

SINGULAIR- montelukast sodium granule
SINGULAIR- montelukast sodium tablet, chewable
SINGULAIR- montelukast sodium tablet, film coated
Organon LLC

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

WARNING: SERIOUS NEUROPSYCHIATRIC EVENTS

See full prescribing information for complete boxed warning.

- **Serious neuropsychiatric events have been reported in patients taking SINGULAIR (5.1).**
- **Discuss benefits and risks of SINGULAIR with patients and caregivers (5.1).**
- **Monitor for neuropsychiatric symptoms in patients taking SINGULAIR (5.1).**
- **Discontinue SINGULAIR immediately if neuropsychiatric symptoms occur (5.1).**
- **Because the benefits of SINGULAIR may not outweigh the potential risk of neuropsychiatric symptoms in patients with allergic rhinitis, reserve use for patients who have an inadequate response or intolerance to alternative therapies (1.3, 5.1).**

RECENT MAJOR CHANGES

Indications and Usage (1.3, 1.4)	02/2021
Dosage and Administration (2.1, 2.2, 2.3, 2.4)	02/2021
Warnings and Precautions (5.1, 5.6)	02/2021

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 6 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. Reserve use for patients who have an inadequate response or intolerance to alternative therapies (1.3).

Limitations of Use:

- Not indicated to treat an acute asthma attack (5.2).

DOSAGE AND ADMINISTRATION

Administration (by indications):

- Asthma: Once daily in the evening for patients 12 months and older (2.1).
- Acute prevention of EIB: One tablet at least 2 hours before exercise for patients 6 years of age and older (2.2).
- Seasonal allergic rhinitis: Once daily for patients 2 years and older (2.3).
- Perennial allergic rhinitis: Once daily for patients 6 months and older (2.3).

Dosage (by age):

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

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

- Tablets: 10 mg (3)
- Chewable tablets: 5 mg and 4 mg (3)
- Oral granules: 4 mg (3)

CONTRAINDICATIONS

Hypersensitivity to any component of SINGULAIR (4).

WARNINGS AND PRECAUTIONS

- Do not prescribe SINGULAIR to treat an acute asthma attack (5.2).
- Advise patients to have appropriate rescue medication available (5.2).
- Inhaled corticosteroid may be reduced gradually. Do not abruptly substitute SINGULAIR for inhaled or oral corticosteroids (5.3).
- Patients with known aspirin sensitivity should continue to avoid aspirin or non-steroidal anti-inflammatory agents while taking SINGULAIR (5.4).
- Systemic eosinophilia, sometimes presenting with clinical features of vasculitis consistent with Churg-Strauss syndrome, has been reported. These events have been sometimes 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 $\geq 5\%$ 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 Organon LLC, a subsidiary of Organon & Co., Inc., at 1-844-674-3200 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch. See 17 for PATIENT COUNSELING INFORMATION and Medication Guide.

Revised: 6/2021

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FULL PRESCRIBING INFORMATION

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 INDICATIONS AND USAGE

1.1 Asthma

SINGULAIR® 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 (EIB)

SINGULAIR is indicated for prevention of exercise-induced bronchoconstriction (EIB) in patients 6 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. Because the benefits of SINGULAIR may not outweigh the risk of neuropsychiatric symptoms in patients with allergic rhinitis [see *Warnings and Precautions (5.1)*], reserve use for patients who have an inadequate response or intolerance to alternative therapies.

1.4 Limitations of Use

SINGULAIR is not indicated for the treatment of an acute asthma attack.

2 DOSAGE AND ADMINISTRATION

2.1 Asthma

For asthma, administer SINGULAIR orally once daily in the evening, with or without food. There have been no clinical trials in patients with asthma to evaluate the relative efficacy of morning versus evening dosing.

The following doses are recommended:

Table 1: Recommended Dosage in Asthma

Age	Dose
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Adult and adolescent patients 15 years of age and older	one 10 mg tablet
Pediatric patients 6 to 14 years of age	one 5 mg chewable tablet
Pediatric patients 2 to 5 years of age	one 4 mg chewable tablet or one packet of oral granules
Pediatric patients 12 to 23 months of age*	one packet 4 mg oral granules

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

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

2.2 Exercise-Induced Bronchoconstriction (EIB)

For prevention of EIB, administer a single dose of SINGULAIR orally at least 2 hours, before exercise. The following doses are recommended:

Table 2: Recommended Dosage in Exercise-Induced Bronchoconstriction (EIB)

Age	Dose
Adult and adolescent patients 15 years of age and older	one 10 mg tablet
Pediatric patients 6 to 14 years of age*	one 5 mg chewable tablet

* Safety and effectiveness in patients younger than 6 years of age have not been established.

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.

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, administer SINGULAIR orally once daily without regard to time of food ingestion. Time of administration in patients with allergic rhinitis can be individualized to suit patient needs.

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

Table 3: Recommended Dosage in Seasonal Allergic Rhinitis

Age	Dose
Adult and adolescent patients 15 years of age and older	one 10 mg tablet
Pediatric patients 6 to 14 years of age	one 5 mg chewable tablet
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.

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

Table 4: Recommended Dosage in Perennial Allergic Rhinitis

Age	Dose
Adult and adolescent patients 15 years of age and older	one 10 mg tablet
Pediatric patients 6 to 14 years of age	one 5 mg chewable tablet

Pediatric patients 2 to 5 years of age	one 4 mg chewable tablet or one packet of 4 mg oral granules
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.

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

2.4 Asthma and Allergic Rhinitis

For patients with both asthma and allergic rhinitis, administer only one SINGULAIR dose orally once daily in the evening.

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

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

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

4 CONTRAINDICATIONS

SINGULAIR is contraindicated in patients with hypersensitivity to any of its components.

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 $\geq 5\%$ 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 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 $\geq 1\%$ of Patients with an Incidence Greater than that in Patients Treated with Placebo

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

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 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 $\geq 2\%$ 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.

The safety profile of SINGULAIR, when administered as a single dose for prevention of EIB in pediatric patients 6 years of age and older, was consistent with the safety profile previously described for SINGULAIR.

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 $\geq 2\%$ 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 $\geq 2\%$ 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 $\geq 2\%$ 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 $\geq 1\%$ 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 $\geq 2\%$ 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 reactions were reported with SINGULAIR with a frequency $\geq 1\%$ 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 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)*].

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 and for the treatment of perennial allergic rhinitis in pediatric patients 6 months 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.

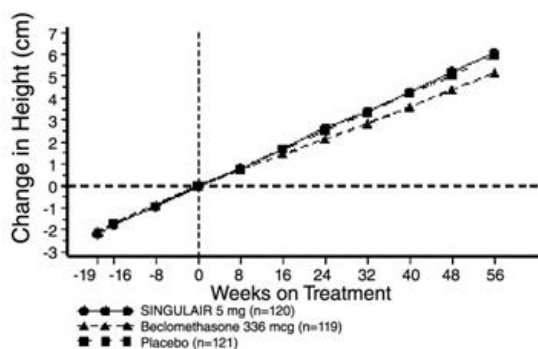
The safety of SINGULAIR 4-mg and 5-mg chewable tablets in pediatric patients aged 2 to 14 years with allergic rhinitis is supported by data from studies conducted in pediatric patients aged 2 to 14 years with asthma. A safety study in pediatric patients 2 to 14 years of age with seasonal allergic rhinitis demonstrated a similar safety profile [see *Adverse Reactions (6.1)*]. The safety 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, 6 months with perennial allergic rhinitis, 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 \pm 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

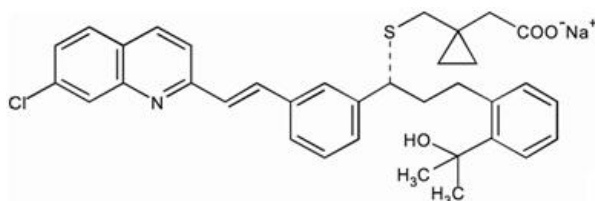
No specific information is available on the treatment of overdose with SINGULAIR. In the event of overdose, it is reasonable to employ the usual supportive measures; e.g., remove unabsorbed material from the gastrointestinal tract, employ clinical monitoring, and institute supportive therapy, if required. 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 CysLT₁ 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 C₃₅H₃₅ClNNaO₃S, 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 (LTC₄, LTD₄, LTE₄) 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 (CysLT₁) 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 CysLT₁ receptor (in preference to other pharmacologically important airway receptors, such as the prostanoid, cholinergic, or β -adrenergic receptor). Montelukast inhibits physiologic actions of LTD₄ at the CysLT₁ 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 LTD₄ in asthmatics. Doses as low as 5 mg cause substantial blockage of LTD₄-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, 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 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

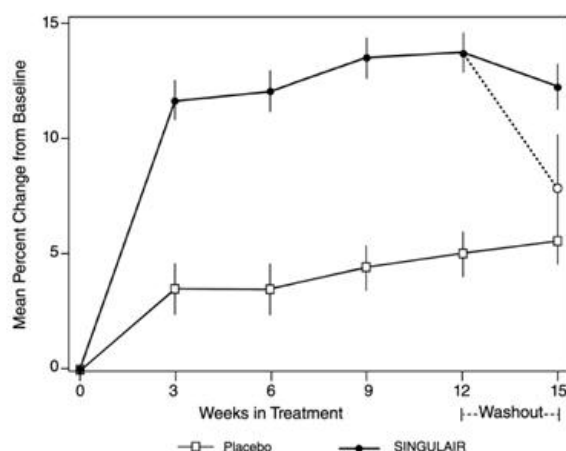
Clinical trials in adults and adolescents 15 years of age and older demonstrated there is no additional clinical benefit to montelukast doses above 10 mg once daily.

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 (FEV₁) of 66% (approximate range, 40 to 90%). The co-primary endpoints in these trials were FEV₁ 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 FEV₁, 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 FEV₁ 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 FEV₁ 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 FEV₁ were similar.

Figure 2: FEV₁ 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)

Endpoint	SINGULAIR			Placebo		
	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 FEV₁ 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 FEV₁ 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 FEV₁ 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 FEV₁ 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 FEV₁, daytime asthma symptoms, PEF, 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)].

14.2 Exercise-Induced Bronchoconstriction (EIB)

Exercise-Induced Bronchoconstriction (Adults, Adolescents, and Pediatric Patients 6 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 FEV₁ 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 7 and are representative of the results from the other two studies.

Table 7: Mean Maximum Percent Fall in FEV₁ 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

The efficacy of SINGULAIR 5-mg chewable tablets, when given as a single dose 2 hours before exercise for the prevention of EIB, was investigated in one multinational, randomized, double-blind, placebo-controlled crossover study that included a total of 64 pediatric patients 6 to 14 years of age with EIB. Exercise challenge testing was conducted at 2 hours and 24 hours following administration of a single dose of study drug (SINGULAIR 5 mg or placebo). The primary endpoint was the mean maximum percent fall in FEV₁ following the 2 hours post-dose exercise challenge. A single dose of SINGULAIR 5 mg demonstrated a statistically significant protective benefit against EIB when taken 2 hours prior to exercise (TABLE 8). Similar results were shown at 24 hours post-dose (a secondary endpoint). Some patients were protected from EIB at 24 hours after administration; however, some patients were not. No timepoints were assessed

between 2 and 24 hours post-dose.

Table 8: Mean Maximum Percent Fall in FEV₁ Following Exercise Challenge in Pediatric Patients (N=64) 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	15	20	-5 (-9, -1)
24 hours	13	17	-4 (-7, -1)

* Least squares-mean

The efficacy of SINGULAIR for prevention of EIB in patients below 6 years of age has not been established.

Daily administration of SINGULAIR for the chronic treatment of asthma has not been established to prevent acute episodes of EIB.

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 FEV₁ 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 FEV₁ and mean time to recovery to within 5% of the pre-exercise FEV₁. 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 FEV₁ 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 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).

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 10); 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 10: 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

SINGULAIR 4 mg Oral Granules: white granules with 500 mg net weight, packed in a child-resistant foil packet.

NDC 78206-171-01 unit of use carton with 30 packets.

SINGULAIR 4 mg Tablets: pink, oval, bi-convex-shaped chewable tablets, with code MSD 711 on one side and SINGULAIR on the other.

NDC 78206-170-01 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.

SINGULAIR 5 mg Tablets: pink, round, bi-convex-shaped chewable tablets, with code

MSD 275 on one side and SINGULAIR on the other.

NDC 78206-173-01 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.

SINGULAIR 10 mg Tablets: beige, rounded square-shaped, film-coated tablets, with code MSD 117 on one side and SINGULAIR on the other.

NDC 78206-172-01 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 78206-172-02 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.

Storage

Store SINGULAIR 4-mg oral granules, 4-mg chewable tablets, 5-mg chewable tablets and 10-mg film-coated tablets at 20°C to 25°C (68°F to 77°F), excursions permitted to 15°C to 30°C (59°F to 86°F) [see USP Controlled Room Temperature]. Protect from moisture and light. Store in original package.

17 PATIENT COUNSELING INFORMATION

For the tablets and chewable tablets, advise the patient and/or caregiver to read the FDA-approved patient labeling (Medication Guide).

For the oral granules, advise the patient and/or caregiver to read the FDA-approved patient labeling (Medication Guide and Instructions for Use).

- Advise patients about the potential risk for serious neuropsychiatric symptoms and behavioral changes with SINGULAIR use [see *Warnings and Precautions (5.1)*].
- Discuss the benefits and risks of SINGULAIR with patients when prescribing or continuing treatment with SINGULAIR [see *Warnings and Precautions (5.1)*].
- Advise patients to monitor for changes in behavior or neuropsychiatric symptoms in patients taking SINGULAIR [see *Warnings and Precautions (5.1)*].
- Instruct patients to discontinue SINGULAIR and contact a healthcare provider immediately if changes in behavior or thinking that are not typical for the patient occur, or if the patient develops suicidal ideation or suicidal behavior [see *Warnings and Precautions (5.1)*].
- Advise patients 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.
- Advise patients 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 [see *Warnings and Precautions (5.2)*].
- Advise patients to seek medical attention 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.
- Instruct patients to continue other anti-asthma medications as prescribed unless instructed by a physician.
- Instruct patients with known aspirin sensitivity to continue avoidance of aspirin or non-steroidal anti-inflammatory agents while taking SINGULAIR [see *Warnings and Precautions (5.4)*].
- Inform phenylketonuric patients that the 4-mg and 5-mg chewable tablets contain phenylalanine (a source of aspartame) [see *Warnings and Precautions (5.6)*].

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uspi-og0476-mf-2106r001

MEDICATION GUIDE
SINGULAIR® (SING-u-lair)
(montelukast sodium)

tablets

chewable tablets

oral granules

What is the most important information I should know about SINGULAIR?

Serious mental health problems have happened in people taking SINGULAIR

or even after treatment has stopped. This can happen in people with or without a history of mental health problems. Stop taking SINGULAIR and tell your healthcare provider right away if you or your child have any unusual changes in behavior or thinking, including any of these symptoms:

- agitation, including aggressive behavior or hostility
- attention problems
- bad or vivid dreams
- depression
- disorientation (confusion)
- feeling anxious
- irritability
- hallucinations (seeing or hearing things that are not really there)
- memory problems
- obsessive-compulsive symptoms
- restlessness
- sleep walking
- stuttering
- suicidal thoughts and actions (including suicide)
- tremor
- trouble sleeping
- uncontrolled muscle movements

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 inflammation of the lining of the nose (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 have an asthma attack, you should follow the instructions your healthcare provider gave you for treating asthma attacks.
2. Prevent exercise-induced asthma in people 6 years of age and older.
3. Help control the symptoms of allergic rhinitis such as sneezing, stuffy nose, runny nose, and itching of the nose. SINGULAIR is used to treat the following in people who have already taken other medicines that did not work well enough or in people who could not tolerate other medicines:
 - 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.

Do not take SINGULAIR if you are allergic to any of its ingredients. See the end of this Medication Guide for a complete list of the ingredients in SINGULAIR.

Before taking SINGULAIR, tell your healthcare provider about all your medical conditions, including if you:

- are allergic to aspirin.
- have phenylketonuria. SINGULAIR chewable tablets contain aspartame, a source of phenylalanine.
- have or have had mental health problems.
- are pregnant or plan to become pregnant. Talk to your healthcare provider if you are pregnant or plan to become pregnant, SINGULAIR may not be right for you.
- are breastfeeding or plan to breastfeed. 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 over the counter 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:

- Read the detailed **Instructions for Use** that comes with SINGULAIR oral granules.
- 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.**

- Stop taking SINGULAIR and tell your healthcare provider right away if you or your child have any unusual changes in behavior or thinking.
- You can take SINGULAIR with food or without food. See the section "**How can I give SINGULAIR oral granules to my child?**" in the **Instructions for Use** 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 healthcare provider right away.

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.
- Always have your rescue inhaler medicine with you for asthma attacks.
- Continue to take your other asthma medicines as prescribed unless your healthcare provider tells you to change how you take these medicines.

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

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

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, including:

- See "**What is the most important information I should know about SINGULAIR?**"
- **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 sometimes 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 | ◦ rash |
| ◦ a flu-like illness | ◦ severe inflammation (pain and swelling) of the sinuses (sinusitis) |

The most common side effects of SINGULAIR include:

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

These are not all the possible side effects of SINGULAIR. Call your doctor 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 room temperature between 68°F to 77°F (20°C to 25°C).
- Keep SINGULAIR in the package it comes in.
- Keep SINGULAIR in a dry place and keep it away from light.
- **Keep SINGULAIR and all medicines out of reach of children.**

General information about the safe and effective use of SINGULAIR.

Medicines are sometimes prescribed for purposes other than those listed in a Medication Guide. 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.

You can ask your pharmacist or healthcare provider for information about SINGULAIR that is written for health professionals.

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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This Medication Guide has been approved by the U.S. Food and Drug Administration

Revised: 6/2021

INSTRUCTIONS FOR USE**SINGULAIR® (SING-u-lair)
(montelukast sodium)
oral granules**

This Instructions for Use contains information on how to use SINGULAIR oral granules.

Important Information:

- Before giving a dose of SINGULAIR oral granules, read this Instructions for Use to be sure you prepare and give the oral granules correctly.
- Give SINGULAIR oral granules to your child exactly as instructed by your healthcare provider.
- Stop giving SINGULAIR and tell your healthcare provider right away if your child has any unusual changes in behavior or thinking.
- Continue to give your child their asthma medicines as prescribed, unless your healthcare provider tells you to change how you give these medicines.
- You can give SINGULAIR oral granules with food or without food.

How can I give SINGULAIR oral granules to my child?

- **Do not** open the packet until ready to use.
- There are different ways you can give SINGULAIR 4-mg oral granules. You should choose the best method for your child:
 - right into the mouth
 - dissolved in 1 teaspoonful (5 mL) of cold or room temperature baby formula or breast milk
 - 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 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.

How should I store SINGULAIR?

- Store SINGULAIR at room temperature between 68°F to 77°F (20°C to 25°C).
- Keep SINGULAIR in the package it comes in.
- Keep SINGULAIR in a dry place and keep it away from light.
- **Keep SINGULAIR and all medicines out of the reach of children.**

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For more information, call 1-844-674-3200

This Instructions for Use has been approved by the U.S. Food and Drug Administration
Revised: June 2021

PRINCIPAL DISPLAY PANEL - 4 mg Packet Carton

**Singulair® 4 mg
(Montelukast Sodium)
ORAL GRANULES**

NDC 78206-171-01

For Pediatric Patients 6 months to 5 years of age.

Dist. by: Organon LLC, a subsidiary of
ORGANON & Co.,
Jersey City, NJ 07302, USA

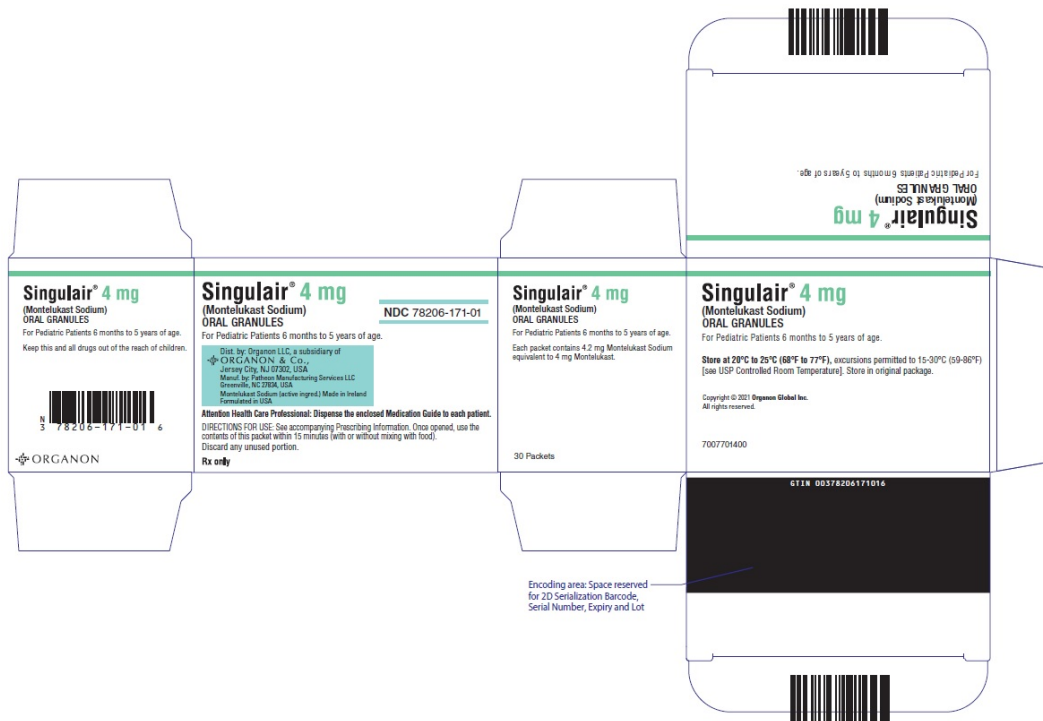
Manuf. by: Patheon Manufacturing Services LLC
Greenville, NC 27834, USA

Montelukast Sodium (active ingred.) Made in Ireland
Formulated in USA

Attention Health Care Professional: Dispense the enclosed Medication Guide to each patient.

DIRECTIONS FOR USE: See accompanying Prescribing Information. Once opened, use the contents of this packet within 15 minutes (with or without mixing with food). Discard any unused portion.

Rx only



PRINCIPAL DISPLAY PANEL - 4 mg Tablet Bottle Label

NDC 78206-170-01

**Singulair®
(Montelukast Sodium)
CHEWABLE Tablets**

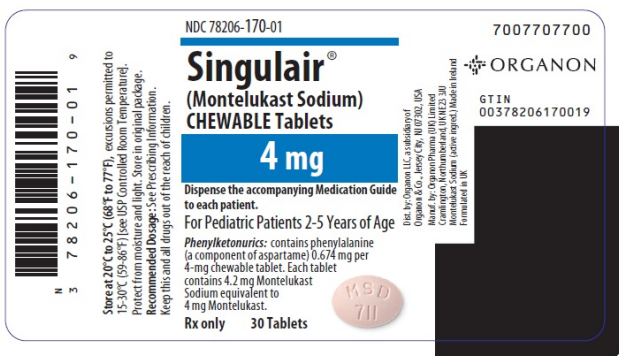
4 mg

Dispense the accompanying Medication Guide to each patient.

For Pediatric Patients 2-5 Years of Age

Phenylketonurics: contains phenylalanine (a component of aspartame) 0.674 mg per 4-mg chewable tablet. Each tablet contains 4.2 mg Montelukast Sodium equivalent to 4 mg Montelukast.

Rx only 30 Tablets



← Encoding area:
Space reserved for 2D Serialization Barcode,
Serial Number, Expiry and Lot

PRINCIPAL DISPLAY PANEL - 5 mg Tablet Bottle Label

NDC 78206-173-01

**Singulair®
(Montelukast Sodium)**

CHEWABLE Tablets

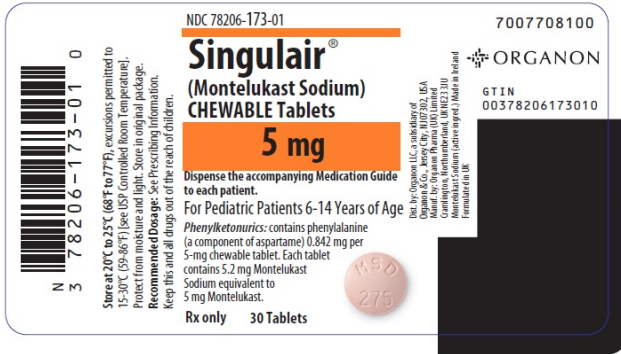
5 mg

Dispense the accompanying Medication Guide to each patient.

For Pediatric Patients 6-14 Years of Age

Phenylketonurics: contains phenylalanine (a component of aspartame) 0.842 mg per 5-mg chewable tablet. Each tablet contains 5.2 mg Montelukast Sodium equivalent to 5 mg Montelukast.

Rx only 30 Tablets



Encoding area:
Space reserved for 2D Serialization Barcode, Serial Number, Expiry and Lot

PRINCIPAL DISPLAY PANEL - 10 mg Tablet Bottle Label

NDC 78206-172-01

**Singulair®
(Montelukast Sodium)
Tablets**

10 mg

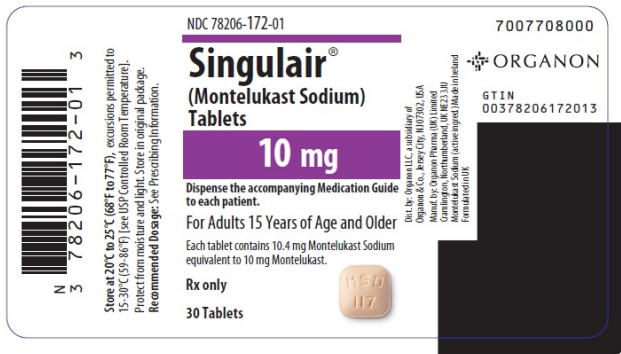
Dispense the accompanying Medication Guide to each patient.

For Adults 15 Years of Age and Older

Each tablet contains 10.4 mg Montelukast Sodium equivalent to 10 mg Montelukast.

Rx only

30 Tablets



Encoding area:
Space reserved for 2D Serialization Barcode, Serial Number, Expiry and Lot

SINGULAIR
montelukast sodium granule

Product Information				
Product Type	HUMAN PRESCRIPTION DRUG	Item Code (Source)	NDC:78206-171	
Route of Administration	ORAL			
Active Ingredient/Active Moiety				
Ingredient Name		Basis of Strength	Strength	
MONTELUKAST SODIUM (UNII: U1O3J18SFL) (MONTELUKAST - UNII:MHM278SD3E)		MONTELUKAST	4 mg	
Inactive Ingredients				
Ingredient Name			Strength	
MANNITOL (UNII: 3OWL53L36A)				
HYDROXYPROPYL CELLULOSE (1600000 WAMW) (UNII: RFW2ET671P)				
MAGNESIUM STEARATE (UNII: 70097M6I30)				
Product Characteristics				
Color	WHITE (white)	Score		
Shape		Size		
Flavor		Imprint Code		
Contains				
Packaging				
#	Item Code	Package Description	Marketing Start Date	Marketing End Date
1	NDC:78206-171-01	30 in 1 CARTON	06/01/2021	
1		1 in 1 PACKET; Type 0: Not a Combination Product		
Marketing Information				
Marketing Category	Application Number or Monograph Citation	Marketing Start Date	Marketing End Date	
NDA	NDA021409	06/01/2021		

SINGULAIR				
montelukast sodium tablet, chewable				
Product Information				
Product Type	HUMAN PRESCRIPTION DRUG	Item Code (Source)	NDC:78206-170	
Route of Administration	ORAL			
Active Ingredient/Active Moiety				
Ingredient Name		Basis of Strength	Strength	
MONTELUKAST SODIUM (UNII: U1O3J18SFL) (MONTELUKAST - UNII:MHM278SD3E)		MONTELUKAST	4 mg	
Inactive Ingredients				
Ingredient Name			Strength	
MANNITOL (UNII: 3OWL53L36A)				
MICROCRYSTALLINE CELLULOSE (UNII: OP1R32D61U)				
HYDROXYPROPYL CELLULOSE (1600000 WAMW) (UNII: RFW2ET671P)				
FERRIC OXIDE RED (UNII: 1K09F3G675)				
CROSCARMELLOSE SODIUM (UNII: M28OL1HH48)				
ASPARTAME (UNII: Z0H242BBR1)				
MAGNESIUM STEARATE (UNII: 70097M6I30)				

Product Characteristics				
Color	PINK	Score	no score	
Shape	OVAL	Size	11mm	
Flavor	CHERRY	Imprint Code	MSD;711;SINGULAIR	
Contains				
Packaging				
#	Item Code	Package Description	Marketing Start Date	Marketing End Date
1	NDC:78206-170-01	30 in 1 BOTTLE; Type 0: Not a Combination Product	06/01/2021	
Marketing Information				
Marketing Category	Application Number or Monograph Citation	Marketing Start Date	Marketing End Date	
NDA	NDA020830	06/01/2021		

SINGULAIR				
montelukast sodium tablet, chewable				
Product Information				
Product Type	HUMAN PRESCRIPTION DRUG	Item Code (Source)	NDC:78206-173	
Route of Administration	ORAL			
Active Ingredient/Active Moiety				
Ingredient Name	Basis of Strength	Strength		
MONTELUKAST SODIUM (UNII: U1O3J18SFL) (MONTELUKAST - UNII:MHM278SD3E)	MONTELUKAST	5 mg		
Inactive Ingredients				
Ingredient Name	Strength			
MANNITOL (UNII: 3OWL53L36A)				
MICROCRYSTALLINE CELLULOSE (UNII: OP1R32D61U)				
HYDROXYPROPYL CELLULOSE (1600000 WAMW) (UNII: RFW2ET671P)				
FERRIC OXIDE RED (UNII: 1K09F3G675)				
CROSCARMELLOSE SODIUM (UNII: M28OL1HH48)				
ASPARTAME (UNII: Z0H242BBR1)				
MAGNESIUM STEARATE (UNII: 70097M6I30)				
Product Characteristics				
Color	PINK	Score	no score	
Shape	ROUND	Size	10mm	
Flavor	CHERRY	Imprint Code	MSD;275;SINGULAIR	
Contains				
Packaging				
#	Item Code	Package Description	Marketing Start Date	Marketing End Date
1	NDC:78206-173-01	30 in 1 BOTTLE; Type 0: Not a Combination Product	06/01/2021	
Marketing Information				
Marketing Category	Application Number or Monograph Citation	Marketing Start Date	Marketing End Date	
NDA	NDA020830	06/01/2021		

SINGULAIR

montelukast sodium tablet, film coated

Product Information

Product Type	HUMAN PRESCRIPTION DRUG	Item Code (Source)	NDC:78206-172
Route of Administration	ORAL		

Active Ingredient/Active Moiety

Ingredient Name	Basis of Strength	Strength
MONTELUKAST SODIUM (UNII: U1O3J18SFL) (MONTELUKAST - UNII:MHM278SD3E)	MONTELUKAST	10 mg

Inactive Ingredients

Ingredient Name	Strength
MICROCRYSTALLINE CELLULOSE (UNII: OP1R32D61U)	
LACTOSE MONOHYDRATE (UNII: EWQ57Q8I5X)	
CROSCARMELLOSE SODIUM (UNII: M28OL1HH48)	
HYDROXYPROPYL CELLULOSE (1600000 WAMW) (UNII: RFW2ET671P)	
MAGNESIUM STEARATE (UNII: 70097M6I30)	
HYPROMELLOSE, UNSPECIFIED (UNII: 3NXW29V3WO)	
TITANIUM DIOXIDE (UNII: 15FIX9V2JP)	
FERRIC OXIDE RED (UNII: 1K09F3G675)	
FERRIC OXIDE YELLOW (UNII: EX438O2MRT)	
CARNAUBA WAX (UNII: R12CBM0EIZ)	

Product Characteristics

Color	BROWN (beige)	Score	no score
Shape	SQUARE (rounded square-shaped)	Size	8mm
Flavor		Imprint Code	MSD;117;SINGULAIR
Contains			

Packaging

#	Item Code	Package Description	Marketing Start Date	Marketing End Date
1	NDC:78206-172-01	30 in 1 BOTTLE; Type 0: Not a Combination Product	06/01/2021	
2	NDC:78206-172-02	90 in 1 BOTTLE; Type 0: Not a Combination Product	06/01/2021	

Marketing Information

Marketing Category	Application Number or Monograph Citation	Marketing Start Date	Marketing End Date
NDA	NDA020829	06/01/2021	

Labeler - Organon LLC (117494753)

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Organon LLC