SCHEDULING STATUS

S3

PROPRIETARY NAME AND DOSAGE FORM

SINGULAIR® SPRINKLES

COMPOSITION

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

SINGULAIR SPRINKLES 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 inflammatory eicosanoids released from various cells including mast cells and eosinophils. These pro-asthmatic mediators bind to cysteinyl leukotriene (CysLT) receptors. The CysLT type-1 ($CysLT_1$) receptor is 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.

The co-administration of applesauce or a high fat, high kilojoule meal with the oral granule formulation did not have a clinically meaningful effect on the pharmacokinetics of montelukast as determined by AUC (1225,7 vs 1223,1 ng•hr/ml with and without applesauce, respectively and 1191,8 vs 1148,5 ng•hr/ml with and without a high fat, high kilojoule meal, respectively).

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 safety of montelukast was also demonstrated in a clinical study in which the 4 mg oral granules were 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 %).

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

SUMMARY OF CLINICAL TRIALS

In a 12-week, placebo-controlled study in paediatric patients 2 to 5 years of age, montelukast 4 mg once daily improved parameters of asthma control compared with placebo irrespective of concomitant controller therapy (inhaled/nebulized corticosteroids or inhaled/nebulized sodium cromoglycate). Sixty percent of patients were not on any other controller therapy. Montelukast improved day-time symptoms (including coughing, wheezing, trouble breathing and activity limitation) and night-time symptoms compared with placebo. Montelukast also decreased "as-needed" beta-agonist use and corticosteroid rescue for worsening asthma compared with placebo. Patients receiving montelukast had more days without asthma than those receiving placebo. A treatment effect was achieved after the first dose.

INDICATIONS

SINGULAIR SPRINKLES 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 SPRINKLES 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 SPRINKLES 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 SPRINKLES 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, SINGULAIR SPRINKLES should not be used during pregnancy or in breastfeeding mothers. It is not known if SINGULAIR SPRINKLES 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 SPRINKLES

Paediatric Patients 2 to 5 Years of Age:

The dosage for paediatric patients 2 to 5 years of age is one packet of 4 mg oral granules daily to be taken in the evening.

Administration of oral granules:

SINGULAIR SPRINKLES can be administered either directly in the mouth, or mixed with a spoonful of cold or room temperature soft food (e.g., applesauce). The packet should not be opened until ready to use. After opening the packet, the full dose of SINGULAIR SPRINKLES must be administered immediately (within 15 minutes). If mixed with food, SINGULAIR SPRINKLES must not be stored for future use. SINGULAIR SPRINKLES are not intended to be dissolved in liquid. However, liquids may be taken subsequent to administration.

General Recommendations:

A therapeutic effect of SINGULAIR SPRINKLES on parameters of asthma control occurs within one day.

SINGULAIR SPRINKLES can be taken with or without food. Patients should be advised to continue taking SINGULAIR SPRINKLES while their asthma is controlled, as well as during periods of worsening asthma.

No dosage adjustment is necessary for the elderly, paediatric patients, for patients with renal insufficiency, or mild-to-moderate hepatic impairment, or for patients of either gender.

Therapy with SINGULAIR SPRINKLES in Relation to Other Treatments for Asthma:

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

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:

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 (two 12-week studies; n=795)	Paediatric Patients 6 to 14 years old (one 8-week study; n=201)	Paediatric Patients 2 to 5 years old (one 12-week study; n=461)
General disorders and administration site conditions			thirst
Gastro-intestinal disorders	abdominal pain		
Nervous system disorders	headache	headache	

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.

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 SPRINKLES 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 SPRINKLES 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, and 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 SPRINKLES for the treatment of acute asthma attacks has not been established.

SINGULAIR SPRINKLES 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 SPRINKLES 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 SPRINKLES can be continued during acute exacerbations of asthma.

While the dose of inhaled corticosteroid may be reduced gradually under medical supervision, SINGULAIR SPRINKLES 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 SPRINKLES. Although SINGULAIR SPRINKLES 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 SINGULAIR SPRINKLES and its metabolites are not excreted in the urine, the pharmacokinetics of SINGULAIR SPRINKLES 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 SPRINKLES 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 SPRINKLES and these underlying conditions has not been established (see SIDE EFFECTS).

Information for Patients:

- Patients should be advised to take SINGULAIR SPRINKLES 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 SINGULAIR SPRINKLES 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 SPRINKLES, 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 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 SPRINKLES.

KNOWN SYMPTOMS OF OVERDOSAGE AND PARTICULARS OF ITS TREATMENT

No specific information is available on the treatment of overdosage with SINGULAIR SPRINKLES.

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 paediatric patients.

There were no adverse experiences 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 SINGULAIR SPRINKLES is dialyzable by peritoneal or haemodialysis.

IDENTIFICATION

SINGULAIR SPRINKLES: White, granular, coarse, free-flowing homogenous solid, with no extraneous particles present.

PRESENTATION

SINGULAIR SPRINKLES (500 mg net weight) is available in foil packets in pack sizes of 28 or 30 packets per carton.

STORAGE INSTRUCTIONS

Store at room temperature below 30 °C, protected from moisture and light.
The packet should not be opened until ready to use. The full dose must be administered immediately (within 15 minutes). If mixed with food, it must not be stored for future use.

Store all medicines out of reach of children.

REGISTRATION NUMBER

SINGULAIR SPRINKLES: A38/10.2.2/0584

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

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