SINGULAIR® 4 MG GRANULES FOR KIDDIES

SINGULAIR® 4 MG CHEWABLE TABLETS FOR PRE-SCHOOL KIDS

SINGULAIR® 5 MG CHEWABLE TABLETS

SINGULAIR® 10 MG TABLETS

INDICATIONS

SINGULAIR is indicated in adult and pediatric patients 12 months of age and older for the prophylaxis and chronic treatment of asthma, including prevention of daytime 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 corticosteroids may be used concomitantly with additive effects to control asthma or to reduce the inhaled corticosteroid dose while maintaining clinical stability.

SINGULAIR is indicated for the relief of daytime and nighttime symptoms of seasonal allergic rhinitis in adults and in pediatric patients 2 years of age and older.

DOSAGE AND 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.

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

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

Adults 15 Years of Age and Older *with Asthma and/or Seasonal 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 Seasonal 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 Seasonal Allergic Rhinitis*
The dosage for pediatric patients 2 to 5 years of age is one 4-mg chewable tablet daily or one sachet of 4-mg oral granules daily.

Pediatric Patients 12 Months to 2 Years of Age with Asthma
The dosage for pediatric patients 12 months to 2 years of age is one sachet 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 sachet should not be opened until ready to use. After opening the sachet, 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.

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.

COMPOSITION
Each tablet/chewable tablet/sachet contains:
Active Ingredient
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 sachet of 4 mg oral granules contains 4.2 mg montelukast sodium, which is the molar equivalent to 4.0 mg of free acid.

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

CONTRAINDICATIONS
Hypersensitivity to any component of this product.

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.

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 [see Clinical Studies].

Neuropsychiatric events have been reported in patients taking SINGULAIR. Post-marketing reports with SINGULAIR use include agitation, aggressive behavior or hostility, anxiousness, depression, disorientation, disturbance in attention, dream abnormalities, hallucinations, insomnia, irritability, memory impairment, restlessness, somnambulism, suicidal thinking and behavior (including suicide), and tremor. The clinical details of some post-marketing reports involving SINGULAIR appear consistent with a drug-induced effect.
Patients and prescribers should be alert for neuropsychiatric events. Patients should be instructed to notify their prescriber if these changes occur. Prescribers should carefully evaluate the risks and benefits of continuing treatment with SINGULAIR if such events occur (see Side Effects).

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 eosinophilic 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.

Phenylketonuric patients should be informed that the 4-mg and 5-mg chewable tablets contain phenylalanine (a component of aspartame), 0.674 and 0.842 mg per 4-mg and 5-mg chewable tablet, respectively.

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 for safety in approximately 2600 adult patients 15 years of age and older in clinical studies. In placebo-controlled clinical studies, the following adverse experiences reported with SINGULAIR occurred in ≥1% of patients and at an incidence greater than or equal to that in patients treated with placebo, regardless of drug relationship:

Table 1: Adverse Experiences Occurring in ≥1% of Patients with an Incidence Greater than that in Patients Treated with Placebo

	SINGULAIR 10 mg/day (%) (n = 1955)	Placebo (%) (n = 1180)
Body As A Whole		
Asthenia/fatigue	1.8	1.2
Fever	1.5	0.9
Pain, abdominal	2.9	2.5
Trauma	1.0	0.8
Digestive System Disorders		
Dyspepsia	2.1	1.1
Gastroenteritis, infectious	1.5	0.5
Pain, dental	1.7	1.0
Nervous System/Psychiatric		
Dizziness	1.9	1.4
Headache	18.4	18.1
Respiratory System Disorders		
Congestion, nasal	1.6	1.3
Cough	2.7	2.4
Influenza	4.2	3.9
Skin/Skin Appendages Disorder		
Rash	1.6	1.2
Laboratory Adverse Experiences*		
ALT increased	2.1	2.0
AST increased	1.6	1.2
Pyuria	1.0	0.9

* Number of patients tested (SINGULAIR and placebo, respectively): ALT and AST, 1935, 1170; pyuria, 1924, 1159.

Cumulatively, 569 patients were treated with SINGULAIR for at least 6 months, 480 for one year and 49 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 476 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 pediatric patients 6 to 14 years of age receiving SINGULAIR, the following events occurred with a frequency ≥2% and more frequently than in pediatric patients who received placebo: pharyngitis, influenza, fever, sinusitis, nausea, diarrhea, dyspepsia, otitis, viral infection, and laryngitis.

In studies evaluating growth rate, the safety profile in these pediatric patients was consistent with the safety profile previously described for SINGULAIR. In a 56-week, double-blind study evaluating growth rate in pediatric patients 6 to 8 years of age receiving SINGULAIR, the following events not previously observed with the use of SINGULAIR in this age group occurred with a frequency ≥2% and more frequently than in pediatric patients who received placebo: headache, rhinitis (infective), varicella, gastroenteritis, atopic dermatitis, acute bronchitis, tooth infection, skin infection, and myopia. Cumulatively, 289 pediatric patients 6 to 14 years of age were treated with SINGULAIR for at least 6 months and 241 for one year 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 pediatric patients 2 to 5 years of age receiving SINGULAIR, the following events occurred with a frequency ≥2% and more frequently than in pediatric patients who received placebo: fever, cough, abdominal pain, diarrhea, headache, rhinorrhea, sinusitis, otitis, influenza, rash, ear pain, gastroenteritis, eczema, urticaria, varicella, pneumonia, dermatitis, and conjunctivitis.

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

Safety and effectiveness in pediatric patients younger than 12 months of age with asthma have not been established.

SINGULAIR has been evaluated for safety in 175 pediatric patients 6 months to 2 years of age.

The safety profile of SINGULAIR in a 6-week, double-blind, placebo-controlled clinical study was generally similar to the safety profile in adults and pediatric patients 2 to 14 years of age. In pediatric patients 6 to 23 months of age receiving SINGULAIR, the following events occurred with a frequency ≥2% and more frequently than in pediatric patients who received placebo: upper respiratory infection, wheezing; otitis media; pharyngitis, tonsillitis, cough; and rhinitis. The frequency of less common adverse events was comparable between SINGULAIR and placebo.

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, the following event was reported with SINGULAIR with a frequency ≥1% and at an incidence greater than placebo: upper respiratory infection, 1.9% of patients receiving SINGULAIR vs. 1.5% of patients receiving placebo.

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, the following events occurred with a frequency ≥2% and at an incidence greater than placebo: headache, otitis media, pharyngitis, and upper respiratory infection.

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 adverse reactions have been identified during post-approval use of SINGULAIR. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

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, hallucinations, insomnia, memory impairment, psychomotor hyperactivity (including irritability, restlessness, and tremor), somnambulism, suicidal thinking and behavior (suicidality)

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). Most of the cases of hepatitis occurred in combination with other confounding factors, such as use of other medications, or when SINGULAIR was administered to patients who had underlying potential for liver disease such as alcohol use or other forms of hepatitis.
Skin and subcutaneous tissue disorders: angioedema, bruising, erythema multiforme, erythema nodosum, pruritus, rash, 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

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product.

Any suspected adverse events should be reported to the Ministry of Health according to the National Regulation by using an online form: https://sideeffects.health.gov.il

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, warfarin, gemfibrozil, itraconazole and Cytochrome P450 (CYP) enzyme inducers.
Although additional specific interaction studies were not performed, SINGULAIR was used concomitantly with a wide range of commonly prescribed drugs in clinical studies without evidence of clinical adverse interactions. These medications included thyroid hormones, sedative hypnotics, nonsteroidal anti-inflammatory agents, benzodiazepines and decongestants.

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, and 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.

USE IN SPECIFIC POPULATIONS

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.

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.

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.

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

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. In the event of overdose, it is reasonable to employ the usual supportive measures; e.g., remove unabsorbed material from the gastrointestinal tract, employ clinical monitoring, and institute supportive therapy, if required.

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.

THERAPEUTIC CLASS
SINGULAIR (montelukast sodium) is a selective and orally active leukotriene receptor antagonist that specifically inhibits the cysteinyl leukotriene CysLT1 receptor.

CLINICAL PHARMACOLOGY
Mechanism of Action

SINGULAIR is a selective orally active leukotriene receptor antagonist that specifically inhibits the cysteinyl leukotriene $CysLT_1$ receptor.

Pharmacodynamics
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 antiinflammatory 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.

Pharmacokinetics
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.
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.

For the 4-mg chewable tablet, C_{max} is achieved 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 coadministration 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).

Safety and efficacy were demonstrated in clinical studies where the 4-mg chewable tablet, 5-mg chewable tablet, and 10-mg film-coated tablet were administered without regard to the timing of food ingestion. The safety of SINGULAIR 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. The steady state volume of distribution of montelukast averages 8 to 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.

Metabolism
Montelukast is extensively metabolized. In studies with therapeutic doses, plasma concentrations of metabolites of montelukast are undetectable at steady state in adults and pediatric patients.
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 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
Gender: The pharmacokinetics of montelukast are similar in males and females.
Elderly: 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.
Race: Pharmacokinetic differences due to race have not been studied. In clinical studies, there do not appear to be any differences in clinically important effects.
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 >9).
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.
Adolescents and Pediatric Patients: The plasma concentration profile of montelukast following administration of the 10-mg film-coated tablet is similar in adolescents ≥15 years old and young adults. The 10-mg film-coated tablet is recommended for use in patients ≥15 years old.

Pharmacokinetic studies show that the plasma profiles of the 4-mg oral granule formulation in pediatric patients 6 months to 2 years of age, the 4-mg chewable tablet in pediatric patients 2 to 5 years of age, and the 5-mg chewable tablets in pediatric patients 6 to 14 years of age were similar to the plasma profile of the 10-mg film-coated tablet in adults. The 5-mg chewable tablet should be used in pediatric patients 6 to 14 years of age

and the 4-mg chewable tablet in pediatric patients 2 to 5 years of age. The 4-mg oral granule formulation should be used for pediatric patients 12 months to 2 years of age. Since the 4-mg oral granule formulation is bioequivalent to the 4-mg chewable tablet, it can also be used as an alternative formulation to the 4-mg chewable tablet in pediatric patients 2 to 5 years of age.

NONCLINICAL TOXICOLOGY

Carcinogenicity

Montelukast sodium was not carcinogenic when administered at oral doses of up to 200 mg/kg/day in a 106-week study in rats, or at oral doses of up to 100 mg/kg/day in a 92-week study in mice. These doses are equivalent to 1000 times and 500 times the recommended adult human dose respectively, based on an adult patient weight of 50 kg.

Mutagenicity

Montelukast sodium was found to be neither genotoxic nor mutagenic. Montelukast sodium was negative in the *in vitro* microbial mutagenesis assay and the V-79 mammalian cell mutagenesis assays, with and without metabolic activation. There was no evidence of genotoxicity in the *in vitro* alkaline elution assay in rat hepatocytes and the *in vitro* chromosomal aberration assays in Chinese hamster ovary cells, with or without a microsomal enzyme activation system. Similarly, there was no induction of chromosomal aberrations in bone marrow cells of male or female mice after the administration of oral doses of up to 1200 mg/kg body weight (3600 mg/m^2), which represent 6000 times the recommended daily adult dose, based on an adult patient weight of 50 kg.

Reproduction

Fertility and reproductive performance were not affected in studies with male rats given oral doses of up to 800 mg/kg/day or with female rats given doses of up to 100 mg/kg/day. These dosages provide margins of 4000-fold and 500-fold respectively above the recommended adult human dose, based on an adult patient weight of 50 kg.

Development

In developmental toxicity studies, there were no treatment related adverse effects at doses up to 400 mg/kg/day in rats and up to 100 mg/kg/day in rabbits. Fetal exposure of montelukast sodium in rats and rabbits does occur and significant concentrations of drug were observed in milk of lactating rats.

CLINICAL STUDIES

CLINICAL STUDIES - ASTHMA

ADULTS 15 YEARS OF AGE AND OLDER

The efficacy of SINGULAIR for the chronic treatment of asthma in adults 15 years of age and older was demonstrated in two (US and Multinational) similarly designed 12-week double-blind, placebo-controlled studies in 1325 patients (795 treated with SINGULAIR and 530 treated with placebo). Patients were symptomatic and using approximately 5 puffs of β-agonist per day on an "as-needed" basis. The mean baseline percent of predicted forced expiratory volume in 1 second (FEV1) was 66% (approximate range, 40 to 90%). In these studies, asthma symptoms, asthma-related outcomes, respiratory function, and "as-needed" β-agonist use, were measured. Endpoints were analyzed in each study and in a combined analysis, according to a prespecified data analysis plan.

The following clinical results were observed:

Asthma Symptoms and Asthma-related Outcomes

SINGULAIR, 10 mg once daily in the evening, significantly improved measurements of patient-reported daytime symptoms and nighttime awakenings in each study and in the combined analysis, compared with placebo. In patients with nocturnal awakenings of at least 2 nights per week, SINGULAIR reduced the nocturnal awakenings by 34% from baseline, significantly better than the reduction of 14% for the placebo group (combined analysis).

SINGULAIR, compared with placebo, significantly improved asthma-related outcome measurements. In the combined analysis, SINGULAIR, compared with placebo, decreased asthma attacks by 37%, corticosteroid rescue by 39%, discontinuations due to worsening asthma by 65%, asthma exacerbations by 38% and increased asthma-free days by 42%.

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 with SINGULAIR compared with placebo in each study and in the combined analysis,.

Respiratory Function

Compared with placebo, SINGULAIR caused significant improvements in parameters of respiratory function (FEV_1 and peak expiratory flow rate, PEFR) in each study and in the combined analysis:

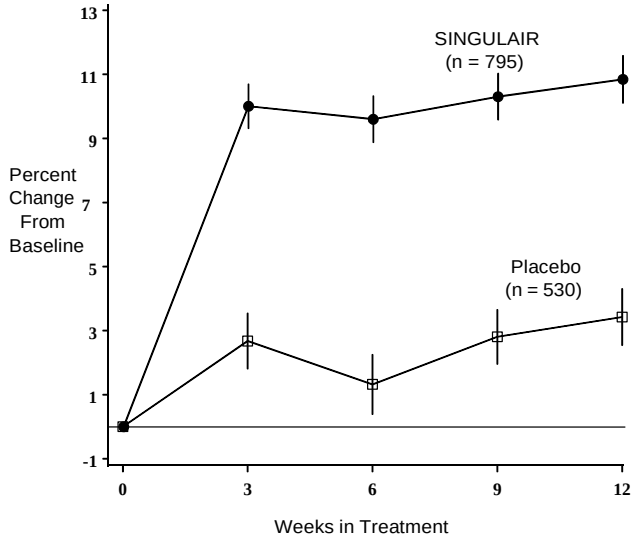
Table 2Effect of SINGULAIR, 10 mg Daily, on Parameters of Respiratory Function in Adults 15 Years and Older (Combined Analysis)

	SINGULAIR n = 795	Placebo n = 530
Morning FEV_1 (% change from baseline)	10.4*	2.7
AM PEFR (L/min change from baseline)	24.5*	3.3
PM PEFR (L/min change from baseline)	17.9*	2.0

*Significantly better than placebo ($p \leq 0.001$)

Figure 1

Effect of SINGULAIR on Morning FEV_1 in Adults 15 Years and Older (Combined Analysis)

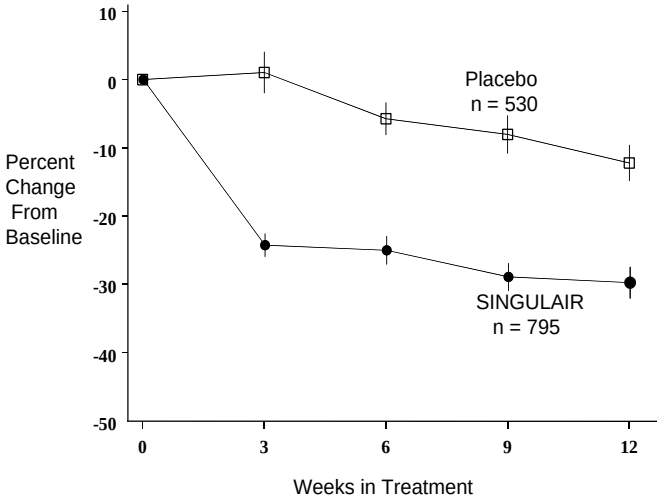


β-agonist Use

Compared with placebo, SINGULAIR significantly decreased the use of "as-needed" β-agonist by 26.1% from baseline compared with 4.6% in the placebo group, in the combined analysis. The decreases were also significant in each of the studies ($p \leq 0.001$) (see Figure 2).

Figure 2

Effect of SINGULAIR on "As-needed" β-agonist Use in Adults 15 Years and Older (Combined



Onset of Action and Maintenance of Benefits
In each study and in the combined analysis, the treatment effect of SINGULAIR, measured by daily diary card parameters, including symptom scores, "as-needed" β-agonist use, and PEFR measurements, was achieved after the first dose and was maintained throughout the dosing interval (24 hours). Treatment effect also remained constant during continuous once-daily administration in extension studies for up to one year. Withdrawal of SINGULAIR in asthmatic patients after 12 weeks of continuous use did not cause rebound worsening of asthma (See also EFFECTS ON EXERCISE-INDUCED BRONCHOCONSTRICTION.)

Effects Relative to Inhaled Corticosteroids
In one of the two 12-week double-blind studies in adults (Multinational), SINGULAIR was compared with inhaled beclomethasone (200 μg twice daily with a spacer device). SINGULAIR demonstrated a more rapid initial response, although over the full duration of the study beclomethasone provided a greater average treatment effect. However, a high percent of patients treated with SINGULAIR achieved similar clinical responses compared with inhaled beclomethasone.

PEDIATRIC PATIENTS 6 TO 14 YEARS OF AGE
The efficacy of SINGULAIR in pediatric patients 6 to 14 years of age was demonstrated in one 8-week double-blind, placebo-controlled study in 336 patients (201 treated with SINGULAIR and 135 treated with placebo) using β-agonist on an "as-needed" basis. The mean baseline percent predicted FEV_1 was 72% (approximate range, 45 to 90%) and approximately 36% of the patients were on inhaled corticosteroids.
Compared with placebo, SINGULAIR, one 5-mg chewable tablet daily in the evening, significantly decreased the percent of days asthma exacerbations occurred. Parents' global asthma evaluations and the pediatric asthma-specific quality-of-life evaluations (in all domains, including normal daily activity and asthma symptoms) were significantly better with SINGULAIR, compared with placebo.
Compared with placebo, there was a significant improvement in morning FEV_1 (8.7% versus 4.2% change from baseline in the placebo group, $p<0.001$) and a significant decrease in total "as-needed"
β-agonist use (11.7% decrease from baseline versus 8.2% increase from baseline in the placebo group, $p\leq0.050$).
Similar to the adult studies, the treatment effect was achieved after the first dose and remained constant during continuous once-daily administration in clinical studies for up to 6 months.

Growth Rate in Pediatric Patients
Two controlled clinical studies have demonstrated that montelukast did not affect the growth rate in prepubertal pediatric patients with asthma. In a study of children aged 6 to 11 years, growth rate as measured by lower leg length growth, was similar in patients treated with montelukast 5 mg once daily for 3 weeks compared with placebo, and was significantly lower in patients treated with inhaled budesonide (200 μg twice daily) for 3 weeks, compared with placebo. In a 56-week study in children aged 6 to 8 years, linear growth rate was similar in patients treated with montelukast 5 mg once daily and placebo (LS means for montelukast and placebo: 5.67 and 5.64 cm/year, respectively), and was significantly lower (LS mean: 4.86 cm/year) in patients treated with inhaled beclomethasone (200 μg twice daily), compared with placebo [difference in LS means (95% CI): -0.78 (-1.06, -0.49) cm/year]. Both montelukast and beclomethasone versus placebo demonstrated significant benefit in rescue medication use in these patients with mild asthma.

PEDIATRIC PATIENTS 12 MONTHS TO 5 YEARS OF AGE
The efficacy of SINGULAIR, one 4-mg chewable tablet daily in the evening, in pediatric patients 2 to 5 years of age was demonstrated in a 12-week double-blind, placebo-controlled study in 689 patients (461 treated with SINGULAIR and 228 treated with placebo). SINGULAIR significantly improved multiple asthma efficacy endpoints and improved parameters of asthma control.

SINGULAIR was significantly better compared with placebo in the following caregiver asthma diary efficacy endpoints: days with daytime asthma symptoms, daytime asthma symptom score (including coughing, wheezing, trouble breathing, and child activities), beta-agonist use, corticosteroid rescue, days without asthma, and overnight asthma symptoms ($p<0.05$). Additionally, there was a favorable trend in treatment effect for the efficacy endpoint, asthma attack ($p=0.107$).

The physician's global assessment and the average of caregiver's and physician's global assessments of asthma were significantly better with SINGULAIR compared with placebo ($p=0.007$ and 0.015, respectively).

A treatment effect was achieved after the first dose. In addition, total blood eosinophil counts were significantly decreased ($p= 0.034$).

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 corticosteroids, and to allow steroid tapering when used concomitantly.

Three large studies demonstrated SINGULAIR has additional benefits in patients taking corticosteroids.

In a randomized, placebo-controlled, parallel-group study (n=226), stable asthmatic patients on initial inhaled corticosteroid doses of approximately 1600 μg per day, reduced their steroid use by approximately 37% during a placebo run-in period. SINGULAIR allowed a further 47% reduction in inhaled corticosteroid dose compared with 30% for placebo over the 12-week active treatment period ($p \leq 0.050$).

In another randomized, placebo-controlled, parallel-group study (n=642) in a similar population of patients maintained but not adequately controlled on inhaled corticosteroids (beclomethasone 400 μg/day), SINGULAIR provided additional clinical benefit, compared with placebo. Complete abrupt removal of beclomethasone in patients receiving both treatments caused clinical deterioration in some patients, suggesting that tapering inhaled corticosteroids as tolerated, rather than abrupt removal of steroids is preferred.

In aspirin-sensitive asthmatic patients, nearly all of whom were receiving concomitant inhaled and/or oral corticosteroids, a 4-week randomized, parallel-group study (n=80) demonstrated that SINGULAIR, compared with placebo, resulted in significant improvement in parameters of asthma control.

EFFECTS ON EXERCISE-INDUCED BRONCHOCONSTRICTION

In a 12-week, parallel group study of 110 adult patients 15 years of age and older, SINGULAIR, 10 mg, prevented exercise-induced bronchoconstriction (EIB) as demonstrated by significant inhibition of the following, compared with placebo:

- the extent and duration of fall in FEV_1 over 60 minutes after exercise (as measured by the area under the % fall in FEV_1 *versus* time curve after exercise, AUC);
- the maximal percent fall in FEV_1 after exercise;
- the time to recovery to within 5% of the pre-exercise FEV_1.

Protection was consistent throughout the 12-week treatment period, indicating that tolerance did not occur. In a separate crossover study, protection was observed after two once-daily doses.

In pediatric patients 6 to 14 years of age, using the 5-mg chewable tablet, an identically designed cross-over study demonstrated similar protection and the protection was maintained throughout the dosing interval (24 hours).

EFFECTS ON ASTHMATIC INFLAMMATION

Several studies have shown SINGULAIR inhibits parameters of asthmatic inflammation. In a placebo-controlled crossover study (n=12), SINGULAIR inhibited early- and late-phase bronchoconstriction due to antigen challenge by 75 and 57%, respectively.

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 in adults, SINGULAIR significantly decreased peripheral blood eosinophils approximately 15% from baseline, compared with placebo. In pediatric patients 6 to 14 years of age SINGULAIR also significantly decreased peripheral blood eosinophils 13% over the 8-week treatment period, compared with placebo.

In a 4-week, randomized, parallel group study (n=40) in adults, SINGULAIR significantly decreased airway eosinophils (as assessed in sputum) by 48% from baseline compared with an increase of 23% from baseline with placebo. In this study, peripheral blood eosinophils significantly decreased, and clinical asthma endpoints improved with treatment with SINGULAIR.

CLINICAL STUDIES - SEASONAL 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); daytime eye symptoms score, and its individual components (tearing, itchy, red, and puffy eyes); global evaluations of allergic rhinitis by patients and by physicians; and composite symptoms score (composed of the daytime nasal and nighttime symptoms scores), 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 seasonal allergic rhinitis in pediatric patients 2 to 14 years of age is supported by extrapolation from the demonstrated efficacy in patients 15 years of age and older with seasonal allergic rhinitis as well as the assumption that the disease course, pathophysiology and the drug's effect are substantially similar among these populations.

STORAGE

SINGULAIR 4 mg granules for kiddies: Store in the original package in order to protect from light and moisture. Do not store above 25°C. After opening, use within 15 minutes.
SINGULAIR 4 mg chewable tablets for preschool kids: Store below 25ºC. Store in the original package in order to protect from light and moisture
SINGULAIR 5 mg chewable tablets: Store below 30ºC. Store in the original package in order to protect from light and moisture.
SINGULAIR 10 mg tablets: Store below 30ºC. Store in the original package in order to protect from light and moisture.

PATIENT COUNSELING INFORMATION

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.

Manufactured by Merck, Sharp & Dohme B.V., Haarlem, Holland
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