical monitoring is recommended when potent hepatic enzyme inducers: phenytoin, phenobarbital or rifampicin are given with **MONTEFLO**.

PREGNANCY AND LACTATION

The safety of this medicine in pregnancy and lactating women has not been established and therefore the use thereof during pregnancy and lactation is not recommended. It is not known if **MONTEFLO** is excreted in human milk.

DOSAGE AND DIRECTIONS FOR USE

MONTEFLO should be taken once daily in the evening.
MONTEFLO 4 chewable tablets *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.
MONTEFLO 5 chewable tablets *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 chewable tablet daily.
MONTEFLO 10 tablets *Adults and Children 15 years of Age and Older with Atopic Asthma:* The dosage for adults 15 years of age and older is one 10 mg tablet daily.
General Recommendations: A therapeutic effect of **MONTEFLO** on parameters of asthma control occurs within one day.
MONTEFLO can be taken with or without food. Patients are advised to continue taking **MONTEFLO** while their asthma is controlled, as well as during periods of worsening asthma. No dosage adjustment is necessary for the elderly, for patients with renal insufficiency, or mild to moderate hepatic impairment, or for patients of either gender. **MONTEFLO** can be added to a patient's existing treatment regimen.

SIDE-EFFECTS AND SPECIAL PRECAUTIONS

Side-effects:
Metabolic and nutritional disorders:
Frequent: Thirst
Nervous system disorders:
Frequent: Headache, dizziness
Frequency not known: Drowsiness, paraesthesia/hypoesthesia, seizure
Gastrointestinal disorders:
Frequent: Abdominal pain, diarrhoea, dyspepsia, gastroenteritis, pain (dental)
Frequency not known: Dry mouth, nausea, vomiting
Infections and infestations:
Frequency not known: Upper respiratory infection, varicella, gastroenteritis
Blood and lymphatic system disorders:
Frequency not known: Increased bleeding tendency, agranulocytosis
Immune system disorders:
Frequency not known: Hypersensitivity reactions including anaphylaxis, hepatic eosinophilic infiltration, angioedema
Psychiatric disorders:
Frequent: insomnia
Frequency not known: Abnormal dreams, hallucinations, agitation including aggressive behaviour, anxiety, depression, irritability, restlessness, suicidal thinking and behaviour (suicidality), tremor
Cardiac disorders:
Frequency not known: Palpitations
Respiratory, thoracic and mediastinal disorders:
Frequent: Congestion (nasal), cough, influenza
Frequency not known: Epistaxis
Hepatobiliary disorders:
Frequent: Elevated levels of serum transaminases (ALT, AST)
Frequency not known: hepatitis (including cholestatic, hepatocellular and mixed-pattern liver injury
Skin and subcutaneous tissue disorders:
Frequent: Rash
Frequency not known: Bruising, erythema nodosum, pruritus, urticaria, eczema
Musculoskeletal and connective tissue disorders:
Arthralgia, myalgia (including muscle cramps)
General disorders and administration site conditions:
Frequent: Asthenia (fatigue), malaise, pyrexia

Patients on therapy with **MONTEFLO** 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 doctors should be alert to eosinophilia, vasculitic rash, worsening pulmonary symptoms, cardiac complications, and/or neuropathy presenting in their patients. **MONTEFLO** should be withdrawn in these patients (see **WARNINGS AND SPECIAL PRECAUTIONS**, Eosinophilic Conditions).

KNOWN SYMPTOMS OF OVERDOSAGE AND PARTICULARS OF ITS TREATMENT
No specific information is available on the treatment of overdosage with **MONTEFLO**. In chronic asthma studies **MONTEFLO** has been administered at doses up to 200 mg/day to adult patients for 22 weeks and in short-term studies, up to 900 mg/day to patients for approximately one week without clinically important adverse experiences. There were no adverse experiences reported in the majority of overdosage reports. The most frequent adverse experiences observed were thirst, somnolence, mydriasis, hyperkinesias and abdominal pain. It is not known whether montelukast is dialysable by peritoneal or haemodialysis.

IDENTIFICATION
MONTEFLO 4: Pink coloured, oval biconvex "shaped", uncoated chewable tablet with a breakline on both sides. The breakline is for appearance only and not to halve the dose.
MONTEFLO 5: Pink coloured, round biconvex "shaped", uncoated chewable tablet with a breakline on both sides. The breakline is for appearance only and not to halve the dose.
MONTEFLO 10: Brown coloured, round biconvex "shaped", uncoated tablet with a breakline on both sides. The breakline is for appearance only and not to halve the dose.

PRESENTATION
MONTEFLO 4, 5 and 10 are available in silver coloured CFBAlu/Alu blister packs of 10 tablets, 30 tablets per pack.

STORAGE INSTRUCTIONS
Store at or below 25 ºC. Protect from light and moisture. Keep the blisters in the outer carton until required for use. KEEP OUT OF REACH OF CHILDREN.

REGISTRATION NUMBER
MONTEFLO 4: 44/10.2.2/0257
MONTEFLO 5: 44/10.2.2/0262
MONTEFLO 10: 44/10.2.2/0286

NAME AND BUSINESS ADDRESS OF THE HOLDER OF THE CERTIFICATE OF REGISTRATION
Trinity Pharma (Pty) Ltd.
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