SINGULAIR® 4 mg
GRANULES FOR KIDDIES

Each sachet of granules contains:
Montelukast 4 mg (as sodium salt)

SINGULAIR® 4 mg
CHEWABLE TABLETS FOR PRE-SCHOOL KIDS

Each chewable tablet contains:
Montelukast 4 mg (as sodium salt)

SINGULAIR® 5 mg
CHEWABLE TABLETS

Each chewable tablet contains:
Montelukast 5 mg (as sodium salt)

SINGULAIR® 10 mg
TABLETS

Each tablet contains:
Montelukast 10 mg (as sodium salt)

WARNING: SERIOUS NEUROPSYCHIATRIC EVENTS

Serious neuropsychiatric (NP) events have been reported with the use of SINGULAIR. The types of events reported were highly variable, and included, but were not limited to, agitation, aggression, depression, sleep disturbances, suicidal thoughts and behavior (including suicide). The mechanisms underlying NP events associated with SINGULAIR use are currently not well understood *[see Warnings and Precautions (5.1)]*.

Because of the risk of NP events, the benefits of SINGULAIR may not outweigh the risks in some patients, particularly when the symptoms of disease may be mild and adequately treated with alternative therapies. Reserve use of SINGULAIR for patients with allergic rhinitis who have an inadequate response or intolerance to alternative therapies *[see Indications and Usage (1.3)]*. In patients with asthma or exercise-induced bronchoconstriction, consider the benefits and risks before prescribing SINGULAIR.

Discuss the benefits and risks of SINGULAIR with patients and caregivers when prescribing SINGULAIR. Advise patients and/or caregivers to be alert for changes in behavior or new NP symptoms when taking SINGULAIR. If changes in behavior are observed, or if new NP symptoms or suicidal thoughts and/or behavior occur, advise patients to discontinue SINGULAIR and contact a healthcare provider immediately *[see Warnings and Precautions (5.1)]*.

1 THERAPEUTIC INDICATIONS

SINGULAIR 4 mg Granules for Kiddies

4 mg Granules for Kiddies is indicated in adults 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 symptoms of seasonal allergic rhinitis in adults and pediatric patients 2 years of age and older.
Because the benefits of Singulair may not outweigh the risk of neuropsychiatric symptoms in patients with seasonal rhinitis [see Warnings and Precautions (5.1)], reserve use for patients who have an intolerance to alternative therapies.

SINGULAIR 4 mg Chewable tablets for Pre-school kids

Singulair 4 mg Chewable Tablets for Preschool Kids is indicated in pediatric patients 2 years 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 symptoms of seasonal allergic rhinitis in adults and pediatric patients 2 years of age and older.
Because the benefits of SINGULAIR may not outweigh the risk of neuropsychiatric symptoms in patients with seasonal rhinitis [see Warnings and Precautions (5.1)], reserve use for patients who have an intolerance to alternative therapies.

SINGULAIR 5 mg Chewable tablets
Singulair 5 mg is indicated in adults and pediatric patients 6 years of age and older for the prophylaxis and chronic treatment of asthma, including prevention of daytime and nighttime symptoms of 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 symptoms of seasonal allergic rhinitis in adults and pediatric patients 6 years of age and older.
Because the benefits of SINGULAIR may not outweigh the risk of neuropsychiatric symptoms in patients with seasonal rhinitis [see Warnings and Precautions (5.1)], reserve use for patients who have an intolerance to alternative therapies.

SINGULAIR 10 mg tablets
Singulair 10 mg is indicated in adults and adolescents 15 years 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 symptoms of seasonal allergic rhinitis in adults and pediatric patients 15 years of age and older.
Because the benefits of SINGULAIR may not outweigh the risk of neuropsychiatric symptoms in patients with seasonal rhinitis [see Warnings and Precautions (5.1)], reserve use for patients who have an intolerance to alternative therapies.

2 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.

Patients who miss a dose should take the next dose at their regular time and should not take 2 doses at the same time.

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.

3 DOSAGE FORMS AND STRENGTHS

- SINGULAIR 10 mg Tablets are beige, rounded square-shaped, film-coated tablets, with code MSD 117 engraved on one side and SINGULAIR on the other.
- SINGULAIR 5 mg Chewable Tablets are pink, round, bi-convex-shaped, with code MSD 275 engraved on one side and SINGULAIR on the other.
- SINGULAIR 4 mg Chewable Tablets for pre-school kids: 4 mg, pink, oval, bi-convex-shaped, with code MSD 711 engraved on one side and SINGULAIR on the other.
- SINGULAIR 4 mg Oral Granules for kiddies: 4 mg, white, granular, coarse, free-flowing homogeneous solid, with no extraneous particles present granules with 500 mg net weight.

4 CONTRAINDICATIONS

SINGULAIR is contraindicated in patients with hypersensitivity to any of its components (listed in section 11).

5 WARNINGS AND PRECAUTIONS

5.1 Neuropsychiatric Events

Serious neuropsychiatric (NP) events have been reported with use of SINGULAIR. These postmarketing reports have been highly variable and included, but were not limited to, agitation, aggressive behavior or hostility, anxiousness, depression, disorientation, disturbance in attention, dream abnormalities, dysphemia (stuttering), hallucinations, insomnia, irritability, memory impairment, obsessive-compulsive symptoms, restlessness, somnambulism, suicidal thoughts and behavior (including suicide), tic, and tremor. NP events have been reported in adult, adolescent, and pediatric patients with and without a previous history of psychiatric disorder. NP events have been reported mostly during SINGULAIR treatment, but some were reported after SINGULAIR discontinuation. Animal studies showed that montelukast distributes into the brain in rats *[see Clinical Pharmacology (12.3)]*; however, the mechanisms underlying SINGULAIR-associated NP events are currently not well understood. Based upon the available data, it is difficult to identify risk factors for or quantify the risk of NP events with SINGULAIR use.

Because of the risk of NP events, the benefits of SINGULAIR may not outweigh the risks in some patients, particularly when the symptoms of disease may be mild and adequately treated with alternative therapies. Reserve use of SINGULAIR for patients with allergic rhinitis who have an inadequate response or intolerance to alternative therapies *[see Indications and Usage (1.3)]*. In patients with asthma or exercise-induced bronchoconstriction, consider the benefits and risks before prescribing SINGULAIR.

Discuss the benefits and risks of SINGULAIR use with patients and caregivers when prescribing SINGULAIR. Advise patients and/or caregivers to be alert for changes in behavior or for new NP symptoms when taking SINGULAIR. If changes in behavior are observed, or if new NP symptoms or suicidal thoughts and/or behavior occur, advise patients to discontinue SINGULAIR and contact a healthcare provider immediately. In many cases, symptoms resolved after stopping SINGULAIR therapy; however, in some cases symptoms persisted after discontinuation of SINGULAIR. Therefore, continue to monitor and provide supportive care until symptoms resolve. Re-evaluate the benefits and risks of restarting treatment with SINGULAIR if such events occur.

5.2 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.

5.3 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.

5.4 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)]*.

5.5 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 have been sometimes 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 Risk in Patients with Phenylketonuria

SINGULAIR contains aspartame, a source of phenylalanine. Phenylalanine can be harmful to patients with phenylketonuria (PKU). Each 4 mg and 5 mg chewable tablet contains 0.674 mg and 0.842 mg of phenylalanine, respectively. Before prescribing SINGULAIR to a patient with PKU, consider the combined daily amount of phenylalanine from all sources, including SINGULAIR.

6 ADVERSE REACTIONS

The following clinically significant adverse reactions are described elsewhere in the labeling:

- Neuropsychiatric Events *[see Warnings and Precautions (5.1)]*

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.

<u>Adults and Adolescents 15 Years of Age and Older with Asthma</u>

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 reactions 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 5: Adverse Reactions 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 Reactions**		
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 reactions was comparable between SINGULAIR and placebo.

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 reaction 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 reactions 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 reactions was comparable between SINGULAIR and placebo. With prolonged treatment, the adverse reaction 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 reactions 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 reactions 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 reactions 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 reactions 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 reaction 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 reactions occurred with a frequency ≥2% and at an incidence greater than placebo: headache, otitis media, pharyngitis, and upper respiratory infection.

6.2 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.

Blood and lymphatic system disorders
increased bleeding tendency, thrombocytopenia

Immune system disorders
hypersensitivity reactions including anaphylaxis, hepatic eosinophilic infiltration

Psychiatric disorders
including, but not limited to, agitation, aggressive behavior or hostility, anxiousness, depression, disorientation, disturbance in attention, dream abnormalities, dysphemia (stuttering), hallucinations, insomnia, irritability, memory impairment, obsessive-compulsive symptoms, restlessness, somnambulism, suicidal thinking and behavior (including suicide), tic, and tremor *[see Boxed Warning, Warnings and Precautions (5.1)]*

Nervous system disorders
drowsiness, paraesthesia/hypoesthesia, seizures

Cardiac disorders
palpitations

Respiratory, thoracic and mediastinal disorders
epistaxis, pulmonary eosinophilia

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 multiforme, erythema nodosum, pruritus, Stevens-Johnson syndrome/toxic epidermal necrolysis, urticaria

Musculoskeletal and connective tissue disorders
arthralgia, myalgia including muscle cramps

Renal and urinary disorders
enuresis in children

General disorders and administration site conditions
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 reactions have been sometimes 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)].*

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorization 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

7 DRUG INTERACTIONS

No dose adjustment is needed when SINGULAIR is co-administered with theophylline, prednisone, prednisolone, oral contraceptives, fexofenadine, digoxin, warfarin, gemfibrozil, itraconazole, 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
Risk Summary

Available data from published prospective and retrospective cohort studies over decades with montelukast use in pregnant women have not established a drug-associated risk of major birth defects *[see Data]*. In animal reproduction studies, no adverse developmental effects were observed with oral administration of montelukast to pregnant rats and rabbits during organogenesis at doses approximately 100 and 110 times, respectively, the maximum recommended human daily oral dose (MRHDOD) based on AUCs *[see Data].*

The estimated background risk of major birth defects and miscarriage for the indicated population is unknown. All pregnancies have a background risk of birth defect, loss, or other adverse outcomes. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2-4% and 15-20%, respectively.

Clinical Considerations

Disease-associated maternal and/or embryo/fetal risk

Poorly or moderately controlled asthma in pregnancy increases the maternal risk of perinatal adverse outcomes such as preeclampsia and infant prematurity, low birth weight, and small for gestational age.

Data

Human Data

Published data from prospective and retrospective cohort studies have not identified an association with SINGULAIR use during pregnancy and major birth defects. Available studies have methodologic limitations, including small sample size, in some cases retrospective data collection, and inconsistent comparator groups.

Animal Data

In embryo-fetal development studies, montelukast administered to pregnant rats and rabbits during organogenesis (gestation days 6 to 17 in rats and 6 to 18 in rabbits) did not cause any adverse developmental effects at maternal oral doses up to 400 and 300 mg/kg/day in rats and rabbits, respectively (approximately 100 and 110 times the AUC in humans at the MRHDOD, respectively).

8.2 Lactation

Risk Summary

A published clinical lactation study reports the presence of montelukast in human milk. Data available on the effects of the drug on infants, either directly *[see Use in Specific Populations (8.4)]* or through breast milk, do not suggest a significant risk of adverse reactions from exposure to SINGULAIR. The effects of the drug on milk production are unknown. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for SINGULAIR and any potential adverse reactions on the breastfed infant from SINGULAIR or from the underlying maternal condition.

8.4 Pediatric Use

Safety and effectiveness of SINGULAIR for asthma have been established in pediatric patients 6 to 14 years of age. Use of SINGULAIR for this indication is supported by evidence from well-controlled studies. Safety and efficacy data in this age group are similar to those seen in adults *[see Adverse Reactions (6.1), Clinical Pharmacology, Specific Populations (12.3), and Clinical Studies (14.1, 14.2)].*

The effectiveness of SINGULAIR for the treatment of seasonal allergic rhinitis in pediatric patients 2 to 14 years of age have been established and is supported by extrapolation from the demonstrated effectiveness 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)].* Effectiveness of SINGULAIR in this age group is extrapolated from the demonstrated effectiveness 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. Effectiveness 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)].* Effectiveness of SINGULAIR in this age group is extrapolated from the demonstrated effectiveness 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.

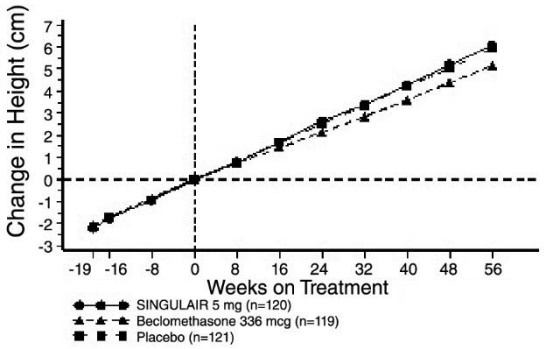
The safety of SINGULAIR 4-mg and 5-mg chewable tablets in pediatric patients aged 2 to 14 years with allergic rhinitis is supported by data from studies conducted in pediatric patients aged 2 to 14 years with asthma. A safety study in pediatric patients 2 to 14 years of age with seasonal allergic rhinitis demonstrated a similar safety profile *[see Adverse Reactions (6.1)].*

The safety and effectiveness in pediatric patients below the age of 12 months with asthma and 6 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 Impairment

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

8.7 Renal Impairment

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

10 OVERDOSAGE

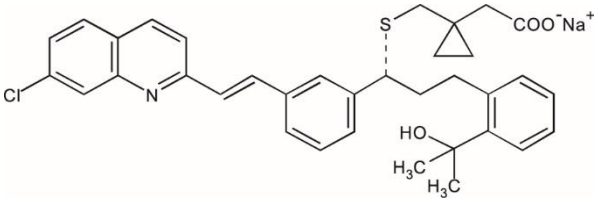
No specific information is available on the treatment of overdosage with SINGULAIR. In the event of overdose, it is reasonable to employ the usual supportive measures; e.g., remove unabsorbed material from the gastrointestinal tract, employ clinical monitoring, and institute supportive therapy, if required. 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, yellow ferric oxide, carnauba wax and red ferric oxide.
Please note that the 10 mg film-coated tablets contain lactose. Each SINGULAIR 10 mg tablet contains 89.3 mg of lactose monohydrate.

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, croscarmellose sodium, cherry flavor, magnesium stearate, aspartame and red ferric oxide.
Each 4 mg and 5 mg chewable tablet contains 0.674 mg and 0.842 mg of phenylalanine, respectively.

Each sachet 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 effectiveness 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 effectiveness 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. Orally administered montelukast distributes into the brain in rats.

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%).

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, 2C8, and 2C9 are involved in the metabolism of montelukast. At clinically relevant concentrations, 2C8 appears to play a major role in the metabolism of montelukast.

Specific Populations

Patients with Hepatic Impairment

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.

Patients with Renal Impairment

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.

Male and Female Patients

The pharmacokinetics of montelukast are similar in males and females.

Racial Groups

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. 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 Interaction Studies

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, fexofenadine, 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), 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 fexofenadine, 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.

Effect of Montelukast on Cytochrome P450 (CYP) Enzymes
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). Based on further *in vitro* results in human liver microsomes, therapeutic plasma concentrations of montelukast do not inhibit CYP 3A4, 2C9, 1A2, 2A6, 2C19, or 2D6.

Cytochrome P450 (CYP) Enzyme Inhibitors
In vitro studies have shown that montelukast is a substrate of CYP 2C8, 2C9, and 3A4. Co-administration of montelukast with itraconazole, a strong CYP 3A4 inhibitor, resulted in no significant increase in the systemic exposure of montelukast. Data from a clinical drug interaction study involving montelukast and gemfibrozil (an inhibitor of both CYP 2C8 and 2C9) demonstrated that gemfibrozil, at a therapeutic dose, increased the systemic exposure of montelukast by 4.4-fold. Co-administration of itraconazole, gemfibrozil, and montelukast did not further increase the systemic exposure of montelukast. Based on available clinical experience, no dosage adjustment of montelukast is required upon co-administration with gemfibrozil *[see Overdosage (10)]*.

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).

14 CLINICAL STUDIES

14.1 Asthma

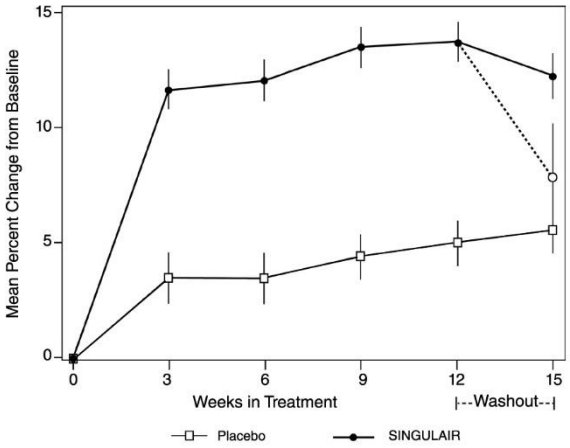
Adults and Adolescents 15 Years of Age and Older with Asthma

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 6. Results on these endpoints were similar in the US study.

Table 6: 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 ($p \leq 0.05$). 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 (5.4)].*

14.3 Seasonal Allergic Rhinitis

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 9. The remaining three trials that demonstrated efficacy showed similar results. Efficacy was demonstrated for seasonal allergic rhinitis when montelukast was administered in the morning or the evening.

Table 9: 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.
† Statistically different from placebo ($p \leq 0.001$).
‡ The study was not designed for statistical comparison between SINGULAIR and the active control (loratadine).

16 HOW SUPPLIED/STORAGE AND HANDLING

SINGULAIR 4 mg Granules for Kiddies are supplied as follows: 7, 10, 28, 30 sachets per pack.

SINGULAIR 4 mg Chewable Tablets for preschool kids are supplied as follows: 7, 10, 28, 30 chewable tablets per pack.

SINGULAIR 5 mg Chewable Tablets are supplied as follows: 7, 10, 28, 30 chewable tablets per pack.

SINGULAIR 10 mg Tablets are supplied as follows: 7, 10, 28, 30 tablets per pack.
Not all pack sizes may be marketed.

Shelf life
The expiry date of the product is indicated on the packaging materials.

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.

17 PATIENT COUNSELING INFORMATION

See Ministry of Health-approved patient leaflet (Patient Information).

Registration Numbers:

SINGULAIR 4 mg granules for kiddies:	130.14.30912
SINGULAIR 4 mg chewable tablets for preschool kids:	121.67.30155
SINGULAIR 5 mg chewable tablets:	109.90.29316
SINGULAIR 10 mg Tablets:	109.91.29317

Manufacturer: Organon LLC, NJ USA

License holder and address: Organon Pharma Israel Ltd., 1 Atir Yeda, Kfar Saba

Revised in December 2024.