SCHEDULING STATUS

S3

PROPRIETARY NAME AND DOSAGE FORM

SINGULAIR® 4 mg Chewable Tablets

COMPOSITION

SINGULAIR 4 mg: Each 4 mg chewable tablet contains montelukast sodium equal to the molar equivalent of 4,0 mg of free acid.

SINGULAIR 4 mg chewable tablet is sugar free

PHARMACOLOGICAL CLASSIFICATION

A.10.2.2 Other anti-asthmatics
Leukotriene receptor antagonist

PHARMACOLOGICAL ACTION

MECHANISM OF ACTION

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

PHARMACOKINETICS

Absorption

Montelukast is absorbed following oral 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 more than 99 % bound to plasma proteins. Studies in rats with radiolabeled montelukast indicate minimal distribution across the blood-brain barrier. In addition, concentrations of radiolabeled material at 24 hours postdose were minimal in all other tissues.

Metabolism

Montelukast is extensively metabolized in the liver. In studies with therapeutic doses, plasma concentrations of metabolites of montelukast are undetectable at steady 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.

In several studies, 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 difference in pharmacokinetics was noted between dosing in the morning or in the evening. During once-daily dosing with 10 mg montelukast, there is little accumulation of the parent drug in plasma (approximately 14 %).

No difference in pharmacokinetics was noted between dosing in the morning or in the evening.

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).

PHARMACODYNAMICS

Montelukast causes potent inhibition of airway cysteinyl leukotriene receptors as demonstrated by the ability to inhibit bronchoconstriction due to inhaled LTD_4 in asthmatic patients.

INDICATIONS

SINGULAIR 4 mg chewable tablet is indicated in paediatric patients 2 to 5 years of age for the prophylaxis and chronic treatment of atopic asthma.

CONTRA-INDICATIONS

- Hypersensitivity to any component of this product.
- Children under the age of 2 years, as safety and efficacy have not been demonstrated.

WARNINGS

See SPECIAL PRECAUTIONS

INTERACTIONS

SINGULAIR may be administered with other therapies routinely used in the prophylaxis and chronic treatment of asthma. In drug-interactions studies, the recommended clinical dose of montelukast did not have clinically important effects on the pharmacokinetics of the following drugs: theophylline, prednisone, prednisolone, oral contraceptives (ethinyl oestradiol/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 of phenobarbital. No dosage adjustment for SINGULAIR is recommended.

In vitro studies have shown that montelukast is an inhibitor of CYP 2C8. However, data from a clinical drug-drug interaction study involving montelukast and rosiglitazone (a probe substrate representative of drugs primarily metabolized by CYP2C8) demonstrated that montelukast does not inhibit CYP2C8 *in vivo.* Therefore SINGULAIR is not anticipated to alter the metabolism of drugs metabolized by this enzyme (e.g. paclitaxel, rosiglitazone and repaglinide)

PREGNANCY AND LACTATION

The safety of this medicine in pregnant and lactating women has not been established.
Since there are no controlled studies in pregnant or nursing women, montelukast should not be used during pregnancy or by nursing mothers. It is not known if SINGULAIR is excreted in human milk.

During worldwide marketing experience, congenital limb defects have been reported in offspring of women treated with SINGULAIR during pregnancy. A causal relationship between these events and SINGULAIR has not been established.

DOSAGE AND DIRECTIONS FOR USE

SINGULAIR should be taken once daily in the evening.

SINGULAIR 4 mg Chewable Tablet

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.

General Recommendations:

A therapeutic effect of SINGULAIR on parameters of asthma control occurs within one day.
SINGULAIR may be taken with or without food. Patients should be advised to continue taking SINGULAIR 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.
Safety and efficacy for more than 12 (twelve) weeks has not been established in controlled clinical trials.

Therapy with SINGULAIR in Relation to Other Treatments for Asthma:

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

SIDE EFFECTS AND SPECIAL PRECAUTIONS

SIDE EFFECTS

In patients with asthma, SINGULAIR has been evaluated in clinical studies as follows:

- 4 mg chewable tablets in paediatric patients with asthma 2 to 5 years of age.

The following drug-related adverse reactions in placebo-controlled clinical studies were reported commonly (greater than 1/100, less than 1/10) in patients with asthma treated with SINGULAIR and at a greater incidence than in patients treated with placebo:

Body System Class	Adult Patients 15 years and older	Paediatric Patients 6 to 14 years old	Paediatric Patients 2 to 5 years old

	(two 12-week studies; n=795)	(one 8-week study; n=201)	(one 12-week study; n=461)
General disorders and administration site conditions			thirst
Gastro-intestinal disorder	abdominal pain		
Nervous system disorders	headache	headache	

Cumulatively, 338 paediatric patients 2 to 5 years of age were treated for 6 months or longer, and 256 patients for 12 months or longer. With prolonged treatment, the safety profile did not change in these patients either.

In rare cases, patients on therapy with SINGULAIR 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. Physicians should be alert to eosinophilia, vasculitic rash, worsening pulmonary symptoms, cardiac complications, and/or neuropathy presenting in their patients. A causal association between SINGULAIR and these underlying conditions has not been established (see SPECIAL PRECAUTIONS, Eosinophilic Conditions).

Post – Marketing Experience

The following side effects have been reported in post-marketing use:

Blood and lymphatic system disorders: increased bleeding tendency

Immune system disorders: hypersensitivity reactions including anaphylaxis, hepatic eosinophilic infiltration

Psychiatric disorders: abnormal dreams and hallucinations, agitation including aggressive behaviour, anxiousness, depression, insomnia, irritability, restlessness, suicidal thinking and behaviour (suicidality), tremor.

Nervous system disorders: dizziness, drowsiness, paraesthesia/hypoesthesia, seizure

Cardiac disorders: palpitations

Respiratory, thoracic and mediastinal disorders: epistaxis

Gastro-intestinal disorders: diarrhoea, dyspepsia, nausea, vomiting

Hepatobiliary disorders: increased alanine aminotransferase (ALT) and aspartate aminotransferase (AST), cholestatic hepatitis

Skin and subcutaneous tissue disorders: angioedema, bruising, erythema nodosum, pruritus, rash, urticaria

Musculoskeletal and connective tissue disorders: arthralgia, myalgia including muscle cramps

General disorders and administration site conditions: oedema, pyrexia

SPECIAL PRECAUTIONS

General

The efficacy of oral SINGULAIR for the treatment of acute asthma attacks has not been established.

SINGULAIR 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.

SINGULAIR 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 SINGULAIR can be continued during acute exacerbations of asthma.

While the dose of inhaled corticosteroid may be reduced gradually under medical supervision, SINGULAIR 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 SINGULAIR. Although SINGULAIR 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 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

In rare cases, patients on therapy with SINGULAIR 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. A causal association between SINGULAIR and these underlying conditions has not been established (see SIDE EFFECTS).

Information for Patients

- Patients should be advised to take SINGULAIR daily as prescribed, even when they are

asymptomatic, as well as during periods of worsening asthma, and to contact their physicians if their asthma is not well controlled.

- Patients should be advised that oral tablets of SINGULAIR 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 SINGULAIR, 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 SINGULAIR should be instructed not to decrease the dose or stop taking any other anti-asthma medications unless instructed by a physician.
- 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 medical practitioner. All patients should have available for rescue a short-acting inhaled beta-agonist.
- Patients with known aspirin sensitivity should be advised to continue avoidance of aspirin or non-steroidal anti-inflammatory agents while taking SINGULAIR chewable Tablets.
- Phenylketonurics: Phenylketonuric patients should be informed that the chewable tablets contain phenylalanine (a component of aspartame) 0,674 mg per 4 mg chewable tablet.

KNOWN SYMPTOMS OF OVERDOSAGE AND PARTICULARS OF ITS TREATMENT

No specific information is available on the treatment of overdosage with SINGULAIR. . In chronic asthma studies, montelukast 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 have been reports of acute overdosage in post-marketing experience and clinical studies with montelukast. These include reports in adults and children with a dose as high as 1000 mg. The clinical and laboratory findings observed were consistent with the safety profile in adults and older paediatric patients.

There were no adverse experiences reported in the majority of overdosage reports. The most frequently occurring adverse experiences observed were consistent with safety profile of SINGULAIR and included abdominal pain, somnolence, thirst, headache, vomiting, and psychomotor hyperactivity.

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

IDENTIFICATION

SINGULAIR 4 mg: A pink, oval, biconvex tablet with a cherry taste and odour. ‘SINGULAIR’ is engraved

on one side and 'MSD 711' on the other.

PRESENTATION

SINGULAIR 4 mg is available in aluminium blister packs of 28 ~~and 14.~~

STORAGE INSTRUCTIONS

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

KEEP OUT OF REACH OF CHILDREN

REGISTRATION NUMBER

SINGULAIR 4 mg: 35/10.2.2/0397

NAME AND BUSINESS ADDRESS OF THE HOLDER OF THE CERTIFICATE OF REGISTRATION

MSD (PTY) LTD
16th Road
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1685

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