Merck Sharp & Dohme Corp., a subsidiary of
MERCK & CO., INC.
Whitehouse Station, NJ 08889, USA

HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use SINGULAIR safely and effectively. See full prescribing information for SINGULAIR.

SINGULAIR®
(montelukast sodium) tablets, chewable tablets, and oral granules
Initial U.S. Approval: 1998

---------- RECENT MAJOR CHANGES ----------
Warnings and Precautions, Neuropsychiatric Events (5.4) 04/2010

---------- INDICATIONS AND USAGE ----------
SINGULAIR® is a leukotriene receptor antagonist indicated for:
- Prophylaxis and chronic treatment of asthma in patients 12 months of age and older (1.1).
- Acute prevention of exercise-induced bronchoconstriction (EIB) in patients 15 years of age and older (1.2).
- Relief of symptoms of allergic rhinitis (AR): seasonal allergic rhinitis (SAR) in patients 2 years of age and older, and perennial allergic rhinitis (PAR) in patients 6 months of age and older (1.3).

---------- DOSAGE AND ADMINISTRATION ----------
Administration (by indications):
- Asthma (2.1): Once daily in the evening for patients 12 months and older.
- Acute prevention of EIB (2.2): 10 mg tablet at least 2 hours before exercise for patients 15 years of age and older.
- Seasonal allergic rhinitis (2.3): Once daily for patients 2 years and older.
- Perennial allergic rhinitis (2.3): Once daily for patients 6 months and older.

Dosage (by age):
- 15 years and older: one 10-mg tablet.
- 6 to 14 years: one 5-mg chewable tablet.
- 2 to 5 years: one 4-mg chewable tablet or one packet of 4-mg oral granules.
- 6 to 23 months: one packet of 4-mg oral granules.

Patients with both asthma and allergic rhinitis should take only one dose daily in the evening (2.4). For oral granules: Must administer within 15 minutes after opening the packet (with or without mixing with food) (2.5).

---------- DOSAGE FORMS AND STRENGTHS ----------
- SINGULAIR 10-mg Film-Coated Tablets
- SINGULAIR 5-mg and 4-mg Chewable Tablets
- SINGULAIR 4-mg Oral Granules

---------- CONTRAINDICATIONS ----------
- Hypersensitivity to any component of this product (4).

---------- WARNINGS AND PRECAUTIONS ----------
- Do not prescribe SINGULAIR to treat an acute asthma attack.
- Advise patients to have appropriate rescue medication available (5.1).
- Inhaled corticosteroid may be reduced gradually. Do not abruptly substitute SINGULAIR for inhaled or oral corticosteroids (5.2).
- Patients with known aspirin sensitivity should continue to avoid aspirin or non-steroidal anti-inflammatory agents while taking SINGULAIR (5.3).
- Neuropsychiatric events have been reported with SINGULAIR. Instruct patients to be alert for neuropsychiatric events. Evaluate the risks and benefits of continuing treatment with SINGULAIR if such events occur (5.4 and 6.2).
- Systemic eosinophilia, sometimes presenting with clinical features of vasculitis consistent with Churg-Strauss syndrome, has been reported. These events usually, but not always, have been associated with the reduction of oral corticosteroid therapy (5.5 and 6.2).
- Inform patients with phenylketonuria that the 4-mg and 5-mg chewable tablets contain phenylalanine (5.6).

---------- ADVERSE REACTIONS ----------
Most common adverse reactions (incidence ≥5% and greater than placebo listed in descending order of frequency): upper respiratory infection, fever, headache, pharyngitis, cough, abdominal pain, diarrhea, otitis media, influenza, rhinorrhea, sinusitis, otitis (6.1).

To report SUSPECTED ADVERSE REACTIONS, contact Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc., at 1-877-888-4231 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling.

Revised: 05/2010

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FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

1.1 Asthma

SINGULAIR[1] is indicated for the prophylaxis and chronic treatment of asthma in adults and pediatric patients 12 months of age and older.

1.2 Exercise-Induced Bronchoconstriction

SINGULAIR is indicated for prevention of exercise-induced bronchoconstriction (EIB) in patients 15 years of age and older.

1.3 Allergic Rhinitis

SINGULAIR is indicated for the relief of symptoms of seasonal allergic rhinitis in patients 2 years of age and older and perennial allergic rhinitis in patients 6 months of age and older.

2 DOSAGE AND ADMINISTRATION

2.1 Asthma

SINGULAIR should be taken once daily in the evening. The following doses are recommended:

For adults and adolescents 15 years of age and older: one 10-mg tablet.

For pediatric patients 6 to 14 years of age: one 5-mg chewable tablet.

For pediatric patients 2 to 5 years of age: one 4-mg chewable tablet or one packet of 4-mg oral granules.

For pediatric patients 12 to 23 months of age: one packet of 4-mg oral granules.

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

There have been no clinical trials in patients with asthma to evaluate the relative efficacy of morning versus evening dosing. The pharmacokinetics of montelukast are similar whether dosed in the morning or evening. Efficacy has been demonstrated for asthma when montelukast was administered in the evening without regard to time of food ingestion.

2.2 Exercise-Induced Bronchoconstriction (EIB) in Patients 15 Years of Age and Older

For prevention of EIB, a single 10 mg dose of SINGULAIR should be taken at least 2 hours before exercise. An additional dose of SINGULAIR should not be taken within 24 hours of a previous dose. Patients already taking SINGULAIR daily for another indication (including chronic asthma) should not take an additional dose to prevent EIB. All patients should have available for rescue a short-acting β-agonist. Safety and effectiveness in patients younger than 15 years of age have not been established. Daily administration of SINGULAIR for the chronic treatment of asthma has not been established to prevent acute episodes of EIB.

2.3 Allergic Rhinitis

For allergic rhinitis, SINGULAIR should be taken once daily. Efficacy was demonstrated for seasonal allergic rhinitis when montelukast was administered in the morning or the evening without regard to time of food ingestion. The time of administration may be individualized to suit patient needs.

The following doses for the treatment of symptoms of seasonal allergic rhinitis are recommended:

For adults and adolescents 15 years of age and older: one 10-mg tablet.

For pediatric patients 6 to 14 years of age: one 5-mg chewable tablet.

For pediatric patients 2 to 5 years of age: one 4-mg chewable tablet or one packet of 4-mg oral granules.

Safety and effectiveness in pediatric patients younger than 2 years of age with seasonal allergic rhinitis have not been established.

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The following doses for the treatment of symptoms of perennial allergic rhinitis are recommended:
For adults and adolescents 15 years of age and older: one 10-mg tablet.
For pediatric patients 6 to 14 years of age: one 5-mg chewable tablet.
For pediatric patients 2 to 5 years of age: one 4-mg chewable tablet or one packet of 4-mg oral granules.
For pediatric patients 6 to 23 months of age: one packet of 4-mg oral granules.
Safety and effectiveness in pediatric patients younger than 6 months of age with perennial allergic rhinitis have not been established.

2.4 Asthma and Allergic Rhinitis

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

2.5 Instructions for Administration of Oral Granules

SINGULAIR 4-mg 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 (with or without mixing with baby formula, breast milk, or food) must be administered within 15 minutes. If mixed with baby formula, breast milk, or food, SINGULAIR oral granules must not be stored for future use. Discard any unused portion. 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. SINGULAIR oral granules can be administered without regard to the time of meals.

3 DOSAGE FORMS AND STRENGTHS

- SINGULAIR 10-mg Film-Coated Tablets are beige, rounded square-shaped tablets, with code MRK 117 on one side and SINGULAIR on the other.
- SINGULAIR 5-mg Chewable Tablets are pink, round, bi-convex-shaped tablets, with code MRK 275 on one side and SINGULAIR on the other.
- SINGULAIR 4-mg Chewable Tablets are pink, oval, bi-convex-shaped tablets, with code MRK 711 on one side and SINGULAIR on the other.
- SINGULAIR 4-mg Oral Granules are white granules with 500 mg net weight, packed in a child-resistant foil packet.

4 CONTRAINDICATIONS

Hypersensitivity to any component of this product.

5 WARNINGS AND PRECAUTIONS

5.1 Acute Asthma

SINGULAIR is not indicated for use in the reversal of bronchospasm in acute asthma attacks, including status asthmaticus. Patients should be advised to have appropriate rescue medication available. Therapy with SINGULAIR can be continued during acute exacerbations of asthma. Patients who have exacerbations of asthma after exercise should have available for rescue a short-acting inhaled β-agonist.

5.2 Concomitant Corticosteroid Use

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

5.3 Aspirin Sensitivity

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 (14.1)]*.

5.4 Neuropsychiatric Events

Neuropsychiatric events have been reported in adult, adolescent, and pediatric patients taking SINGULAIR. Post-marketing reports with SINGULAIR use include agitation, aggressive behavior or hostility, anxiousness, depression, disorientation, dream abnormalities, hallucinations, insomnia, irritability, 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 Adverse Reactions (6.2)].*

5.5 Eosinophilic Conditions

Patients with asthma on therapy with SINGULAIR may present with systemic eosinophilia, sometimes presenting with clinical features of vasculitis consistent with Churg-Strauss syndrome, a condition which is often treated with systemic corticosteroid therapy. These events usually, but not always, have been associated with the reduction of oral corticosteroid therapy. Physicians should be alert to eosinophilia, vasculitic rash, worsening pulmonary symptoms, cardiac complications, and/or neuropathy presenting in their patients. A causal association between SINGULAIR and these underlying conditions has not been established *[see Adverse Reactions (6.2)].*

5.6 Phenylketonuria

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.

6 ADVERSE REACTIONS

6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in clinical practice. In the following description of clinical trials experience, adverse reactions are listed regardless of causality assessment.

The most common adverse reactions (incidence ≥5% and greater than placebo; listed in descending order of frequency) in controlled clinical trials were: upper respiratory infection, fever, headache, pharyngitis, cough, abdominal pain, diarrhea, otitis media, influenza, rhinorrhea, sinusitis, otitis.

Adults and Adolescents 15 Years of Age and Older with Asthma

SINGULAIR has been evaluated for safety in approximately 2950 adult and adolescent patients 15 years of age and older in clinical trials. In placebo-controlled clinical trials, the following adverse experiences reported with SINGULAIR occurred in greater than or equal to 1% of patients and at an incidence greater than that in patients treated with placebo:

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		
Pain, abdominal	2.9	2.5
Asthenia/fatigue	1.8	1.2
Fever	1.5	0.9
Trauma	1.0	0.8
Digestive System Disorders		
Dyspepsia	2.1	1.1
Pain, dental	1.7	1.0
Gastroenteritis, infectious	1.5	0.5
Nervous System/Psychiatric		
Headache	18.4	18.1
Dizziness	1.9	1.4
Respiratory System Disorders		
Influenza	4.2	3.9
Cough	2.7	2.4
Congestion, nasal	1.6	1.3
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.

The frequency of less common adverse events was comparable between SINGULAIR and placebo.

The safety profile of SINGULAIR, when administered as a single dose for prevention of EIB in adult and adolescent patients 15 years of age and older, was consistent with the safety profile previously described for SINGULAIR.

Cumulatively, 569 patients were treated with SINGULAIR for at least 6 months, 480 for one year, and 49 for two years in clinical trials. With prolonged treatment, the adverse experience profile did not significantly change.

Pediatric Patients 6 to 14 Years of Age with Asthma

SINGULAIR has been evaluated for safety in 476 pediatric patients 6 to 14 years of age. Cumulatively, 289 pediatric patients were treated with SINGULAIR for at least 6 months, and 241 for one year or longer in clinical trials. The safety profile of SINGULAIR in the 8-week, double-blind, pediatric efficacy trial was generally similar to the adult safety profile. 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. The frequency of less common adverse events was comparable between SINGULAIR and placebo. With prolonged treatment, the adverse experience profile did not significantly change.

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.

Pediatric Patients 2 to 5 Years of Age with Asthma

SINGULAIR has been evaluated for safety in 573 pediatric patients 2 to 5 years of age in single- and multiple-dose studies. 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 one year or longer in clinical trials. 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.

Pediatric Patients 6 to 23 Months 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 to 23 months 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 and Adolescents 15 Years of Age and Older with Seasonal Allergic Rhinitis

SINGULAIR has been evaluated for safety in 2199 adult and adolescent patients 15 years of age and older in clinical trials. SINGULAIR administered once daily in the morning or in the evening had a safety profile similar to that of placebo. In placebo-controlled clinical trials, 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 in a 2-week, multicenter, double-blind, placebo-controlled, parallel-group safety study. SINGULAIR administered once daily in the evening had 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.

Adults and Adolescents 15 Years of Age and Older with Perennial Allergic Rhinitis

SINGULAIR has been evaluated for safety in 3357 adult and adolescent patients 15 years of age and older with perennial allergic rhinitis of whom 1632 received SINGULAIR in two, 6-week, clinical studies. SINGULAIR administered once daily had a safety profile consistent with that observed in patients with seasonal allergic rhinitis and similar to that of placebo. In these two studies, the following events were reported with SINGULAIR with a frequency ≥1% and at an incidence greater than placebo: sinusitis, upper respiratory infection, sinus headache, cough, epistaxis, and increased ALT. The incidence of somnolence was similar to that of placebo.

Pediatric Patients 6 Months 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 safety in patients 2 to 14 years of age with seasonal allergic rhinitis. The safety in patients 6 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.

6.2 Post-Marketing 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.

Blood and lymphatic system disorders: increased bleeding tendency.

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

Psychiatric disorders: agitation including aggressive behavior or hostility, anxiousness, depression, disorientation, dream abnormalities, hallucinations, insomnia, irritability, restlessness, somnambulism, suicidal thinking and behavior (including suicide), tremor *[see Warnings and Precautions (5.4)]*.

Nervous system disorders: drowsiness, paraesthesia/hypoesthesia, seizures.

Cardiac disorders: palpitations.
Respiratory, thoracic and mediastinal disorders: epistaxis.
Gastrointestinal disorders: diarrhea, dyspepsia, nausea, pancreatitis, vomiting.
Hepatobiliary disorders: Cases of cholestatic hepatitis, hepatocellular liver-injury, and mixed-pattern liver injury have been reported in patients treated with SINGULAIR. Most of these 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 nodosum, pruritus, urticaria.
Musculoskeletal and connective tissue disorders: arthralgia, myalgia including muscle cramps.
General disorders and administration site conditions: edema.
Patients with asthma on therapy with SINGULAIR may present with systemic eosinophilia, sometimes presenting with clinical features of vasculitis consistent with Churg-Strauss syndrome, a condition which is often treated with systemic corticosteroid therapy. These events usually, but not always, have been associated with the reduction of oral corticosteroid therapy. Physicians should be alert to eosinophilia, vasculitic rash, worsening pulmonary symptoms, cardiac complications, and/or neuropathy presenting in their patients *[see Warnings and Precautions (5.5)]*.

7 DRUG INTERACTIONS

No dose adjustment is needed when SINGULAIR is co-administered with theophylline, prednisone, prednisolone, oral contraceptives, terfenadine, digoxin, warfarin, thyroid hormones, sedative hypnotics, non-steroidal anti-inflammatory agents, benzodiazepines, decongestants, and Cytochrome P450 (CYP) enzyme inducers *[see Clinical Pharmacology (12.3)]*.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Category B: There are no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, SINGULAIR should be used during pregnancy only if clearly needed.

Teratogenic Effect: No teratogenicity was observed in rats and rabbits at doses approximately 100 and 110 times, respectively, the maximum recommended daily oral dose in adults based on AUCs *[see Nonclinical Toxicology (13.2)]*.

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.

Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc., maintains a registry to monitor the pregnancy outcomes of women exposed to SINGULAIR while pregnant. Patients and healthcare providers are encouraged to report any prenatal exposure to SINGULAIR by calling the Pregnancy Registry at 1-800-986-8999.

8.3 Nursing Mothers

Studies in rats have shown that montelukast is excreted in milk. It is not known if montelukast 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.

8.4 Pediatric Use

Safety and efficacy of SINGULAIR have been established in adequate and well-controlled studies in pediatric patients with asthma 6 to 14 years of age. Safety and efficacy profiles in this age group are similar to those seen in adults *[see Adverse Reactions (6.1), Clinical Pharmacology, Special Populations (12.3), and Clinical Studies (14.1)]*.

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 6 months 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.

The safety of SINGULAIR 4-mg chewable tablets in pediatric patients 2 to 5 years of age with asthma has been demonstrated by adequate and well-controlled data *[see Adverse Reactions (6.1)]*. Efficacy of SINGULAIR in this age group is extrapolated from the demonstrated efficacy in patients 6 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. Efficacy in this age group is supported by exploratory efficacy assessments from a large, well-controlled safety study conducted in patients 2 to 5 years of age.

The safety of SINGULAIR 4-mg oral granules in pediatric patients 12 to 23 months of age with asthma has been demonstrated in an analysis of 172 pediatric patients, 124 of whom were treated with SINGULAIR, in a 6-week, double-blind, placebo-controlled study *[see Adverse Reactions (6.1)]*. Efficacy of SINGULAIR in this age group is extrapolated from the demonstrated efficacy in patients 6 years of age and older with asthma based on similar mean systemic exposure (AUC), and that the disease course, pathophysiology and the drug's effect are substantially similar among these populations, supported by efficacy data from a safety trial in which efficacy was an exploratory assessment.

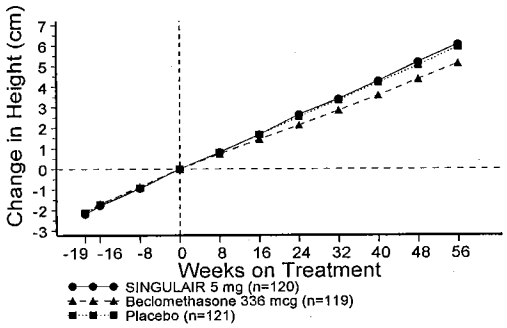
The safety of SINGULAIR 4-mg and 5-mg chewable tablets in pediatric patients aged 2 to 14 years with allergic rhinitis is supported by data from studies conducted in pediatric patients aged 2 to 14 years with asthma. A safety study in pediatric patients 2 to 14 years of age with seasonal allergic rhinitis demonstrated a similar safety profile *[see Adverse Reactions (6.1)]*. The safety of SINGULAIR 4-mg oral granules in pediatric patients as young as 6 months of age with perennial allergic rhinitis is supported by extrapolation from safety data obtained from studies conducted in pediatric patients 6 months to 23 months of age with asthma and from pharmacokinetic data comparing systemic exposures in patients 6 months to 23 months of age to systemic exposures in adults.

The safety and effectiveness in pediatric patients below the age of 12 months with asthma and 6 months with perennial allergic rhinitis have not been established. The safety and effectiveness in pediatric patients below the age of 15 years with exercise-induced bronchoconstriction have not been established.

Growth Rate in Pediatric Patients

A 56-week, multi-center, double-blind, randomized, active- and placebo-controlled parallel group study was conducted to assess the effect of SINGULAIR on growth rate in 360 patients with mild asthma, aged 6 to 8 years. Treatment groups included SINGULAIR 5 mg once daily, placebo, and beclomethasone dipropionate administered as 168 mcg twice daily with a spacer device. For each subject, a growth rate was defined as the slope of a linear regression line fit to the height measurements over 56 weeks. The primary comparison was the difference in growth rates between SINGULAIR and placebo groups. Growth rates, expressed as least-squares (LS) mean (95% CI) in cm/year, for the SINGULAIR, placebo, and beclomethasone treatment groups were 5.67 (5.46, 5.88), 5.64 (5.42, 5.86), and 4.86 (4.64, 5.08), respectively. The differences in growth rates, expressed as least-squares (LS) mean (95% CI) in cm/year, for SINGULAIR minus placebo, beclomethasone minus placebo, and SINGULAIR minus beclomethasone treatment groups were 0.03 (-0.26, 0.31), -0.78 (-1.06, -0.49); and 0.81 (0.53, 1.09), respectively. Growth rate (expressed as mean change in height over time) for each treatment group is shown in FIGURE 1.

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



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

8.5 Geriatric Use

Of the total number of subjects in clinical studies of montelukast, 3.5% were 65 years of age and over, and 0.4% were 75 years of age and over. No overall differences in safety or effectiveness were observed between these subjects and younger subjects, and other reported clinical experience has not identified differences in responses between the elderly and younger patients, but greater sensitivity of some older individuals cannot be ruled out. 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.

8.6 Hepatic Insufficiency

No dosage adjustment is required in patients with mild-to-moderate hepatic insufficiency *[see Clinical Pharmacology (12.3)]*.

8.7 Renal Insufficiency

No dosage adjustment is recommended in patients with renal insufficiency *[see Clinical Pharmacology (12.3)]*.

10 OVERDOSAGE

No mortality occurred following single oral doses of montelukast up to 5000 mg/kg in mice (estimated exposure was approximately 335 and 210 times the AUC for adults and children, respectively, at the maximum recommended daily oral dose) and rats (estimated exposure was approximately 230 and 145 times the AUC for adults and children, respectively, at the maximum recommended daily oral dose).

No specific information is available on the treatment of overdosage with SINGULAIR. In chronic asthma studies, montelukast has been administered at doses up to 200 mg/day to adult patients for 22 weeks and, in short-term studies, up to 900 mg/day to patients for approximately a 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 post-marketing 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.

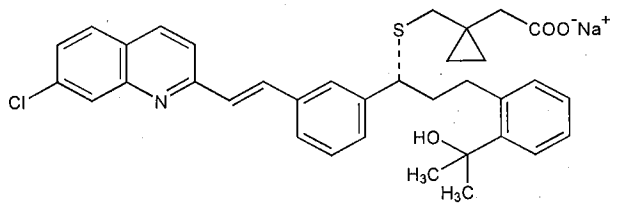
It is not known whether montelukast is removed by peritoneal dialysis or hemodialysis.

11 DESCRIPTION

Montelukast sodium, the active ingredient in SINGULAIR, is a selective and orally active leukotriene receptor antagonist that inhibits the cysteinyl leukotriene $CysLT_1$ receptor.

Montelukast sodium is described chemically as [*R*-(*E*)]-1-[[[1-[3-[2-(7-chloro-2-quinolinyl)ethenyl]phenyl]-3-[2-(1-hydroxy-1-methylethyl)phenyl]propyl]thio]methyl]cyclopropaneacetic acid, monosodium salt.

The empirical formula is $C_{35}H_{35}ClNNaO_3S$, and its molecular weight is 608.18. The structural formula is:



Montelukast sodium is a hygroscopic, optically active, white to off-white powder. Montelukast sodium is freely soluble in ethanol, methanol, and water and practically insoluble in acetonitrile.

Each 10-mg film-coated SINGULAIR tablet contains 10.4 mg montelukast sodium, which is equivalent to 10 mg of montelukast, and the following inactive ingredients: microcrystalline cellulose, lactose monohydrate, 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 SINGULAIR tablet contains 4.2 and 5.2 mg montelukast sodium, respectively, which are equivalent to 4 and 5 mg of montelukast, respectively. Both chewable tablets contain the following inactive ingredients: mannitol, microcrystalline cellulose, hydroxypropyl cellulose, red ferric oxide, croscarmellose sodium, cherry flavor, aspartame, and magnesium stearate.

Each packet of SINGULAIR 4-mg oral granules contains 4.2 mg montelukast sodium, which is equivalent to 4 mg of montelukast. The oral granule formulation contains the following inactive ingredients: mannitol, hydroxypropyl cellulose, and magnesium stearate.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

The cysteinyl leukotrienes (LTC_4, LTD_4, LTE_4) are products of arachidonic acid metabolism and are released from various cells, including mast cells and eosinophils. These eicosanoids 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 airway edema, smooth muscle contraction, and altered cellular activity associated with the inflammatory process. 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.

Montelukast is an orally active compound that 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 inhibits physiologic actions of LTD_4 at the $CysLT_1$ receptor without any agonist activity.

12.2 Pharmacodynamics

Montelukast causes inhibition of airway cysteinyl leukotriene receptors as demonstrated by the ability to inhibit bronchoconstriction due to inhaled LTD_4 in asthmatics. Doses as low as 5 mg cause substantial blockage of LTD_4-induced bronchoconstriction. In a placebo-controlled, crossover study (n=12),

SINGULAIR inhibited early- and late-phase bronchoconstriction due to antigen challenge by 75% and 57%, respectively.

The effect of SINGULAIR on eosinophils in the peripheral blood was examined in clinical trials. In patients with asthma aged 2 years and older who received SINGULAIR, a decrease in mean peripheral blood eosinophil counts ranging from 9% to 15% was noted, compared with placebo, over the double-blind treatment periods. In patients with seasonal allergic rhinitis aged 15 years and older who received SINGULAIR, a mean increase of 0.2% in peripheral blood eosinophil counts was noted, compared with a mean increase of 12.5% in placebo-treated patients, over the double-blind treatment periods; this reflects a mean difference of 12.3% in favor of SINGULAIR. The relationship between these observations and the clinical benefits of montelukast noted in the clinical trials is not known *[see Clinical Studies (14)]*.

12.3 Pharmacokinetics

Absorption

Montelukast is rapidly absorbed following oral administration. After administration of the 10-mg film-coated tablet to fasted adults, the mean peak montelukast plasma concentration (C_{max}) is achieved in 3 to 4 hours (T_{max}). The mean oral bioavailability is 64%. The oral bioavailability and C_{max} are not influenced by a standard meal in the morning.

For the 5-mg chewable tablet, the mean C_{max} is achieved in 2 to 2.5 hours after administration to adults in the fasted state. The mean oral bioavailability is 73% in the fasted state versus 63% when administered with a standard meal in the morning.

For the 4-mg chewable tablet, the mean 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 co-administration of the oral granule formulation with applesauce did not have a clinically significant effect on the pharmacokinetics of montelukast. A high fat meal in the morning did not affect the AUC of montelukast oral granules; however, the meal decreased C_{max} by 35% and prolonged T_{max} from 2.3 ± 1.0 hours to 6.4 ± 2.9 hours.

The safety and efficacy of SINGULAIR in patients with asthma were demonstrated in clinical trials in which the 10-mg film-coated tablet and 5-mg chewable tablet formulations were administered in the evening without regard to the time of food ingestion. The safety of SINGULAIR in patients with asthma was also demonstrated in clinical trials in which the 4-mg chewable tablet and 4-mg oral granule formulations were administered in the evening without regard to the time of food ingestion. The safety and efficacy of SINGULAIR in patients with seasonal allergic rhinitis were demonstrated in clinical trials in which the 10-mg film-coated tablet was administered in the morning or evening without regard to the time of food ingestion.

The comparative pharmacokinetics of montelukast when administered as two 5-mg chewable tablets versus one 10-mg film-coated tablet have not been evaluated.

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 CYP3A4 and 2C9 are involved in the metabolism of montelukast. Clinical studies investigating the effect of known inhibitors of CYP3A4 (e.g., ketoconazole, erythromycin) or 2C9 (e.g., fluconazole) on montelukast pharmacokinetics have not been conducted. Based on further *in vitro* results in human liver microsomes, therapeutic plasma concentrations of montelukast do not inhibit CYP3A4, 2C9, 1A2, 2A6, 2C19, or 2D6 *[see Drug Interactions (7) and Clinical Pharmacology, Drug-Drug Interactions (12.3)]*. *In vitro* studies have shown that montelukast is a potent inhibitor of CYP2C8; 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,* and therefore is not

anticipated to alter the metabolism of drugs metabolized by this enzyme *[see Drug Interactions (7) and Clinical Pharmacology, Drug-Drug Interactions (12.3)]*.

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. During once-daily dosing with 10-mg montelukast, there is little accumulation of the parent drug in plasma (14%).

Special Populations

Hepatic Insufficiency: Patients with mild-to-moderate hepatic insufficiency and clinical evidence of cirrhosis had evidence of decreased metabolism of montelukast resulting in 41% (90% CI=7%, 85%) higher mean montelukast AUC following a single 10-mg dose. The elimination of montelukast was 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. The pharmacokinetics of SINGULAIR in patients with more severe hepatic impairment or with hepatitis have not been evaluated.

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.

Gender: The pharmacokinetics of montelukast are similar in males and females.

Race: Pharmacokinetic differences due to race have not been studied.

Adolescents and Pediatric Patients: Pharmacokinetic studies evaluated the systemic exposure of the 4-mg oral granule formulation in pediatric patients 6 to 23 months of age, the 4-mg chewable tablets in pediatric patients 2 to 5 years of age, the 5-mg chewable tablets in pediatric patients 6 to 14 years of age, and the 10-mg film-coated tablets in young adults and adolescents ≥15 years of age.

The plasma concentration profile of montelukast following administration of the 10-mg film-coated tablet is similar in adolescents ≥15 years of age and young adults. The 10-mg film-coated tablet is recommended for use in patients ≥15 years of age.

The mean systemic exposure of 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 is similar to the mean systemic exposure 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 should be used in pediatric patients 2 to 5 years of age.

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 (4296 ng•hr/mL [range 1200 to 7153]) was 60% higher and the mean C_{max} (667 ng/mL [range 201 to 1058]) was 89% higher than those observed in adults (mean AUC 2689 ng•hr/mL [range 1521 to 4595]) and mean C_{max} (353 ng/mL [range 180 to 548]). 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 (3574 ng•hr/mL [range 2229 to 5408]) was 33% higher and the mean C_{max} (562 ng/mL [range 296 to 814]) 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 *[see Adverse Reactions (6.1)]*. The 4-mg oral granule formulation should be used for pediatric patients 12 to 23 months of age for the treatment of asthma, or for pediatric patients 6 to 23 months of age for the treatment of perennial allergic rhinitis. 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.

Drug-Drug Interactions

Theophylline, Prednisone, and Prednisolone: SINGULAIR has been administered with other therapies routinely used in the prophylaxis and chronic treatment of asthma with no apparent increase in adverse reactions. In drug-interaction studies, the recommended clinical dose of montelukast did not have clinically

important effects on the pharmacokinetics of the following drugs: theophylline, prednisone, and prednisolone.

Montelukast at a dose of 10 mg once daily dosed to pharmacokinetic steady state, did not cause clinically significant changes in the kinetics of a single intravenous dose of theophylline [predominantly a cytochrome P450 (CYP) 1A2 substrate]. Montelukast at doses of ≥100 mg daily dosed to pharmacokinetic steady state, did not cause any clinically significant change in plasma profiles of prednisone or prednisolone following administration of either oral prednisone or intravenous prednisolone.

Oral Contraceptives, Terfenadine, Digoxin, and Warfarin: In drug interaction studies, the recommended clinical dose of montelukast did not have clinically important effects on the pharmacokinetics of the following drugs: oral contraceptives (norethindrone 1 mg/ethinyl estradiol 35 mcg), terfenadine, digoxin, and warfarin. Montelukast at doses of ≥100 mg daily dosed to pharmacokinetic steady state did not significantly alter the plasma concentrations of either component of an oral contraceptive containing norethindrone 1 mg/ethinyl estradiol 35 mcg. Montelukast at a dose of 10 mg once daily dosed to pharmacokinetic steady state did not change the plasma concentration profile of terfenadine (a substrate of CYP3A4) or fexofenadine, the carboxylated metabolite, and did not prolong the QTc interval following co-administration with terfenadine 60 mg twice daily; did not change the pharmacokinetic profile or urinary excretion of immunoreactive digoxin; did not change the pharmacokinetic profile of warfarin (primarily a substrate of CYP2C9, 3A4 and 1A2) or influence the effect of a single 30-mg oral dose of warfarin on prothrombin time or the International Normalized Ratio (INR).

Thyroid Hormones, Sedative Hypnotics, Non-Steroidal Anti-Inflammatory Agents, Benzodiazepines, and Decongestants: 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, non-steroidal anti-inflammatory agents, benzodiazepines, and decongestants.

Cytochrome P450 (CYP) Enzyme Inducers: Phenobarbital, which induces hepatic metabolism, decreased the area under the plasma concentration curve (AUC) of montelukast approximately 40% following a single 10-mg dose of montelukast. No dosage adjustment for SINGULAIR is recommended. It is reasonable to employ appropriate clinical monitoring when potent CYP enzyme inducers, such as phenobarbital or rifampin, are co-administered with SINGULAIR.

Montelukast is a potent inhibitor of CYP2C8 *in vitro.* However, data from a clinical drug-drug interaction study involving montelukast and rosiglitazone (a probe substrate representative of drugs primarily metabolized by CYP2C8) in 12 healthy individuals demonstrated that the pharmacokinetics of rosiglitazone are not altered when the drugs are coadministered, indicating 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).

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

No evidence of tumorigenicity was seen in carcinogenicity studies of either 2 years in Sprague-Dawley rats or 92 weeks in mice at oral gavage doses up to 200 mg/kg/day or 100 mg/kg/day, respectively. The estimated exposure in rats was approximately 120 and 75 times the AUC for adults and children, respectively, at the maximum recommended daily oral dose. The estimated exposure in mice was approximately 45 and 25 times the AUC for adults and children, respectively, at the maximum recommended daily oral dose.

Montelukast demonstrated no evidence of mutagenic or clastogenic activity in the following assays: the microbial mutagenesis assay, the V-79 mammalian cell mutagenesis assay, the alkaline elution assay in rat hepatocytes, the chromosomal aberration assay in Chinese hamster ovary cells, and in the *in vivo* mouse bone marrow chromosomal aberration assay.

In fertility studies in female rats, montelukast produced reductions in fertility and fecundity indices at an oral dose of 200 mg/kg (estimated exposure was approximately 70 times the AUC for adults at the maximum recommended daily oral dose). No effects on female fertility or fecundity were observed at an oral dose of 100 mg/kg (estimated exposure was approximately 20 times the AUC for adults at the

maximum recommended daily oral dose). Montelukast had no effects on fertility in male rats at oral doses up to 800 mg/kg (estimated exposure was approximately 160 times the AUC for adults at the maximum recommended daily oral dose).

13.2 Animal Toxicology and/or Pharmacology

Reproductive Toxicology Studies

No teratogenicity was observed at oral doses up to 400 mg/kg/day and 300 mg/kg/day in rats and rabbits, respectively. These doses were approximately 100 and 110 times the maximum recommended daily oral dose in adults, respectively, based on AUCs. Montelukast crosses the placenta following oral dosing in rats and rabbits *[see Pregnancy (8.1)]*.

14 CLINICAL STUDIES

14.1 Asthma

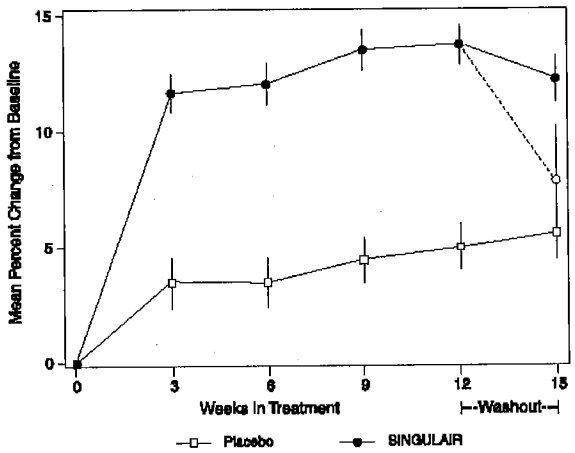
Adults and Adolescents 15 Years of Age and Older with Asthma

Clinical trials in adults and adolescents 15 years of age and older demonstrated there is no additional clinical benefit to montelukast doses above 10 mg once daily.

The efficacy of SINGULAIR for the chronic treatment of asthma in adults and adolescents 15 years of age and older was demonstrated in two (U.S. and Multinational) similarly designed, randomized, 12-week, double-blind, placebo-controlled trials in 1576 patients (795 treated with SINGULAIR, 530 treated with placebo, and 251 treated with active control). The median age was 33 years (range 15 to 85); 56.8% were females and 43.2% were males. The ethnic/racial distribution in these studies was 71.6% Caucasian, 17.7% Hispanic, 7.2% other origins and 3.5% Black. Patients had mild or moderate asthma and were non-smokers who required approximately 5 puffs of inhaled β-agonist per day on an "as-needed" basis. The patients had a mean baseline percent of predicted forced expiratory volume in 1 second (FEV_1) of 66% (approximate range, 40 to 90%). The co-primary endpoints in these trials were FEV_1 and daytime asthma symptoms. In both studies after 12 weeks, a random subset of patients receiving SINGULAIR was switched to placebo for an additional 3 weeks of double-blind treatment to evaluate for possible rebound effects.

The results of the U.S. trial on the primary endpoint, morning FEV_1, expressed as mean percent change from baseline averaged over the 12-week treatment period, are shown in FIGURE 2. Compared with placebo, treatment with one SINGULAIR 10-mg tablet daily in the evening resulted in a statistically significant increase in FEV_1 percent change from baseline (13.0%-change in the group treated with SINGULAIR vs. 4.2%-change in the placebo group, $p<0.001$); the change from baseline in FEV_1 for SINGULAIR was 0.32 liters compared with 0.10 liters for placebo, corresponding to a between-group difference of 0.22 liters ($p<0.001$, 95% CI 0.17 liters, 0.27 liters). The results of the Multinational trial on FEV_1 were similar.

FIGURE 2
FEV_1 Mean Percent Change from Baseline
(U.S. Trial: SINGULAIR N=406; Placebo N=270)
(ANOVA Model)



The effect of SINGULAIR on other primary and secondary endpoints, represented by the Multinational study is shown in TABLE 2. Results on these endpoints were similar in the US study.

TABLE 2
Effect of SINGULAIR on Primary and Secondary Endpoints
in a Multinational Placebo-controlled Trial
(ANOVA Model)

	SINGULAIR			Placebo		
Endpoint	N	Baseline	Mean Change from Baseline	N	Baseline	Mean Change from Baseline
Daytime Asthma Symptoms (0 to 6 scale)	372	2.35	-0.49*	245	2.40	-0.26
β-agonist (puffs per day)	371	5.35	-1.65*	241	5.78	-0.42
AM PEFR (L/min)	372	339.57	25.03*	244	335.24	1.83
PM PEFR (L/min)	372	355.23	20.13*	244	354.02	-0.49
Nocturnal Awakenings (#/week)	285	5.46	-2.03*	195	5.57	-0.78

* p<0.001, compared with placebo

Both studies evaluated the effect of SINGULAIR on secondary outcomes, including asthma attack (utilization of health-care resources such as an unscheduled visit to a doctor's office, emergency room, or hospital; or treatment with oral, intravenous, or intramuscular corticosteroid), and use of oral corticosteroids for asthma rescue. In the Multinational study, significantly fewer patients (15.6% of patients) on SINGULAIR experienced asthma attacks compared with patients on placebo (27.3%, $p < 0.001$). In the US study, 7.8% of patients on SINGULAIR and 10.3% of patients on placebo experienced asthma attacks, but the difference between the two treatment groups was not significant ($p = 0.334$). In the Multinational study, significantly fewer patients (14.8% of patients) on SINGULAIR were prescribed oral corticosteroids for asthma rescue compared with patients on placebo (25.7%, $p < 0.001$). In the US study, 6.9% of patients on SINGULAIR and 9.9% of patients on placebo were prescribed oral corticosteroids for asthma rescue, but the difference between the two treatment groups was not significant ($p = 0.196$).

Onset of Action and Maintenance of Effects

In each placebo-controlled trial in adults, 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). No significant change in treatment effect was observed during continuous once-daily evening administration in non-placebo-controlled extension trials for up to one year. Withdrawal of SINGULAIR in asthmatic patients after 12 weeks of continuous use did not cause rebound worsening of asthma.

Pediatric Patients 6 to 14 Years of Age with Asthma

The efficacy of SINGULAIR in pediatric patients 6 to 14 years of age was demonstrated in one 8-week, double-blind, placebo-controlled trial in 336 patients (201 treated with SINGULAIR and 135 treated with placebo) using an inhaled β-agonist on an "as-needed" basis. The patients had a mean baseline percent

predicted FEV_1 of 72% (approximate range, 45 to 90%) and a mean daily inhaled β-agonist requirement of 3.4 puffs of albuterol. Approximately 36% of the patients were on inhaled corticosteroids. The median age was 11 years (range 6 to 15); 35.4% were females and 64.6% were males. The ethnic/racial distribution in this study was 80.1% Caucasian, 12.8% Black, 4.5% Hispanic, and 2.7% other origins.

Compared with placebo, treatment with one 5-mg SINGULAIR chewable tablet daily resulted in a significant improvement in mean morning FEV_1 percent change from baseline (8.7% in the group treated with SINGULAIR vs. 4.2% change from baseline in the placebo group, $p<0.001$). There was a significant decrease in the mean percentage change in daily "as-needed" inhaled β-agonist use (11.7% decrease from baseline in the group treated with SINGULAIR vs. 8.2% increase from baseline in the placebo group, $p<0.05$). This effect represents a mean decrease from baseline of 0.56 and 0.23 puffs per day for the montelukast and placebo groups, respectively. Subgroup analyses indicated that younger pediatric patients aged 6 to 11 had efficacy results comparable to those of the older pediatric patients aged 12 to 14.

Similar to the adult studies, no significant change in the treatment effect was observed during continuous once-daily administration in one open-label extension trial without a concurrent placebo group for up to 6 months.

Pediatric Patients 2 to 5 Years of Age with Asthma

The efficacy of SINGULAIR for the chronic treatment of asthma in pediatric patients 2 to 5 years of age was explored in a 12-week, placebo-controlled safety and tolerability study in 689 patients, 461 of whom were treated with SINGULAIR. The median age was 4 years (range 2 to 6); 41.5% were females and 58.5% were males. The ethnic/racial distribution in this study was 56.5% Caucasian, 20.9% Hispanic, 14.4% other origins, and 8.3% Black.

While the primary objective was to determine the safety and tolerability of SINGULAIR in this age group, the study included exploratory efficacy evaluations, including daytime and overnight asthma symptom scores, β-agonist use, oral corticosteroid rescue, and the physician's global evaluation. The findings of these exploratory efficacy evaluations, along with pharmacokinetics and extrapolation of efficacy data from older patients, support the overall conclusion that SINGULAIR is efficacious in the maintenance treatment of asthma in patients 2 to 5 years of age.

Effects in Patients on Concomitant Inhaled Corticosteroids

Separate trials in adults evaluated the ability of SINGULAIR to add to the clinical effect of inhaled corticosteroids and to allow inhaled corticosteroid tapering when used concomitantly.

One randomized, placebo-controlled, parallel-group trial (n=226) enrolled adults with stable asthma with a mean FEV_1 of approximately 84% of predicted who were previously maintained on various inhaled corticosteroids (delivered by metered-dose aerosol or dry powder inhalers). The median age was 41.5 years (range 16 to 70); 52.2% were females and 47.8% were males. The ethnic/racial distribution in this study was 92.0% Caucasian, 3.5% Black, 2.2% Hispanic, and 2.2% Asian. The types of inhaled corticosteroids and their mean baseline requirements included beclomethasone dipropionate (mean dose, 1203 mcg/day), triamcinolone acetonide (mean dose, 2004 mcg/day), flunisolide (mean dose, 1971 mcg/day), fluticasone propionate (mean dose, 1083 mcg/day), or budesonide (mean dose, 1192 mcg/day). Some of these inhaled corticosteroids were non-U.S.-approved formulations, and doses expressed may not be ex-actuator. The pre-study inhaled corticosteroid requirements were reduced by approximately 37% during a 5- to 7-week placebo run-in period designed to titrate patients toward their lowest effective inhaled corticosteroid dose. Treatment with SINGULAIR resulted in a further 47% reduction in mean inhaled corticosteroid dose compared with a mean reduction of 30% in the placebo group over the 12-week active treatment period ($p\leq0.05$). It is not known whether the results of this study can be generalized to patients with asthma who require higher doses of inhaled corticosteroids or systemic corticosteroids.

In another randomized, placebo-controlled, parallel-group trial (n=642) in a similar population of adult patients previously maintained, but not adequately controlled, on inhaled corticosteroids (beclomethasone 336 mcg/day), the addition of SINGULAIR to beclomethasone resulted in statistically significant improvements in FEV_1 compared with those patients who were continued on beclomethasone alone or those patients who were withdrawn from beclomethasone and treated with montelukast or placebo alone

over the last 10 weeks of the 16-week, blinded treatment period. Patients who were randomized to treatment arms containing beclomethasone had statistically significantly better asthma control than those patients randomized to SINGULAIR alone or placebo alone as indicated by FEV_1, daytime asthma symptoms, PEFR, nocturnal awakenings due to asthma, and "as-needed" β-agonist requirements.

In adult patients with asthma with documented aspirin sensitivity, nearly all of whom were receiving concomitant inhaled and/or oral corticosteroids, a 4-week, randomized, parallel-group trial (n=80) demonstrated that SINGULAIR, compared with placebo, resulted in significant improvement in parameters of asthma control. The magnitude of effect of SINGULAIR in aspirin-sensitive patients was similar to the effect observed in the general population of asthma patients studied. The effect of SINGULAIR on the bronchoconstrictor response to aspirin or other non-steroidal anti-inflammatory drugs in aspirin-sensitive asthmatic patients has not been evaluated *[see Warnings and Precautions (5.3)]*.

14.2 Exercise-Induced Bronchoconstriction (EIB)

Exercise-Induced Bronchoconstriction - Single-Dose Administration (Adults and Adolescents 15 years of age and older)

The efficacy of SINGULAIR, 10 mg, when given as a single dose 2 hours before exercise for the prevention of EIB was investigated in three (U.S. and Multinational), randomized, double-blind, placebo-controlled crossover studies that included a total of 160 adult and adolescent patients 15 years of age and older with EIB. Exercise challenge testing was conducted at 2 hours, 8.5 or 12 hours, and 24 hours following administration of a single dose of study drug (SINGULAIR 10 mg or placebo). The primary endpoint was the mean maximum percent fall in FEV_1 following the 2 hours post-dose exercise challenge in all three studies (Study A, Study B, and Study C). In Study A, a single dose of SINGULAIR 10 mg demonstrated a statistically significant protective benefit against EIB when taken 2 hours prior to exercise. Some patients were protected from EIB at 8.5 and 24 hours after administration; however, some patients were not. The results for the mean maximum percent fall at each timepoint in Study A are shown in TABLE 3 and are representative of the results from the other two studies.

TABLE 3
Mean Maximum Percent Fall in FEV_1 Following Exercise Challenge in Study A (N=47)
ANOVA Model

Time of exercise challenge following medication administration	Mean Maximum percent fall in FEV_1*		Treatment difference % for SINGULAIR versus Placebo (95%CI)*
	SINGULAIR	Placebo	
2 hours	13	22	-9 (-12, -5)
8.5 hours	12	17	-5 (-9, -2)
24 hours	10	14	-4 (-7, -1)

*Least squares-mean

Daily administration of SINGULAIR for the chronic treatment of asthma has not been established to prevent acute episodes of EIB. The efficacy of SINGULAIR for prevention of EIB in patients below 15 years of age has not been established.

In a 12-week, randomized, double-blind, parallel group study of 110 adult and adolescent asthmatics 15 years of age and older, with a mean baseline FEV_1 percent of predicted of 83% and with documented exercise-induced exacerbation of asthma, treatment with SINGULAIR, 10 mg, once daily in the evening, resulted in a statistically significant reduction in mean maximal percent fall in FEV_1 and mean time to recovery to within 5% of the pre-exercise FEV_1. Exercise challenge was conducted at the end of the dosing interval (i.e., 20 to 24 hours after the preceding dose). This effect was maintained throughout the 12-week treatment period indicating that tolerance did not occur. SINGULAIR did not, however, prevent clinically significant deterioration in maximal percent fall in FEV_1 after exercise (i.e., ≥20% decrease from pre-exercise baseline) in 52% of patients studied. In a separate crossover study in adults, a similar effect was observed after two once-daily 10-mg doses of SINGULAIR.

In pediatric patients 6 to 14 years of age, using the 5-mg chewable tablet, a 2-day crossover study demonstrated effects similar to those observed in adults when exercise challenge was conducted at the end of the dosing interval (i.e., 20 to 24 hours after the preceding dose).

14.3 Allergic Rhinitis (Seasonal and Perennial)

Seasonal Allergic Rhinitis

The efficacy of SINGULAIR tablets for the treatment of seasonal allergic rhinitis was investigated in 5 similarly designed, randomized, double-blind, parallel-group, placebo- and active-controlled (loratadine) trials conducted in North America. The 5 trials enrolled a total of 5029 patients, of whom 1799 were treated with SINGULAIR tablets. Patients were 15 to 82 years of age 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 entry.

The period of randomized treatment was 2 weeks in 4 trials and 4 weeks in one trial. The primary outcome variable was mean change from baseline in daytime nasal symptoms score (the average of individual scores of nasal congestion, rhinorrhea, nasal itching, sneezing) as assessed by patients on a 0-3 categorical scale.

Four of the five trials showed a significant reduction in daytime nasal symptoms scores with SINGULAIR 10-mg tablets compared with placebo. The results of one trial are shown below. The median age in this trial was 35.0 years (range 15 to 81); 65.4% were females and 34.6% were males. The ethnic/racial distribution in this study was 83.1% Caucasian, 6.4% other origins, 5.8% Black, and 4.8% Hispanic. The mean changes from baseline in daytime nasal symptoms score in the treatment groups that received SINGULAIR tablets, loratadine, and placebo are shown in TABLE 4. The remaining three trials that demonstrated efficacy showed similar results.

TABLE 4
Effects of SINGULAIR on Daytime Nasal Symptoms Score* in a Placebo- and Active-controlled Trial in Patients with Seasonal Allergic Rhinitis
(ANCOVA Model)

Treatment Group (N)	Baseline Mean Score	Mean Change from Baseline	Difference Between Treatment and Placebo (95% CI) Least-Squares Mean
SINGULAIR 10 mg (344)	2.09	-0.39	-0.13‡ (-0.21, -0.06)
Placebo (351)	2.10	-0.26	N.A.
Active Control† (Loratadine 10 mg) (599)	2.06	-0.46	-0.24‡ (-0.31, -0.17)

* Average of individual scores of nasal congestion, rhinorrhea, nasal itching, sneezing as assessed by patients on a 0-3 categorical scale.
† The study was not designed for statistical comparison between SINGULAIR and the active control (loratadine).
‡ Statistically different from placebo ($p \leq 0.001$).

Perennial Allergic Rhinitis

The efficacy of SINGULAIR tablets for the treatment of perennial allergic rhinitis was investigated in 2 randomized, double-blind, placebo-controlled studies conducted in North America and Europe. The two studies enrolled a total of 3357 patients, of whom 1632 received SINGULAIR 10-mg tablets. Patients 15 to 82 years of age with perennial allergic rhinitis as confirmed by history and a positive skin test to at least one relevant perennial allergen (dust mites, animal dander, and/or mold spores), who had active symptoms at the time of study entry, were enrolled.

In the study in which efficacy was demonstrated, the median age was 35 years (range 15 to 81); 64.1% were females and 35.9% were males. The ethnic/racial distribution in this study was 83.2% Caucasian, 8.1% Black, 5.4% Hispanic, 2.3% Asian, and 1.0% other origins. SINGULAIR 10-mg tablets once daily was shown to significantly reduce symptoms of perennial allergic rhinitis over a 6-week treatment period

(TABLE 5); in this study the primary outcome variable was mean change from baseline in daytime nasal symptoms score (the average of individual scores of nasal congestion, rhinorrhea, and sneezing).

TABLE 5
Effects of SINGULAIR on Daytime Nasal Symptoms Score* in a Placebo-controlled Trial in Patients with Perennial Allergic Rhinitis (ANCOVA Model)

Treatment Group (N)	Baseline Mean Score	Mean Change from Baseline	Difference Between Treatment and Placebo (95% CI) Least-Squares Mean
SINGULAIR 10 mg (1000)	2.09	-0.42	-0.08† (-0.12, -0.04)
Placebo (980)	2.10	-0.35	N.A.

* Average of individual scores of nasal congestion, rhinorrhea, sneezing as assessed by patients on a 0-3 categorical scale.
† Statistically different from placebo ($p \leq 0.001$).

The other 6-week study evaluated SINGULAIR 10 mg (n=626), placebo (n=609), and an active-control (cetirizine 10 mg; n=120). The primary analysis compared the mean change from baseline in daytime nasal symptoms score for SINGULAIR vs. placebo over the first 4 weeks of treatment; the study was not designed for statistical comparison between SINGULAIR and the active-control. The primary outcome variable included nasal itching in addition to nasal congestion, rhinorrhea, and sneezing. The estimated difference between SINGULAIR and placebo was -0.04 with a 95% CI of (-0.09, 0.01). The estimated difference between the active-control and placebo was -0.10 with a 95% CI of (-0.19, -0.01).

16 HOW SUPPLIED/STORAGE AND HANDLING

No. 3841 — SINGULAIR Oral Granules, 4 mg, are white granules with 500 mg net weight, packed in a child-resistant foil packet. They are supplied as follows:

NDC 0006-3841-30 unit of use carton with 30 packets.

No. 3796 — SINGULAIR Tablets, 4 mg, are pink, oval, bi-convex-shaped chewable tablets, with code MRK 711 on one side and SINGULAIR on the other. They are supplied as follows:

NDC 0006-0711-31 unit of use high-density polyethylene (HDPE) bottles of 30 with a polypropylene child-resistant cap, an aluminum foil induction seal, and silica gel desiccant

NDC 0006-0711-54 unit of use high-density polyethylene (HDPE) bottles of 90 with a polypropylene child-resistant cap, an aluminum foil induction seal, and silica gel desiccant

NDC 0006-0711-28 unit dose paper and aluminum foil-backed aluminum foil peelable blister packs of 100.

No. 3760 — SINGULAIR Tablets, 5 mg, are pink, round, bi-convex-shaped chewable tablets, with code MRK 275 on one side and SINGULAIR on the other. They are supplied as follows:

NDC 0006-0275-31 unit of use high-density polyethylene (HDPE) bottles of 30 with a polypropylene child-resistant cap, an aluminum foil induction seal, and silica gel desiccant

NDC 0006-0275-54 unit of use high-density polyethylene (HDPE) bottles of 90 with a polypropylene child-resistant cap, an aluminum foil induction seal, and silica gel desiccant

NDC 0006-0275-28 unit dose paper and aluminum foil-backed aluminum foil peelable blister packs of 100

NDC 0006-0275-82 bulk packaging high-density polyethylene (HDPE) bottles of 1000 with a non-child-resistant white plastic closure with a wax paper/pulp liner, an aluminum foil induction seal, and silica gel desiccant.

No. 3761 — SINGULAIR Tablets, 10 mg, are beige, rounded square-shaped, film-coated tablets, with code MRK 117 on one side and SINGULAIR on the other. They are supplied as follows:

NDC 0006-0117-31 unit of use high-density polyethylene (HDPE) bottles of 30 with a polypropylene child-resistant cap, an aluminum foil induction seal, and silica gel desiccant

NDC 0006-0117-54 unit of use high-density polyethylene (HDPE) bottles of 90 with a polypropylene child-resistant cap, an aluminum foil induction seal, and silica gel desiccant

NDC 0006-0117-28 unit dose paper and aluminum foil-backed aluminum foil peelable blister pack of 100

NDC 0006-0117-80 bulk packaging high-density polyethylene (HDPE) bottles of 8000 with a non-child-resistant white plastic closure with a wax paper/pulp liner, an aluminum foil induction seal, and silica gel desiccant.

Storage

Store SINGULAIR 4-mg oral granules, 4-mg chewable tablets, 5-mg chewable tablets and 10-mg film-coated tablets at 25°C (77°F), excursions permitted to 15-30°C (59-86°F) [see USP Controlled Room Temperature]. Protect from moisture and light. Store in original package.

Storage for Bulk Bottles

Store bottles of 1000 SINGULAIR 5-mg chewable tablets and 8000 SINGULAIR 10-mg film-coated tablets at 25°C (77°F), excursions permitted to 15-30°C (59-86°F) [see USP Controlled Room Temperature]. Protect from moisture and light. Store in original container. When product container is subdivided, repackage into a well-closed, light-resistant container.

17 PATIENT COUNSELING INFORMATION

[See FDA-Approved Patient Labeling (17.2).]

17.1 Information for Patients

- Patients should be advised to take SINGULAIR daily as prescribed, even when they are asymptomatic, as well as during periods of worsening asthma, and to contact their physicians if their asthma is not well controlled.
- Patients should be advised that oral SINGULAIR is not for the treatment of acute asthma attacks. They should have appropriate short-acting inhaled β-agonist medication available to treat asthma exacerbations. Patients who have exacerbations of asthma after exercise should be instructed to have available for rescue a short-acting inhaled β-agonist. Daily administration of SINGULAIR for the chronic treatment of asthma has not been established to prevent acute episodes of EIB.
- Patients should be advised that, while using SINGULAIR, medical attention should be sought if short-acting inhaled bronchodilators are needed more often than usual, or if more than the maximum number of inhalations of short-acting bronchodilator treatment prescribed for a 24-hour period are needed.
- Patients receiving SINGULAIR should be instructed not to decrease the dose or stop taking any other anti-asthma medications unless instructed by a physician.
- Patients should be instructed to notify their physician if neuropsychiatric events occur while using SINGULAIR.
- Patients with known aspirin sensitivity should be advised to continue avoidance of aspirin or non-steroidal anti-inflammatory agents while taking SINGULAIR.

17.2 FDA-Approved Patient Labeling

See the full patient prescribing information for SINGULAIR.

US Patent No.: 5,565,473

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Patient Information
SINGULAIR® (SING-u-lair)
(montelukast sodium)
Tablets

SINGULAIR®
(montelukast sodium)
Chewable Tablets

SINGULAIR®
(montelukast sodium)
Oral Granules

Read the Patient Information Leaflet that comes with SINGULAIR before you start taking it and each time you get a refill. There may be new information. This leaflet does not take the place of talking with your healthcare provider about your medical condition or your treatment.

What is SINGULAIR?

- SINGULAIR is a prescription medicine that blocks substances in the body called leukotrienes. This may help to improve symptoms of asthma and allergic rhinitis. SINGULAIR does not contain a steroid.

SINGULAIR is used to:

1. Prevent asthma attacks and for the long-term treatment of asthma in adults and children ages 12 months and older.

   Do not take SINGULAIR if you need relief right away for a sudden asthma attack. If you get an asthma attack, you should follow the instructions your healthcare provider gave you for treating asthma attacks.

2. Prevent exercise-induced asthma in people 15 years of age and older.

3. Help control the symptoms of allergic rhinitis (sneezing, stuffy nose, runny nose, itching of the nose). SINGULAIR is used to treat:
   - outdoor allergies that happen part of the year (seasonal allergic rhinitis) in adults and children ages 2 years and older, **and**
   - indoor allergies that happen all year (perennial allergic rhinitis) in adults and children ages 6 months and older.

Who should not take SINGULAIR?

Do not take SINGULAIR if you are allergic to any of its ingredients.

See the end of this leaflet for a complete list of the ingredients in SINGULAIR.

What should I tell my healthcare provider before taking SINGULAIR?

Before taking SINGULAIR, tell your healthcare provider if you:

- are allergic to aspirin
- have phenylketonuria. SINGULAIR chewable tablets contain aspartame, a source of phenylalanine

- have any other medical conditions
- are pregnant or plan to become pregnant. If you are pregnant or plan to become pregnant, SINGULAIR may not be right for you. If you become pregnant while taking SINGULAIR, talk to your healthcare provider about reporting your pregnancy to the Pregnancy Registry for SINGULAIR, or you can enroll in this registry by calling 1-800-986-8999.
- are breast-feeding or plan to breast-feed. It is not known if SINGULAIR passes into your breast milk. Talk to your healthcare provider about the best way to feed your baby while taking SINGULAIR.

Tell your healthcare provider about all the medicines you take, including prescription and non-prescription medicines, vitamins, and herbal supplements. Some medicines may affect how SINGULAIR works, or SINGULAIR may affect how your other medicines work.

How should I take SINGULAIR?

For anyone who takes SINGULAIR:

- Take SINGULAIR exactly as prescribed by your healthcare provider. Your healthcare provider will tell you how much SINGULAIR to take, and **when to take it.**
- Do not stop taking SINGULAIR or change when you take it without talking with your healthcare provider.
- You can take SINGULAIR with food or without food. See the information below in the section "How should I give SINGULAIR oral granules to my child?" for information about what foods and liquids can be taken with SINGULAIR oral granules.
- **If you or your child misses a dose of SINGULAIR, just take the next dose at your regular time.** Do not take 2 doses at the same time.
- If you take too much SINGULAIR, call your doctor.

For adults and children 12 months of age and older with asthma:

- Take SINGULAIR 1 time each day, in the evening. Continue to take SINGULAIR every day for as long as your healthcare provider prescribes it, even if you have no asthma symptoms.
- Tell your healthcare provider right away if your asthma symptoms get worse, or if you need to use your rescue inhaler medicine more often for asthma attacks.
- **Do not take SINGULAIR if you need relief right away from a sudden asthma attack.** If you get an asthma attack, you should follow the instructions your healthcare provider gave you for treating asthma attacks.
- Always have your rescue inhaler medicine with you for asthma attacks.
- Do not stop taking or lower the dose of your other asthma medicines unless your healthcare provider tells you to.

For patients 15 years of age and older for the prevention of exercise-induced asthma:

- Take SINGULAIR at least 2 hours before exercise.
- Always have your rescue inhaler medicine with you for asthma attacks.
- If you take SINGULAIR every day for chronic asthma or allergic rhinitis, **do not** take another dose to prevent exercise-induced asthma. Talk to your healthcare provider about your treatment for exercise-induced asthma.
- **Do not take 2 doses of SINGULAIR within 24 hours (1 day).**

For adults and children 2 years of age and older with seasonal allergic rhinitis, or for adults and children 6 months of age and older with perennial allergic rhinitis:

- Take SINGULAIR 1 time each day, at about the same time each day.

How should I give SINGULAIR oral granules to my child?

Give SINGULAIR oral granules to your child exactly as instructed by your healthcare provider.

Do not open the packet until ready to use.

SINGULAIR 4-mg oral granules can be given:

- right in the mouth; or
- dissolved in 1 teaspoonful (5 mL) of cold or room temperature baby formula or breast milk; or
- mixed with 1 spoonful of one of the following soft foods at cold or room temperature: applesauce, mashed carrots, rice, or ice cream.

Give the child all of the mixture right away, within 15 minutes.

Do not store any leftover SINGULAIR mixture (oral granules mixed with food, baby formula, or breast milk) for use at a later time. Throw away any unused portion.

Do not mix SINGULAIR oral granules with any liquid drink other than baby formula or breast milk. Your child may drink other liquids after swallowing the mixture.

What is the dose of SINGULAIR?

The dose of SINGULAIR prescribed for your or your child's condition is based on age:

- 6 to 23 months: one packet of 4-mg oral granules.
- 2 to 5 years: one 4-mg chewable tablet or one packet of 4-mg oral granules.
- 6 to 14 years: one 5-mg chewable tablet.
- 15 years and older: one 10-mg tablet.

What should I avoid while taking SINGULAIR?

If you have asthma and aspirin makes your asthma symptoms worse, continue to avoid taking aspirin or other medicines called non-steroidal anti-inflammatory drugs (NSAIDs) while taking SINGULAIR.

What are the possible side effects of SINGULAIR?

SINGULAIR may cause serious side effects.

- **Behavior and mood-related changes.** Tell your healthcare provider right away if you or your child have any of these symptoms while taking SINGULAIR:
  - agitation including aggressive behavior or hostility
  - bad or vivid dreams
  - depression
  - disorientation (confusion)
  - feeling anxious
  - hallucinations (seeing or hearing things that are not really there)
  - irritability
  - restlessness
  - sleep walking
  - suicidal thoughts and actions (including suicide)
  - tremor
  - trouble sleeping

- **Increase in certain white blood cells (eosinophils) and possible inflamed blood vessels throughout the body (systemic vasculitis).** Rarely, this can happen in people with asthma who take SINGULAIR. This usually, but not always, happens in people who also take a steroid medicine by mouth that is being stopped or the dose is being lowered.
  Tell your healthcare provider right away if you get one or more of these symptoms:
  - a feeling of pins and needles or numbness of arms or legs

- a flu-like illness
- rash
- severe inflammation (pain and swelling) of the sinuses (sinusitis)

The most common side effects with SINGULAIR include:

- upper respiratory infection
- fever
- headache
- sore throat
- cough
- stomach pain
- diarrhea
- earache or ear infection
- flu
- runny nose
- sinus infection

Other side effects with SINGULAIR include:

- increased bleeding tendency
- allergic reactions [including swelling of the face, lips, tongue, and/or throat (which may cause trouble breathing or swallowing), hives and itching]
- dizziness, drowsiness, pins and needles/numbness, seizures (convulsions or fits)
- palpitations
- nose bleed, stuffy nose
- diarrhea, heartburn, indigestion, inflammation of the pancreas, nausea, stomach or intestinal upset, vomiting
- hepatitis
- bruising, rash
- joint pain, muscle aches and muscle cramps
- tiredness, swelling

Tell your healthcare provider if you have any side effect that bothers you or that does not go away. These are not all the possible side effects of SINGULAIR. For more information ask your healthcare provider or pharmacist.

Call your healthcare provider for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

How should I store SINGULAIR?

- Store SINGULAIR at 59°F to 86°F (15°C to 30°C).
- Keep SINGULAIR in the container it comes in.
- Keep SINGULAIR in a dry place and away from light.

General Information about the safe and effective use of SINGULAIR

Medicines are sometimes prescribed for purposes other than those mentioned in Patient Information Leaflets. Do not use SINGULAIR for a condition for which it was not prescribed. Do not give SINGULAIR to other people even if they have the same symptoms you have. It may harm them. **Keep SINGULAIR and all medicines out of the reach of children.**

This leaflet summarizes information about SINGULAIR. If you would like more information, talk to your healthcare provider. You can ask your pharmacist or healthcare provider for information about SINGULAIR that is written for health professionals. For more information, go to www.singulair.com or call the Merck National Service Center at 1-800-NSC-Merck (1-800-672-6372).

What are the ingredients in SINGULAIR?

Active ingredient: montelukast sodium

Inactive ingredients:

- 4-mg oral granules: mannitol, hydroxypropyl cellulose, and magnesium stearate.
- 4-mg and 5-mg chewable tablets: mannitol, microcrystalline cellulose, hydroxypropyl cellulose, red ferric oxide, croscarmellose sodium, cherry flavor, aspartame, and magnesium stearate.

  People with Phenylketonuria: SINGULAIR 4-mg chewable tablets contain 0.674 mg of phenylalanine, and SINGULAIR 5-mg chewable tablets contain 0.842 mg of phenylalanine.
- 10-mg tablet: microcrystalline cellulose, lactose monohydrate, croscarmellose sodium, hydroxypropyl cellulose, and magnesium stearate. The film coating contains: hydroxypropyl methylcellulose, hydroxypropyl cellulose, titanium dioxide, red ferric oxide, yellow ferric oxide, and carnauba wax.

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