SCHEDULING STATUS

S3

PROPRIETARY NAME AND DOSAGE FORM

SINGULAIR® 5 mg Chewable Tablets

SINGULAIR® 10 mg Film-coated Tablets

COMPOSITION

SINGULAIR 5 mg: Each 5 mg chewable tablet contains 5,2 mg montelukast sodium which is the molar equivalent to 5,0 mg of free acid.

SINGULAIR 10 mg: Each 10 mg film-coated tablet contains 10,4 mg montelukast sodium, which is the molar equivalent to 10,0 mg of free acid.

SINGULAIR 5 mg is sugar free

SINGULAIR 10 mg contains lactose.

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 (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 and allergic rhinitis. In asthma, leukotriene-mediated effects include 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 10 mg film-coated 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.

For the 5 mg chewable tablet, the C_{max} 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.

Distribution

Montelukast is more than 99 % bound to plasma proteins. The steady-state volume of distribution of montelukast averages 8 to 11 litres. 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:

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 %).

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.

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. Doses as low as 5 mg cause substantial blockage of LTD_4-induced bronchoconstriction.

INDICATIONS

SINGULAIR 5 mg chewable tablets are indicated in paediatric patients over 6 years of age for the prophylaxis and chronic treatment of atopic asthma.

SINGULAIR 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 SINGULAIR is indicated in asthma, SINGULAIR may also provide some symptomatic relief of seasonal allergic rhinitis.

CONTRA-INDICATIONS

- Hypersensitivity to any component of this product.
- Children under the age of 6 years, as safety and efficacy of 5 mg and 10 mg tablets 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, and seasonal allergic rhinitis. 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 a potent 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 did not significantly inhibit CYP2C8 *in vivo.* Therefore, montelukast 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 breastfeeding women, montelukast should not be used during pregnancy or by breastfeeding mothers. It is not known if SINGULAIR is excreted in human milk.

During worldwide marketing experience, congenital limb defects have been reported in the offspring of women being 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 10 mg 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 film-coated tablet daily. 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.

SINGULAIR 5 mg Chewable Tablet

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.
SINGULAIR 5 mg has not been studied in seasonal allergic rhinitis in children with asthma.

General Recommendations:

A therapeutic effect of SINGULAIR on parameters of asthma control occurs within one day.
SINGULAIR tablets and chewable tablets can 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 the elderly, children 6-14 years, for patients with renal insufficiency, or mild-to-moderate hepatic impairment, or for patients of either gender.

Therapy with SINGULAIR in Relation to Other Treatments for Asthma:

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

Reduction in Concomitant Therapy:

One randomized, placebo-controlled, parallel-group trial (n=226) enrolled stable asthmatic adults with a mean FEV_1 of approximately 84 % of predicted, who were previously maintained on various inhaled corticosteroids. The pre-study inhaled corticosteroid requirements were reduced by approximately 37 % during a 5- to 7-week placebo run-in period designed to titrate patients toward their lowest effective inhaled corticosteroid dose. Treatment with SINGULAIR resulted in a further 47 % reduction in mean inhaled corticosteroid dose compared with a mean reduction of 30 % in the placebo group over the 12-week active treatment period (p less than or equal to 0,05). Approximately 40 % of the montelukast-treated patients and 29 % of the placebo-treated patients could be tapered off inhaled corticosteroids and remained off inhaled corticosteroids at the conclusion of the study (p=NS). It is not known whether the results of this study are generalizable to asthmatics who require higher doses of inhaled corticosteroids or systemic corticosteroids.

SIDE EFFECTS AND SPECIAL PRECAUTIONS

SIDE EFFECTS

Side effects generally did not require discontinuation of therapy.

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

- 10 mg film coated tablets in adult patients with asthma 15 years of age and older
- 5 mg chewable tablets in paediatric patients with asthma 6 to 14 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:

PATIENTS WITH ASTHMA

Body system class	Adult patients 15 years and older (two 12 week studies; n=795)	Paediatric Patients 6 to 14 years old (one 8 week study; n=201)
Nervous system disorder	Headache	Headache
Gastro-intestinal disorders	Abdominal pain	Abdominal pain

With prolonged treatment in clinical trials with a limited number of patients for up to 2 years for adults, and up to 6 months for paediatric patients 6 to 14 years of age, the safety profile did not change.

SINGULAIR 10-mg film-coated tablets have been evaluated in approximately 400 asthmatic patients 15 years of age and older with seasonal allergic rhinitis. The safety profile in asthmatic patients with seasonal allergic rhinitis was consistent with that observed in patients with asthma.

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:

Infections and infestations: upper respiratory infection

Blood and lymphatic system disorders: increased bleeding tendency

Immune system disorders: hypersensitivity reactions including anaphylaxis, hepatic eosinophilic infiltration.
Psychiatric disorders: abnormal dreams, hallucinations, agitation including aggressive behaviour or hostility, anxiousness, depression, insomnia, irritability, restlessness, somnambulism, suicidal thinking and behaviour (suicidality), tremor
Nervous system disorders: dizziness, drowsiness, paraesthesia/hypoethesia, seizure
Cardiac disorders: palpitations
Respiratory, thoracic and mediastinal disorders: epistaxis
Gastro-intestinal disorders: diarrhoea, dyspepsia, nausea, vomiting
Hepato-biliary disorders: increased alanine aminotransferase (ALT) and aspartate aminotransferase AST, hepatitis (including cholestatic, hepatocellular, and mixed-pattern liver injury)
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 sites 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.

Use in Elderly

In clinical studies, there were no age-related differences in the efficacy or safety profiles of SINGULAIR.

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. 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 **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 physician. 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.

Available formulations:

- SINGULAIR 5 mg chewable tablets are available for treatment of children 6 to 14 years old.
- SINGULAIR 10 mg film-coated tablets are available for the treatment of adolescents 15 years of age and older and of adults.

Chewable tablets:

- Phenylketonurics: Phenylketonuric patients should be informed that the chewable tablet contains phenylalanine (a component of aspartame) 0,842 mg per 5 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, SINGULAIR 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 postmarketing experience and clinical studies with SINGULAIR. 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 paediatric patients.

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

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

IDENTIFICATION

SINGULAIR 5 mg: A pink, round, biconvex tablet with SINGULAIR engraved on one side and 'MSD 275' on the other.

SINGULAIR 10 mg: A beige, rounded square film-coated tablet with SINGULAIR engraved on one side and 'MSD 117' on the other.

PRESENTATION

SINGULAIR 5 mg is available in blister packs of 14 and 28.

SINGULAIR 10 mg is available in blister packs of 14 and 28.

STORAGE INSTRUCTIONS

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

Store all medicines out of reach of children.

REGISTRATION NUMBERS

SINGULAIR 5 mg : 32/10.2.2/0321

SINGULAIR 10 mg : 32/10.2.2/0322

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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