SG-MK0476-MF-052019

PRODUCT CIRCULAR

Tablets/Chewable Tablets/Oral Granules
SINGULAIR®
(montelukast sodium)

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 1 year 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 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 1 year of age and older). Because the benefits of SINGULAIR may not outweigh the risk of neuropsychiatric symptoms in patients with allergic rhinitis, reserve use for patients who have an inadequate response or intolerance to alternative therapies.

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 1 to 2 Years of Age with Asthma
The dosage for pediatric patients 1 to 2 years of age is one packet of 4-mg oral granules daily to be taken in the evening.

Pediatric Patients 1 Year to 2 Years of Age with Perennial Allergic Rhinitis
The dosage for pediatric patients 1 year 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, dissolved in 1 teaspoonful (5 mL) of cold or room temperature baby formula or breast milk, or mixed with a spoonful of cold or room temperature soft foods; based on stability studies, only applesauce, carrots, rice or ice cream should be used. The packet should not be 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, 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. CLINICAL PHARMACOLOGY

Pharmacodynamic properties

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. In allergic rhinitis, CysLTs are released from the nasal mucosa after allergen exposure during both early- and late-phase reactions and are associated with symptoms of allergic rhinitis. Intranasal challenge with CysLTs has been shown to increase nasal airway resistance and symptoms of nasal obstruction.

Montelukast is a potent, orally active compound with anti-inflammatory properties which significantly improves parameters of asthmatic inflammation. Based on biochemical and pharmacological bioassays, it 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 β -adrenergic receptor). Montelukast potently inhibits physiologic actions of LTC_4, LTD_4, and LTE_4 at the $CysLT_1$ receptor without any agonist activity.

In asthmatic patients, montelukast causes potent inhibition of airway cysteinyl leukotriene receptors as demonstrated by the ability to inhibit bronchoconstriction due to inhaled LTD_4. Doses as low as 5 mg cause substantial blockage of LTD_4-induced

bronchoconstriction. Montelukast causes bronchodilation within 2 hours of oral administration; these effects were additive to the bronchodilation caused by a β -agonist.

Clinical Studies – Asthma

In clinical studies, SINGULAIR is effective in adult and pediatric patients 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 effective alone or in combination with other agents used in the maintenance treatment of chronic asthma. SINGULAIR and inhaled corticosteroid may be used concomitantly with additive effects to control asthma or to reduce the inhaled corticosteroid dose while maintaining clinical stability.

Adults 15 years of age and older

In two similarly-designed 12-week double-blind placebo-controlled studies in adult asthmatic patients 15 years of age and older, SINGULAIR, 10 mg once daily in the evening, demonstrated significant improvements in parameters of asthma control measuring asthma symptoms, asthma-related outcomes, respiratory function and "as-needed" β -agonist use.

SINGULAIR significantly improved patient-reported daytime symptoms and nocturnal awakenings, compared with placebo. Asthma-specific outcomes, including asthma attacks, corticosteroid rescue, discontinuations due to worsening asthma, asthma exacerbations and asthma-free days were also significantly better than placebo. Physicians' and patients' global asthma evaluations and asthma-specific quality-of-life evaluations (in all domains, including normal daily activity and asthma symptoms) were significantly better than placebo. SINGULAIR caused significant improvements in morning forced expiratory volume in 1 second (FEV_1), AM and PM peak expiratory flow rate

(PEFR) and significantly decreased the use of “as-needed” β -agonist, compared with placebo.

The treatment effect was achieved after the first dose and was maintained throughout the 24-hour dosing interval. Treatment effect also remained constant during continuous once-daily administration in extension studies for up to one year. Withdrawal of SINGULAIR after 12 weeks of use did not cause rebound worsening of asthma.

Compared with inhaled beclomethasone (200 μ g twice daily with a spacer device), SINGULAIR demonstrated a more rapid initial response although over the full duration of the 12-week study, beclomethasone provided a greater average treatment effect. However, a high percentage of patients treated with SINGULAIR achieved similar clinical responses compared with inhaled beclomethasone.

Pediatric patients 6 to 14 years of age

In pediatric patients 6 to 14 years of age, one 5-mg chewable tablet daily in the evening, significantly decreased asthma exacerbations, and improved parents’ global evaluations and the pediatric asthma-specific quality-of-life evaluations, compared with placebo. SINGULAIR also significantly improved morning FEV_1 and decreased total daily “as-needed” β -agonist use. Treatment effect was achieved after the first dose and remained constant during once-daily administration for up to 6 months.

Growth Rate in Pediatric Patients

Two controlled clinical studies have demonstrated that SINGULAIR did not affect the growth rate of prepubertal pediatric patients with asthma.

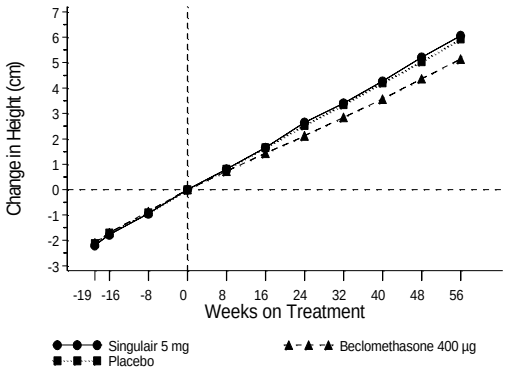
Growth rate was evaluated in a double-blind study of 71 pediatric patients aged 6 to 11 years (67 completed the study and were evaluated for growth): 35 patients were treated in

a crossover fashion with SINGULAIR and placebo; 32 patients were treated in a crossover fashion with inhaled budesonide and placebo. Growth rate as measured by lower leg length growth was similar in patients treated with SINGULAIR 5 mg once daily for 3 weeks compared with placebo, whereas growth rate was significantly lower (p=0.002) in patients treated with inhaled budesonide dosed at 200 mcg (one puff of 200 mcg) twice daily for 3 weeks, compared with placebo.

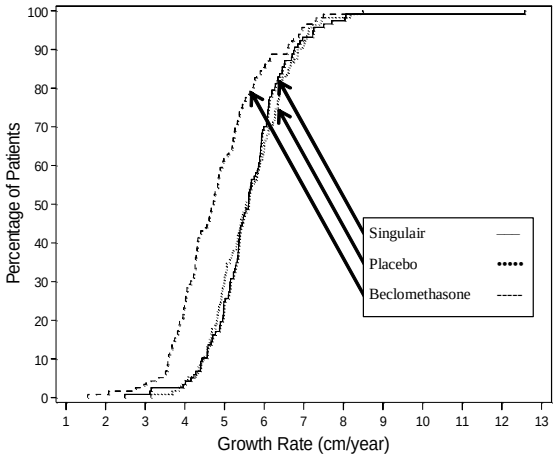
In a 56-week, multi-center, double-blind, randomized, active- and placebo-controlled parallel group study the effect of SINGULAIR on growth rate was evaluated in 360 patients aged 6 to 8 years; 120 patients treated with SINGULAIR. The observed mean linear growth rates in the placebo run-in period were similar in the three treatment arms. The mean growth rate in patients treated with SINGULAIR 5 mg once daily was similar to that of placebo during the treatment period, while the mean growth rate in patients treated with inhaled beclomethasone dipropionate dosed at 200 mcg (two puffs of 100 mcg ex-valve) twice daily with a spacer device was significantly below the mean growth rate of patients receiving SINGULAIR (p<0.001) or placebo (p<0.001) (see FIGURE 1). Across the distribution of growth rates during treatment, growth rates for the beclomethasone group were reduced compared to those of SINGULAIR. The SINGULAIR and placebo groups had similar growth rates (see FIGURE 2). Both SINGULAIR and inhaled beclomethasone demonstrated significant benefit versus placebo in the exploratory efficacy endpoints of rescue medication use in these patients with mild asthma.

FIGURE 1
Change in Height (cm) from Randomization Visit by Scheduled Week
(Treatment Group Mean ± Standard Error† of the Mean)

FIGURE 2
Cumulative Percentage of Patients
by Growth Rate (cm/year) Over 56 Weeks of Treatment



† The standard errors of the treatment group means in change in height are too small to be visible on the plot.



Pediatric patients 6 months to 5 years of age

In a 12-week, placebo-controlled study in pediatric patients 2 to 5 years of age, SINGULAIR 4 mg once daily consistently improved parameters of asthma control irrespective of concomitant controller therapy use compared with placebo. Sixty percent of patients were not on any other controller therapy. SINGULAIR significantly improved daytime symptoms (including coughing, wheezing, trouble breathing and activity limitation) and nighttime symptoms compared with placebo. SINGULAIR also significantly decreased "as-needed" β -agonist use and corticosteroid rescue compared with placebo. Patients receiving SINGULAIR had significantly more days without asthma than those receiving placebo. A treatment effect was achieved after the first dose. In addition, total blood eosinophil counts were significantly decreased.

Efficacy of SINGULAIR is supported in pediatric patients 6 months to 2 years of age by extrapolation from the demonstrated efficacy in patients 2 years of age and older with asthma, and is based on similar pharmacokinetic data, as well as the assumption that the disease course, pathophysiology and the drug's effect are substantially similar among these populations.

Effects in patients on concomitant inhaled corticosteroids

Separate studies in adults demonstrated the ability of SINGULAIR to add to the clinical effect of inhaled corticosteroid and allow steroid tapering when used concomitantly. In a placebo-controlled study, patients taking initial inhaled corticosteroid doses of approximately 1600 μ g per day reduced their steroid use by approximately 37% during a placebo run-in period. SINGULAIR allowed a further 47% reduction of the inhaled corticosteroid dose, compared with 30% for placebo. In another study, SINGULAIR provided additional clinical benefit to a similar population of patients maintained but not adequately controlled on inhaled corticosteroid (beclomethasone 400 μ g per day). Complete abrupt removal of beclomethasone in patients receiving both SINGULAIR and beclomethasone caused clinical deterioration in some patients, suggesting that tapering as tolerated rather than abrupt removal is preferred. In aspirin-sensitive patients, nearly all of whom were receiving concomitant inhaled and/or oral corticosteroids, SINGULAIR resulted in significant improvement in the parameters of asthma control.

Effects on exercise-induced bronchoconstriction

SINGULAIR, 10 mg once daily, prevented exercise-induced bronchoconstriction (EIB) in adults 15 years of age and older. In a 12-week study, SINGULAIR significantly inhibited the extent and duration of fall in FEV_1 over 60 minutes after exercise, the maximal percent fall in FEV_1 after exercise, and the time to recovery to within 5% of the pre-exercise FEV_1. Protection was consistent through the treatment period indicating that tolerance did not occur. In a separate cross-over study, protection was observed after two once-daily doses. In pediatric patients 6 to 14 years of age, using the 5-mg chewable tablet, a similarly designed cross-over study demonstrated similar protection and the protection was maintained throughout the dosing interval (24 hours).

Effects on asthmatic inflammation

In clinical studies SINGULAIR inhibited both early- and late-phase bronchoconstriction due to antigen challenge. Because inflammatory cell (eosinophil) infiltration is an important feature of asthma, the effects of SINGULAIR on eosinophils in the peripheral blood and airway were examined. In Phase IIb/III clinical studies, SINGULAIR significantly decreased peripheral blood eosinophils approximately 15% from baseline, compared with placebo. In pediatric patients 6 to 14 years of age, SINGULAIR decreased peripheral blood eosinophils 13% over the 8-week treatment period, compared with placebo. SINGULAIR also significantly decreased airway eosinophils in sputum, compared with placebo. In this study, peripheral blood eosinophils decreased and clinical asthma endpoints improved with treatment with SINGULAIR.

Effects in Patients with Asthma and Seasonal Allergic Rhinitis

In a clinical study in adult asthmatic patients 15 years of age and older with concomitant seasonal allergic rhinitis, montelukast 10-mg tablets administered once daily demonstrated a statistically significant improvement in the primary variable, Daily Rhinitis Symptoms score (average of the Daytime Nasal Symptoms score [mean of nasal congestion, rhinorrhea, sneezing, nasal itching] and the Nighttime Symptoms score [mean of nasal congestion upon awakening, difficulty going to sleep, and nighttime awakenings scores]), compared with placebo. Global evaluations of allergic rhinitis by patients and physicians, and global evaluations of asthma by patients and physicians, were also significantly improved, compared with placebo.

Clinical Studies - Allergic Rhinitis

The efficacy of SINGULAIR for the treatment of seasonal allergic rhinitis was investigated in similarly designed randomized, 2-week, double-blind, placebo-controlled trials including 4924 patients (1751 patients were treated with SINGULAIR). Patients were 15 years of age and older with a history of seasonal allergic rhinitis, a positive skin test to at least one

relevant seasonal allergen, and active symptoms of seasonal allergic rhinitis at study initiation.

In a combined analysis of three pivotal studies, SINGULAIR 10-mg tablets administered to 1189 patients once daily in the evening resulted in a statistically significant improvement in the primary endpoint, daytime nasal symptoms score, and its individual components (nasal congestion, rhinorrhea, nasal itching and sneezing); nighttime symptoms score, and its individual components (nasal congestion upon awakening, difficulty going to sleep, and nighttime awakenings); composite symptoms score (composed of the daytime nasal and nighttime symptoms scores); and global evaluations of allergic rhinitis by patients and by physicians, compared with placebo.

In a separate 4-week study in which SINGULAIR was administered once daily in the morning, the efficacy over the initial 2 weeks was significantly different from placebo and consistent with the effect observed in studies using evening dosing. Additionally, the effect over the entire 4 weeks was consistent with the 2-week results.

In patients with seasonal allergic rhinitis aged 15 years and older who received SINGULAIR, a median decrease of 13% in peripheral blood eosinophil counts was noted, compared with placebo, over the double-blind treatment periods.

The efficacy of SINGULAIR for the treatment of perennial allergic rhinitis was investigated in two, similarly designed randomized, 6-week, double-blind, placebo-controlled studies including 3235 patients (1632 patients were treated with SINGULAIR). Patients were 15 to 82 years of age with a history of perennial allergic rhinitis, positive skin test results to relevant perennial allergens (including dust mites, animal dander, and mold spores), and active symptoms of perennial allergic rhinitis at study initiation.

In one study, SINGULAIR 10-mg tablets administered to 1000 patients once daily resulted in a statistically significant improvement in the primary endpoint, Daytime Nasal

Symptoms score, and its individual components (nasal congestion, rhinorrhea, and sneezing), compared with placebo. SINGULAIR also demonstrated patient-perceived improvement of allergic rhinitis as assessed by the secondary endpoints of Global Evaluation of Allergic Rhinitis by Patient, and Rhinoconjunctivitis Quality-of-Life overall score (average of scores for the 7 domains of activity, sleep, non-nose/non-eye symptoms, practical problems, nasal symptoms, eye symptoms, and emotions), compared with placebo.

The efficacy of SINGULAIR for the treatment of seasonal allergic rhinitis in pediatric patients 2 to 14 years of age, and for the treatment of perennial allergic rhinitis in pediatric patients 1 year to 14 years of age is supported by extrapolation from the demonstrated efficacy in patients 15 years of age and older with allergic rhinitis as well as the assumption that the disease course, pathophysiology and the drug's effect are substantially similar among these populations.

Pharmacokinetic properties

Absorption

Montelukast is rapidly and nearly completely 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. Safety and efficacy were demonstrated in clinical studies where the 10-mg film-coated tablet was administered without regard to the timing of food ingestion.

For the 5-mg chewable tablet, C_{max} is achieved in 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.

For the 4-mg chewable tablet, C_{max} is achieved in 2 hours after administration in pediatric patients 2 to 5 years of age in the fasted state.

The 4-mg oral granule formulation is bioequivalent to the 4-mg chewable tablet when administered to adults in the fasted state. The co-administration of applesauce or a standard 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 standard meal, respectively).

Distribution

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

Biotransformation

Montelukast is extensively metabolized. In studies with therapeutic doses, plasma concentrations of metabolites of montelukast are undetectable at steady state in adults and children.

In vitro studies using human liver microsomes indicate that cytochrome P450 3A4, 2C8, 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 fecal collections and <0.2% was recovered in urine. Coupled with estimates of montelukast oral bioavailability, this indicates that 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 (~14%).

Characteristics in Patients

Elderly Patients, and Patients with Renal or Hepatic Insufficiency

No dosage adjustment is necessary for the elderly, for patients with renal insufficiency or mild to moderate hepatic insufficiency. There are no clinical data in patients with severe hepatic insufficiency (Child-Pugh score > 9).

Paediatric Patients

In children 6 to 11 months of age, the systemic exposure to montelukast and the variability of plasma montelukast concentrations were higher than those observed in adults. Based on population analyses, the mean AUC was 60% higher and mean C_{max} was 89% higher than those observed in adults. The systemic exposure in children 12 to 23 months of age was less variable, but was still higher than that observed in adults. The mean AUC was 33% higher and the mean C_{max} was 60% higher than those observed in adults. Safety and tolerability of montelukast in a single-dose pharmacokinetic study in 26 children 6 to 23 months of age were similar to that of patients two years and above.

The safety and effectiveness in pediatric patients younger than 1 year of age with perennial allergic rhinitis and in patients below the age of 12 months with asthma have not been established.

V. CONTRAINDICATIONS

- Hypersensitivity to any component of this product

VI. 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). Post-marketing reports with SINGULAIR use include agitation including aggressive behavior or hostility, anxiousness, depression, disorientation, disturbance in attention, dream abnormalities, dysphemia (stuttering), hallucinations, insomnia, memory impairment, obsessive-compulsive symptoms, psychomotor hyperactivity (including irritability, restlessness and tremor), somnambulism, suicidal thinking and behavior (suicidality) and tic. The clinical details of some post-marketing reports involving SINGULAIR appear consistent with a drug-induced effect.

These neuropsychiatric events have been reported in patients with and without a previous history of psychiatric disorder. Neuropsychiatric events have been reported mostly during SINGULAIR treatment, but some were reported after SINGULAIR discontinuation. Based

upon the available data, it is difficult to identify risk factors for or quantify the risk of neuropsychiatric events with SINGULAIR use.

Physicians should discuss the benefits and risks of SINGULAIR use with patients and caregivers when prescribing SINGULAIR. Patients and/or caregivers should be advised to be alert for changes in behavior or for new neuropsychiatric symptoms when taking SINGULAIR. If changes in behavior are observed, or if new neuropsychiatric symptoms or suicidal thoughts and/or behavior occur, patients should be advised to contact a healthcare provider immediately. In many cases, symptoms resolved after stopping SINGULAIR therapy; however, in some cases symptoms persisted after discontinuation of SINGULAIR. Therefore, patients should be monitored and provided supportive care until symptoms resolve.

Prescribers should carefully evaluate the risks and benefits of continuing treatment with SINGULAIR if such events occur.

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 β -agonists as prophylaxis and have available for rescue a short-acting inhaled β -agonist.

Patients with known aspirin hypersensitivity 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 NSAIDs in aspirin-sensitive asthmatic patients.

In rare cases, patients receiving anti-asthma agents including leukotriene receptor antagonists have experienced 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 eosinophillic vasculitis. These cases have been sometimes associated with the reduction or withdrawal of oral corticosteroid therapy. Although a causal relationship with leukotriene receptor antagonism has not been established, caution and appropriate clinical monitoring are recommended in patients receiving SINGULAIR.

VII. PREGNANCY

SINGULAIR should be used during pregnancy only if clearly needed. Available data from published prospective and retrospective cohort studies with montelukast use in pregnant women evaluating major birth defects have not established a drug-associated risk. Available studies have methodologic limitations, including small sample size, in some cases retrospective data collection, and inconsistent comparator groups.

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.

VIII. 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.

IX. 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.

X. USE IN THE ELDERLY

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

XI. 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 CYP 2C8) demonstrated that montelukast does not inhibit CYP 2C8 *in vivo*. Therefore, montelukast is not anticipated to alter the metabolism of drugs metabolized by this enzyme (e.g., paclitaxel, rosiglitazone, repaglinide).

In vitro studies have shown that montelukast is a substrate of CYP 2C8, 2C9, and 3A4. Data from a clinical drug-drug interaction study involving montelukast and gemfibrozil (an

inhibitor of both CYP 2C8 and 2C9) demonstrated that gemfibrozil increased the systemic exposure of montelukast by 4.4-fold. Co-administration of itraconazole, a strong CYP 3A4 inhibitor, with gemfibrozil and montelukast did not further increase the systemic exposure of montelukast. The effect of gemfibrozil on systemic exposure of montelukast is not considered to be clinically meaningful based on clinical safety data with doses greater than the 10 mg approved dose in adults (e.g., 200 mg/day to adult patients for 22 weeks, and up to 900 mg/day to patients for approximately one week) where clinically important adverse experiences were not observed. Therefore, no dosage adjustment of montelukast is required upon co-administration with gemfibrozil. Based on *in vitro* data, clinically important drug interactions with other known inhibitors of CYP 2C8 (e.g., trimethoprim) are not anticipated. In addition, co-administration of montelukast with itraconazole alone resulted in no significant increase in the systemic exposure of montelukast.

XII. 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 Asthma and Seasonal Allergic Rhinitis

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.

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.

Pediatric Patients 1 to 14 Years of Age with Perennial Allergic Rhinitis

The safety in patients 2 to 14 years of age with perennial allergic rhinitis is supported by the established safety in patients 2 to 14 years of age with seasonal allergic rhinitis. The safety in patients 12 to 23 months of age is supported by data from pharmacokinetic and safety and efficacy studies in asthma in this pediatric population and from adult pharmacokinetic studies.

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.

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, thrombocytopenia

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

Psychiatric disorders: agitation including aggressive behavior or hostility, anxiousness, depression, disorientation, disturbance in attention, dream abnormalities, dysphemia (stuttering), hallucinations, insomnia, memory impairment, obsessive-compulsive symptoms, psychomotor hyperactivity (including irritability, restlessness and tremor), somnambulism, suicidal thinking and behavior (suicidality), tic

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

Cardiac disorders: palpitations

Respiratory, thoracic and mediastinal disorders: epistaxis; pulmonary eosinophilia

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 multiforme, erythema nodosum, pruritus, rash, Steven Johnson Syndrome, toxic epidermal necrolysis, urticaria

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

Renal and urinary disorders: enuresis in children

General disorders and administration site conditions: asthenia/fatigue, edema, pyrexia

XIII. INFORMATION FOR PATIENTS

Patients should be advised to take SINGULAIR daily as prescribed, even when they are asymptomatic as well as during periods of asthma worsening, and to contact their physicians if their asthma is not well controlled. Patients should be advised that oral SINGULAIR is not for the treatment of acute asthma attacks. They should have appropriate rescue medication available.

XIV. 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.

XV. STORAGE

Store the 10-mg film-coated tablets, the 4-mg and 5-mg chewable tablets, and the packets of 4-mg oral granules at or below 30°C, protected from moisture and light.

XVI. COMPOSITION

XVIa. Active Ingredients:

Each 10-mg film-coated tablet contains 10.4 mg montelukast sodium, which is the molar equivalent to 10.0 mg of free acid. Each 5-mg chewable tablet contains 5.2 mg montelukast sodium, which is the molar equivalent to 5.0 mg of free acid. Each 4-mg chewable tablet and each packet of 4-mg oral granules contains 4.2 mg montelukast sodium, which is the molar equivalent to 4.0 mg of free acid.

XVIb. Inactive Ingredients:

Each 10-mg film-coated tablet contains the following inactive ingredients: microcrystalline cellulose, lactose monohydrate (89.3 mg), croscarmellose sodium, hydroxypropyl cellulose, and magnesium stearate. The film coating consists of: hydroxypropyl methylcellulose, hydroxypropyl cellulose, titanium dioxide, red ferric oxide, yellow ferric oxide, and carnauba wax.

Each 4-mg and 5-mg chewable tablet contains the following inactive ingredients: mannitol, microcrystalline cellulose, hydroxypropyl cellulose, red ferric oxide, croscarmellose sodium, cherry flavor, aspartame, and magnesium stearate.

Each packet of 4-mg oral granules contains the following inactive ingredients: mannitol, hydroxypropyl cellulose, and magnesium stearate.

XVII. AVAILABILITY

SINGULAIR 4 mg chewable tablets, each containing 4.2 mg of montelukast sodium, which is the molar equivalent to 4 mg of free acid, is supplied in packs of 28 tablets.

SINGULAIR 4 mg oral granules, each packet containing 4.2 mg of montelukast sodium, which is the molar equivalent to 4 mg of free acid, is supplied in packs of 28 packets.

SINGULAIR 5 mg chewable tablets, each containing 5.2 mg of montelukast sodium, which is the molar equivalent to 5 mg of free acid, is supplied in packs of 28 tablets.

SINGULAIR 10 mg film-coated tablets, each containing 10.4 mg of montelukast sodium, which is the molar equivalent to 10 mg of free acid, is supplied in packs of 28 tablets.

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ORGANON