PRODUCT CIRCULAR

Tablets/Chewable Tablets/Oral Granules
SINGULAIR®†
(montelukast sodium, MSD)

I. THERAPEUTIC CLASS

SINGULAIR (montelukast sodium) is a selective and orally active leukotriene receptor antagonist that specifically inhibits the cysteinyl leukotriene $CysLT_1$ receptor.

II. INDICATIONS

SINGULAIR is indicated in adult and pediatric patients 6 months of age and older for the prophylaxis and chronic treatment of asthma, including the prevention of day- and nighttime symptoms, the treatment of aspirin-sensitive asthmatic patients, and the prevention of exercise-induced bronchoconstriction.

SINGULAIR is indicated for the relief of daytime and nighttime symptoms of seasonal allergic rhinitis (seasonal allergic rhinitis in adults and pediatric patients 2 years of age and older, and perennial allergic rhinitis in adults and pediatric patients 6 months of age and older).

III. DOSAGE AND ADMINISTRATION

SINGULAIR should be taken once daily. For asthma, the dose should be taken in the evening. For allergic rhinitis, the time of administration may be individualized to suit patient needs.

Patients with both asthma and allergic rhinitis should take only one tablet daily in the evening.

Adults 15 Years of Age and Older with Asthma and/or Allergic Rhinitis
The dosage for adults 15 years of age and older is one 10-mg tablet daily.

Pediatric Patients 6 to 14 Years of Age with Asthma and/or Allergic Rhinitis
The dosage for pediatric patients 6 to 14 years of age is one 5-mg chewable tablet daily.

Pediatric Patients 2 to 5 Years of Age with Asthma and/or Allergic Rhinitis
The dosage for pediatric patients 2 to 5 years of age is one 4-mg chewable tablet daily or one packet of 4-mg oral granules daily.

Pediatric Patients 6 Months to 2 Years of Age with Asthma or Perennial Allergic Rhinitis
The dosage for pediatric patients 6 months to 2 years of age is one packet of 4-mg oral granules daily.

Administration of oral granules:

SINGULAIR oral granules can be administered either directly in the mouth, mixed with a spoonful of cold or room temperature soft food (e.g., applesauce), or dissolved in 1 teaspoonful (5 mL) of cold or room temperature baby formula or breast milk. The packet should not be

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opened until ready to use. After opening the packet, the full dose of SINGULAIR oral granules must be administered immediately (within 15 minutes). If mixed with food, or dissolved in baby formula or breast milk, SINGULAIR oral granules must not be stored for future use. SINGULAIR oral granules are not intended to be dissolved in any liquid other than baby formula or breast milk for administration. However, liquids may be taken subsequent to administration.

General Recommendations
The therapeutic effect of SINGULAIR on parameters of asthma control occurs within one day. SINGULAIR tablets, chewable tablets and oral granules 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 pediatric patients, for the elderly, 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:

Bronchodilator Treatments: SINGULAIR 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 can be reduced as tolerated.

Inhaled Corticosteroids: Treatment with SINGULAIR provides additional clinical benefit to patients treated with inhaled corticosteroids. A reduction in the corticosteroid dose can be made as tolerated. The dose should be reduced gradually with medical supervision. In some patients, the dose of inhaled corticosteroids can be tapered off completely. SINGULAIR should not be abruptly substituted for inhaled corticosteroids.

IV. CONTRAINDICATIONS

- Hypersensitivity to any component of this product

V. PRECAUTIONS

The efficacy of oral SINGULAIR for the treatment of acute asthma attacks has not been established. Therefore, oral SINGULAIR should not be used to treat acute asthma attacks. Patients should be advised to have appropriate rescue medication available.

While the dose of concomitant inhaled corticosteroid may be reduced gradually under medical supervision, SINGULAIR should not be abruptly substituted for inhaled or oral corticosteroids.

Neuropsychiatric events have been reported in patients taking SINGULAIR (see SIDE EFFECTS). Since other factors may have contributed to these events, it is not known if they are related to SINGULAIR. Physicians should discuss these adverse experiences with their patients and/or caregivers. Patients and/or caregivers should be instructed to notify their physician if these changes occur.

The reduction in systemic corticosteroid dose in patients receiving anti-asthma agents including leukotriene receptor antagonists has been followed in rare cases by the occurrence of one or more of the following: eosinophilia, vasculitic rash, worsening pulmonary symptoms, cardiac complications, and/or neuropathy sometimes diagnosed as Churg-Strauss syndrome, a systemic eosinophilic vasculitis. Although a causal relationship with leukotriene receptor

antagonism has not been established, caution and appropriate clinical monitoring are recommended when systemic corticosteroid reduction is considered in patients receiving SINGULAIR.

VI. PREGNANCY

SINGULAIR has not been studied in pregnant women. SINGULAIR should be used during pregnancy only if clearly needed.

During worldwide marketing experience, congenital limb defects have been rarely reported in the offspring of women being treated with SINGULAIR during pregnancy. Most of these women were also taking other asthma medications during their pregnancy. A causal relationship between these events and SINGULAIR has not been established.

VII. NURSING MOTHERS

It is not known if SINGULAIR is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when SINGULAIR is given to a nursing mother.

VIII. PEDIATRIC USE

SINGULAIR has been studied in pediatric patients 6 months to 14 years of age (see Dosage and Administration). Safety and effectiveness in pediatric patients younger than 6 months of age have not been studied. Studies have shown that SINGULAIR does not affect the growth rate of pediatric patients.

IX. USE IN THE ELDERLY

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

X. DRUG INTERACTIONS

SINGULAIR may be administered with other therapies routinely used in the prophylaxis and chronic treatment of asthma, and in the treatment of 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 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 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, montelukast is not anticipated to alter the metabolism of drugs metabolized by this enzyme (e.g., paclitaxel, rosiglitazone, repaglinide).

XI. SIDE EFFECTS

SINGULAIR has been generally well tolerated. Side effects, which usually were mild, generally did not require discontinuation of therapy. The overall incidence of side effects reported with SINGULAIR was comparable to placebo.

Adults 15 Years of Age and Older with Asthma
SINGULAIR has been evaluated in approximately 2600 adult patients 15 years of age and older in clinical studies. In two similarly designed, 12-week placebo-controlled clinical studies, the only adverse experiences reported as drug related in ≥ 1% of patients treated with SINGULAIR and at a greater incidence than in patients treated with placebo were abdominal pain and headache. The incidences of these events were not significantly different in the two treatment groups.

Cumulatively, 544 patients were treated with SINGULAIR for at least 6 months, 253 for one year and 21 for 2 years in clinical studies. With prolonged treatment, the adverse experience profile did not change.

Pediatric Patients 6 to 14 Years of Age with Asthma
SINGULAIR has been evaluated in approximately 475 pediatric patients 6 to 14 years of age. The safety profile in pediatric patients is generally similar to the adult safety profile and to placebo.

In an 8-week, placebo-controlled clinical study, the only adverse experience reported as drug related in > 1% of patients treated with SINGULAIR and at a greater incidence than in patients treated with placebo was headache. The incidence of headache was not significantly different in the two treatment groups.

In studies evaluating growth rate, the safety profile in these pediatric patients was consistent with the safety profile previously described for SINGULAIR.

Cumulatively, 263 pediatric patients 6 to 14 years of age were treated with SINGULAIR for at least 3 months and 164 for 6 months or longer. With prolonged treatment, the adverse experience profile did not change.

Pediatric Patients 2 to 5 Years of Age with Asthma
SINGULAIR has been evaluated in 573 pediatric patients 2 to 5 years of age. In a 12-week, placebo-controlled clinical study, the only adverse experience reported as drug related in > 1% of patients treated with SINGULAIR and at a greater incidence than in patients treated with placebo was thirst. The incidence of thirst was not significantly different in the two treatment groups.

Cumulatively, 426 pediatric patients 2 to 5 years of age were treated with SINGULAIR for at least 3 months, 230 for 6 months or longer, and 63 patients for 12 months or longer. With prolonged treatment, the adverse experience profile did not change.

Pediatric Patients 6 Months to 2 Years of Age with Asthma
SINGULAIR has been evaluated in 175 pediatric patients 6 months to 2 years of age. In a 6-week, placebo-controlled clinical study, the adverse experiences reported as drug related in > 1% of patients treated with SINGULAIR and at a greater incidence than in patients treated with placebo were diarrhea, hyperkinesia, asthma, eczematous dermatitis and rash. The

incidences of these adverse experiences were not significantly different in the two treatment groups.

Adults 15 Years of Age and Older with Seasonal Allergic Rhinitis
SINGULAIR has been evaluated in 2199 adult patients 15 years of age and older for the treatment of seasonal allergic rhinitis in clinical studies. SINGULAIR administered once daily in the morning or in the evening was generally well tolerated with a safety profile similar to that of placebo. In placebo-controlled clinical studies, no adverse experiences reported as drug related in ≥1% of patients treated with SINGULAIR and at a greater incidence than in patients treated with placebo were observed. In a 4-week, placebo-controlled clinical study, the safety profile was consistent with that observed in 2-week studies. The incidence of somnolence was similar to that of placebo in all studies.

Pediatric Patients 2 to 14 Years of Age with Seasonal Allergic Rhinitis
SINGULAIR has been evaluated in 280 pediatric patients 2 to 14 years of age for the treatment of seasonal allergic rhinitis in a 2-week, placebo-controlled, clinical study. SINGULAIR administered once daily in the evening was generally well tolerated with a safety profile similar to that of placebo. In this study, no adverse experiences reported as drug related in ≥ 1% of patients treated with SINGULAIR and at a greater incidence than in patients treated with placebo were observed.

Adults 15 Years of Age and Older with Perennial Allergic Rhinitis
SINGULAIR has been evaluated in 3235 adult and adolescent patients 15 years of age and older with perennial allergic rhinitis in two, 6-week, placebo-controlled, clinical studies. SINGULAIR administered once daily was generally well tolerated, with a safety profile consistent with that observed in patients with seasonal allergic rhinitis and similar to that of placebo. In these two studies, no adverse experiences reported as drug related in ≥1% of patients treated with SINGULAIR and at a greater incidence than in patients treated with placebo were observed. The incidence of somnolence was similar to that of placebo.

Pooled Analyses of Clinical Trials Experience
A pooled analysis of 41 placebo-controlled clinical studies (35 studies in patients 15 years of age and older; 6 studies in pediatric patients 6 to 14 years of age) was performed using a validated assessment method of suicidality. Among the 9929 patients who received SINGULAIR and 7780 patients who received placebo in these studies, there was one patient with suicidal ideation in the group taking SINGULAIR. There were no completed suicides, suicide attempts or preparatory acts toward suicidal behavior in either treatment group.

A separate pooled analysis of 46 placebo-controlled clinical studies (35 studies in patients 15 years of age and older; 11 studies in pediatric patients 3 months to 14 years of age) assessing behavior-related adverse experiences (BRAEs) was performed. Among the 11,673 patients who received SINGULAIR and 8827 patients who received placebo in these studies, the frequency of patients with at least one BRAE was 2.73% in patients who received SINGULAIR and 2.27% in patients who received placebo; the odds ratio was 1.12 (95% CI [0.93; 1.36]).

The clinical trials included in these pooled analyses were not designed specifically to examine suicidality or BRAEs.

Postmarketing Experience
The following side effects have been reported in postmarketing use:
Infections and infestations: upper respiratory infection
Blood and lymphatic system disorders: increased bleeding tendency

Immune system disorders: hypersensitivity reactions including anaphylaxis, very rarely hepatic eosinophilic infiltration
Psychiatric disorders: agitation including aggressive behavior or hostility, anxiousness, depression, disorientation, dream abnormalities,hallucinations, insomnia, irritability, restlessness, somnambulism, suicidal thinking and behavior (suicidality), tremor
Nervous system disorders: dizziness, drowsiness, paraesthesia/hypoesthesia, very rarely seizure
Cardiac disorders: palpitations
Respiratory, thoracic and mediastinal disorders: epistaxis
Gastrointestinal disorders: diarrhea, dyspepsia, nausea, vomiting
Hepatobiliary disorders: increased ALT and AST, very rarely 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 site conditions: asthenia/fatigue, edema, pyrexia
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XII. OVERDOSAGE

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 pediatric 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 montelukast is dialyzable by peritoneal- or hemodialysis.

XIII. AVAILABILITY

Singulair® (montelukast sodium, MSD) is available as:

- 4mg Oral Granules in sachet pack of 1X28’s
- 4mg chewable tablet in blister pack of 1X14’s
- 5mg chewable tablet in blister pack of 1X14’s
- 10mg tablet in blister pack of 1X14’s