PRODUCT MONOGRAPH

# SINGULAIR®

montelukast (as montelukast sodium)

10 mg tablets

4 and 5 mg chewable tablets

4 mg granules per packet for oral use

Leukotriene Receptor Antagonist

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**SINGULAIR®**
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(as montelukast sodium)

Montelukast chewable tablets 4 mg and 5 mg
(as montelukast sodium)

Montelukast granules 4 mg
(as montelukast sodium)

## PART I: HEALTH PROFESSIONAL INFORMATION

### SUMMARY PRODUCT INFORMATION

| Route of Administration | Dosage Form / Strength | Non-Medicinal Ingredients |
|---|---|---|
| oral | tablets/ 10 mg | 10 mg film-coated tablet: carnauba wax, croscarmellose sodium, hydroxypropyl cellulose, hydroxypropyl methylcellulose, lactose monohydrate (89.3 mg), magnesium stearate, microcrystalline cellulose, red ferric oxide, titanium dioxide, and yellow ferric oxide. |
| | chewable tablets/ 4 mg, 5 mg | 4 mg and 5 mg chewable tablet: aspartame, cherry flavor, croscarmellose sodium, hydroxypropyl cellulose, magnesium stearate, mannitol, and microcrystalline cellulose, and red ferric oxide. |
| | granules/ 4 mg | 4 mg packet of oral granules: hydroxypropyl cellulose, magnesium stearate and mannitol.<br><br>Phenylketonurics: SINGULAIR® 4 mg and 5 mg chewable tablets contain 0.674 and 0.842 mg phenylalanine, respectively. |

### INDICATIONS AND CLINICAL USE

SINGULAIR® (montelukast sodium) is indicated in adult and pediatric patients 2 years of age and older for the prophylaxis and chronic treatment of asthma, including prevention of day- and

night-time symptoms, the treatment of acetylsalicylic acid (ASA)-sensitive asthmatic patients, and the prevention of exercise-induced bronchoconstriction.

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

In patients who continue to experience asthma symptoms, SINGULAIR® can be an additional treatment option following initial management with an "as needed" short-acting beta-agonist (SABA), an inhaled corticosteroid, or inhaled corticosteroid together with a long-acting beta agonist.

In adults, SINGULAIR® can be a treatment option after "as needed" SABAs if patients remain symptomatic and cannot or will not use an inhaler device or would prefer not to be treated with an inhaled corticosteroid.

In children, SINGULAIR® can be a treatment option after "as needed" SABAs if patients remain symptomatic and cannot appropriately use an inhaler device.

SINGULAIR® can be a treatment option in patients who experience exercise-induced bronchoconstriction.

SINGULAIR® is indicated for the relief of symptoms of seasonal allergic rhinitis in patients 15 years old or older. SINGULAIR® should be considered when other treatments are not effective or not tolerated.

## CONTRAINDICATIONS

- Patients who are hypersensitive to this drug or to any ingredient in the formulation. For a complete listing, see the DOSAGE FORMS, COMPOSITION AND PACKAGING section of the product monograph.

## WARNINGS AND PRECAUTIONS

### Information to be Provided to the Patient

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

**Chewable Tablets**
**Phenylketonurics:** Phenylketonuric patients should be informed that the 4 mg and the 5 mg chewable tablets contains phenylalanine (a component of aspartame) 0.674 and 0.842 mg per 4 mg and 5 mg chewable tablet.

**General**
The efficacy of oral SINGULAIR® for the treatment of acute asthma attacks has not been established. Therefore, SINGULAIR® should not be used to treat acute asthma attacks. Patients should be advised to have appropriate rescue medication available.

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

When SINGULAIR® is prescribed for the prevention of exercise-induced bronchoconstriction, patients should be advised to always have readily available appropriate rescue medication.

Patients with known acetylsalicylic acid (ASA) sensitivity should continue avoidance of ASA or non-steroidal anti-inflammatory agents while taking SINGULAIR®. Although SINGULAIR® is effective in improving airway function in asthmatic patients with documented ASA sensitivity, it has not been shown to truncate bronchoconstrictor response to ASA and other non-steroidal anti-inflammatory drugs in ASA-sensitive asthmatic patients.

**Neuropsychiatric post-marketing events**
Neuropsychiatric events have been reported in adult, adolescent, and paediatric patients taking SINGULAIR®. Post-market reports with SINGULAIR® use include agitation, aggressive behaviour or hostility, anxiousness, depression, disorientation, disturbance in attention, dream abnormalities, hallucinations, insomnia, irritability, memory impairment, restlessness, somnambulism, suicidal thinking and behaviour (including suicide), and tremor. The clinical details of some post-marketing reports involving SINGULAIR® appear consistent with a drug-induced effect.

Physicians should discuss these adverse experiences with their patients and /or caregivers. Patients and/or caregivers should be instructed to notify their physician if these changes occur. Physicians should carefully evaluate the risks and benefits of continuing treatment with SINGULAIR® if such events occur.

**Eosinophilic Conditions**
In rare cases, 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 reported as occurring both with and without steroid withdrawal or reduction. Physicians should be alert to eosinophilia, vasculitic rash, arthralgia, worsening pulmonary symptoms, cardiac complications, and/or neuropathy presenting in their patients (see ADVERSE REACTIONS). A causal association between SINGULAIR® and these underlying conditions has not been established.

**Hepatic/Biliary**
**Hepatic Insufficiency:** Patients with mild-to-moderate hepatic insufficiency and clinical evidence of cirrhosis had evidence of decreased metabolism of montelukast resulting in approximately 41% higher mean montelukast area under the plasma concentration curve (AUC) following a single 10-mg dose. The elimination of montelukast is slightly prolonged compared with that in healthy subjects (mean half-life, 7.4 hours). No dosage adjustment is required in patients with mild-to-moderate hepatic insufficiency. There are no clinical data in patients with severe hepatic insufficiency (Child-Pugh score >9).

**Post-Marketing Surveillance:** In post-marketing surveillance, elevations in serum transaminases have been reported in patients who were treated with SINGULAIR®. These events were usually asymptomatic and transient. Serious hepatic adverse events such as jaundice have been reported although no deaths or liver transplantations have been attributed to the use of SINGULAIR® (see ADVERSE REACTIONS).

**Special Populations**
**Pregnant Women:** SINGULAIR® has not been studied in pregnant women. SINGULAIR® should be used during pregnancy only if clearly needed.

During worldwide marketing experience, congenital limb defects have been rarely reported in the offspring of women being treated with SINGULAIR® during pregnancy. Most of these women were also taking other asthma medications during their pregnancy. A causal relationship between these events and SINGULAIR® has not been established.

**Nursing Women:** It is not known if SINGULAIR® is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when SINGULAIR® is given to a nursing mother.

**Pediatrics (<15 years):** Safety and efficacy of SINGULAIR® have been established in adequate and well-controlled studies in pediatric patients with asthma 6 to 14 years of age. Safety and efficacy profiles in this age group are similar to that seen in adults (see ADVERSE REACTIONS, Clinical Trial Adverse Drug Reactions and SCIENTIFIC INFORMATION, CLINICAL TRIALS).

The safety of SINGULAIR® 4 mg chewable tablets in pediatric patients 2 to 5 years of age with asthma has been demonstrated in a 12-week double-blind, placebo-controlled study in 689 patients (see ACTION AND CLINICAL PHARMACOLOGY and also ADVERSE REACTIONS). Efficacy of SINGULAIR® in this age group is based on extrapolation of the demonstrated efficacy in adults 15 years of age and older and pediatric patients 6 to 14 years of age with asthma, and that the disease course, pathophysiology and the drug's effect are substantially similar among these populations. The findings of the exploratory efficacy evaluations along with pharmacokinetics and extrapolation of 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 (see ACTION AND CLINICAL PHARMACOLOGY).

SINGULAIR® has been evaluated for safety in a 6-week, placebo-controlled clinical study in 175 asthma patients 6 months to 2 years of age receiving 4 mg as oral granules daily in the evening. There were no safety concerns compared to older pediatric patients (see ADVERSE REACTIONS, Pediatric Patients 6 Months to 2 Years of Age with Asthma). Since this study was not powered to detect between group differences in efficacy endpoints, the efficacy of SINGULAIR® could not be determined in this age group.

**Geriatrics (>65 years of age):** In clinical studies, there were no age-related differences in the efficacy or safety profiles of SINGULAIR®.

**Effects on Ability to Drive and Use Machines**
There is no evidence that SINGULAIR® affects the ability to drive and use machines.

## ADVERSE REACTIONS

### Adverse Drug Reaction Overview
SINGULAIR® has been generally well tolerated. Side effects, which usually were mild, generally did not require discontinuation of therapy. The overall incidence of side effects reported with SINGULAIR® was comparable to placebo.

### Clinical Trial Adverse Drug Reactions
**Adults 15 Years of Age and Older with Asthma**
SINGULAIR® has been evaluated for safety in approximately 2600 adult patients 15 years of age and older in clinical studies. In two similarly designed, 12-week placebo-controlled clinical studies, the only adverse experiences reported as drug-related in ≥1% of patients treated with SINGULAIR® and at a greater incidence than in patients treated with placebo were abdominal pain and headache. The incidences of these events were not significantly different in the two treatment groups.

In placebo-controlled clinical trials, the following adverse experiences reported with SINGULAIR® occurred in ≥1% of patients and at an incidence greater than or equal to that in patients treated with placebo, regardless of drug relationship:

**Adverse Experiences Occurring in ≥1% of Patients with an Incidence ≥ to that in Patients Treated with Placebo, Regardless of Drug Relationship**

| | SINGULAIR® 10 mg/day (%) (n=1955) | Placebo (%) (n=1180) |
|---|---|---|
| **Body As A Whole** | | |
| Asthenia/fatigue | 1.8 | 1.2 |
| Fever | 1.5 | 0.9 |
| Pain, abdominal | 2.9 | 2.5 |
| Trauma | 1.0 | 0.8 |
| **Digestive System Disorders** | | |
| Diarrhea | 3.1 | 3.1 |
| Dyspepsia | 2.1 | 1.1 |
| Gastroenteritis, infectious | 1.5 | 0.5 |
| Pain, dental | 1.7 | 1.0 |
| **Nervous System/Psychiatric** | | |
| Dizziness | 1.9 | 1.4 |
| Headache | 18.4 | 18.1 |
| Insomnia | 1.3 | 1.3 |
| **Respiratory System Disorders** | | |
| Congestion, nasal | 1.6 | 1.3 |
| Cough | 2.7 | 2.4 |
| Influenza | 4.2 | 3.9 |
| **Skin/Skin Appendages Disorder** | | |
| Rash | 1.6 | 1.2 |
| **Laboratory Adverse Experiences*** | | |
| ALT increased | 2.1 | 2.0 |
| AST increased | 1.6 | 1.2 |
| Pyuria | 1.0 | 0.9 |

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

Cumulatively, 544 patients were treated with SINGULAIR® for at least 6 months, 253 for one year and 21 for two years in clinical trials. With prolonged treatment, the adverse experience profile did not change.

## Pediatric Patients 6 to 14 Years of Age with Asthma

SINGULAIR® has been evaluated for safety in approximately 475 pediatric patients 6 to 14 years of age. Cumulatively, 263 pediatric patients 6 to 14 years of age were treated with SINGULAIR® for at least 3 months, 164 for 6 months or longer in clinical trials. The safety profile in pediatric patients is generally similar to the adult safety profile and to placebo. With prolonged treatment, the adverse experience profile did not change.

In a 56-week double-blind study evaluating growth rate in pediatric patients 6 to 8 years of age receiving SINGULAIR®, the following events not previously observed with the use of SINGULAIR® occurred with a frequency ≥2% and more frequently than in pediatric patients who received placebo, regardless of causality assessment: atopic dermatitis, myopia, rhinitis (infective), skin infection, tooth infection, headache, varicella, gastroenteritis and acute bronchitis.

**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 a 12-week, placebo-controlled clinical study, the only adverse experience reported as drug-related in >1% of patients treated with SINGULAIR® and at a greater incidence than in patients treated with placebo was thirst. The incidence of thirst was not significantly different in the two treatment groups. Cumulatively, 363 patients 2 to 5 years of age were treated with SINGULAIR®. Of these, 338 were continuously treated for at least 6 months and 256 for >1 year. The safety profile of SINGULAIR® in pediatric patients 2 to 5 years of age is generally similar to the safety profiles in adults 15 years of age and older in pediatric patients 6 to 14 years of age, and to placebo. With prolonged treatment, the adverse experience profile did not change.

**Pediatric Patients 6 Months to 2 Years of Age with Asthma**
SINGULAIR® has been evaluated in 175 pediatric patients 6 months to 2 years of age. In a 6-week, placebo-controlled clinical study, the adverse experiences reported as drug related in >1% of patients treated with SINGULAIR® and at a greater incidence than in patients treated with placebo were diarrhea, hyperkinesia, asthma, eczematous dermatitis and rash. The incidences of these adverse experiences were not significantly different in the two treatment groups.

**Adults 15 Years of Age and Older with Seasonal Allergic Rhinitis**
SINGULAIR® has been evaluated in 1751 adult patients 15 years of age and older for the treatment of seasonal allergic rhinitis in clinical studies. SINGULAIR® administered once daily at bedtime was generally well tolerated with a safety profile similar to that of placebo. In similar designed, 2-week, placebo-controlled, clinical studies, no adverse experience reported as drug related in ≥1% of patients treated with SINGULAIR® and at a greater incidence than in patients treated with placebo were observed. The incidence of somnolence was similar to that of placebo.

**Post-Market Adverse Drug Reactions**
The following adverse drug reactions have been reported very rarely (<1/10,000) in post marketing use of SINGULAIR®. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

**Infections and Infestations:** upper respiratory infection

**Blood and lymphatic system disorders:** increased bleeding tendency, thrombocytopenia.

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

**Psychiatric disorders:** agitation including aggressive behavior or hostility (including temper tantrums in pediatric patients), very rarely reported as serious; anxiousness, depression, disorientation, disturbance in attention, irritability, memory impairment, restlessness, somnambulism, sleep disorders including dream abnormalities and insomnia, suicidal thinking and behavior (suicidality), tic, tremor, and visual hallucinations.

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

**Cardiac disorders:** palpitations

**Respiratory, thoracic and mediastinal disorders:** epistaxis, pulmonary eosinophilia

**Gastrointestinal disorders:** diarrhea, dyspepsia, nausea, vomiting

**Skin and subcutaneous tissue disorders:** angioedema, bruising, erythema multiforme, erythema nodosum, pruritus, rash, urticaria

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

**Hepato-biliary disorders:** increased ALT, AST, and isolated cases of hepatitis, (including cholestatic, hepatocellular, and mixed-pattern liver injury). In post-marketing surveillance, elevations in serum transaminases have been reported in patients who were treated with SINGULAIR®. These events were usually asymptomatic and transient. Serious hepatic adverse events such as jaundice have been reported although no deaths or liver transplantations have been attributed to the use of SINGULAIR® (see WARNINGS AND PRECAUTIONS).

**Renal and urinary disorders:** enuresis in children

**General disorders:** asthenia/fatigue, edema, pyrexia

**Eosinophilic Conditions**
In rare cases, 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 reported as occurring both with and without steroid withdrawal or reduction. Physicians should be alert to eosinophilia, vasculitic rash, arthralgia, 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 WARNINGS AND PRECAUTIONS, Eosinophilic Conditions).

## DRUG INTERACTIONS

**Overview**
SINGULAIR® may be administered with other therapies routinely used in the prophylaxis and chronic treatment of asthma, and in the treatment of allergic rhinitis (see Drug-Drug Interactions).

Although additional specific interaction studies were not performed, SINGULAIR® was used concomitantly with a wide range of commonly prescribed drugs in clinical studies without evidence of clinical adverse interactions. These medications included thyroid hormones, sedative hypnotics, nonsteroidal anti-inflammatory agents, benzodiazepines and decongestants.

*In vitro* studies have shown that montelukast is a potent inhibitor of CYP 2C8. However, data from a clinical drug-drug interaction study involving montelukast and rosiglitazone (a probe substrate representative of drugs primarily metabolized by CYP 2C8) in 12 healthy individuals demonstrated that the pharmacokinetics of rosiglitazone are not altered when the drugs are coadministered, indicating that montelukast does not inhibit CYP 2C8 *in vivo*. Therefore, montelukast is not anticipated to alter the metabolism of drugs metabolized by this enzyme (e.g., paclitaxel, rosiglitazone, repaglinide). 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.

*In vitro* studies have shown that montelukast is a substrate of CYP 2C8, 2C9, and 3A4. Data from a clinical drug-drug interaction study involving montelukast and gemfibrozil (an inhibitor of both CYP 2C8 and 2C9) demonstrated that gemfibrozil increased the systemic exposure of montelukast by 4.4-fold. Based on clinical experience, no dosage adjustment of montelukast is required upon co-administration with gemfibrozil (see OVERDOSAGE). Based on *in vitro* data, clinically important drug interactions with other known inhibitors of CYP 2C8 (e.g., trimethoprim) are not anticipated. Co-administration of montelukast with itraconazole, a strong CYP 3A4 inhibitor, resulted in no significant increase in the systemic exposure of montelukast. In addition, co-administration of itraconazole, gemfibrozil and montelukast did not further increase the systematic exposure of montelukast.

**Drug-Drug Interactions**

Montelukast 10 mg once daily to pharmacokinetic steady state:

- did not cause clinically significant changes in the kinetics of an intravenous dose of theophylline.
- did not change the pharmacokinetic profile of warfarin or influence the effect of a single 30 mg oral dose of warfarin on prothrombin time or INR (International Normalized Ratio).
- did not change the pharmacokinetic profile or urinary excretion of immunoreactive digoxin.
- did not change the plasma concentration profile of terfenadine or its carboxylated metabolite and does not prolong the QTc interval following co-administration with terfenadine 60 mg twice daily.

Montelukast at doses of ≥100 mg daily 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 μg.
- did not cause any clinically significant change in plasma profiles of either prednisone and prednisolone following administration of either oral prednisone or IV prednisolone.

Phenobarbital, which induces hepatic metabolism, decreased the AUC of montelukast approximately 40% following a single 10 mg dose of montelukast; no dosage adjustment for SINGULAIR® is recommended.

## DOSAGE AND ADMINISTRATION

### Dosing Considerations

The safety and efficacy of SINGULAIR® was demonstrated in clinical trials where it was administered in the evening without regard to the time of food ingestion. There have been no clinical trials evaluating the relative efficacy of morning versus evening dosing. However, no difference in pharmacokinetics was noted between morning and evening dosing.

### General Recommendations

The therapeutic effect of SINGULAIR® on parameters of asthma occurs within one day. SINGULAIR® tablets, chewable tablets, and oral granules can be taken with or without food. Patients should be advised to continue taking SINGULAIR® while their asthma is controlled, as well as during periods of worsening asthma.

### Therapy with SINGULAIR® in Relation to Other Treatments for Asthma

SINGULAIR® can also be added to a patient's existing treatment regimen.

**Bronchodilator Treatments:** SINGULAIR® can be added to the treatment regimen of patients who are not adequately controlled on bronchodilator alone. When a clinical response is evident (usually after the first dose), the patient's bronchodilator therapy can be reduced as tolerated.

**Inhaled Corticosteroids:** Treatment with SINGULAIR® provides additional clinical benefit to patients treated with inhaled corticosteroids. A reduction in the corticosteroid dose can be made as tolerated. The dose should be reduced gradually with medical supervision. In some patients, the dose of inhaled corticosteroids can be tapered off completely. It remains to be determined whether the withdrawal from inhaled corticosteroids can be maintained for extended periods, or possibly indefinitely. SINGULAIR® should not be abruptly substituted for inhaled corticosteroids.

**Oral Corticosteroids:** Limited data suggest that SINGULAIR® may provide additional clinical benefit in patients currently treated with oral corticosteroids.

### Recommended Dose and Dosage Adjustment

**Adults 15 Years of Age and Older with Asthma and/or Seasonal Allergic Rhinitis**

The dosage for adults 15 years of age and older is one 10 mg tablet daily to be taken in the evening.

**Pediatric Patients 6 to 14 Years of Age with Asthma**

The dosage for pediatric patients 6 to 14 years of age is one 5 mg chewable tablet daily to be taken in the evening. No dosage adjustment within this age group is necessary.

**Pediatric Patients 2 to 5 Years of Age with Asthma**
The dosage for pediatric patients 2 to 5 years of age is one 4 mg chewable tablet daily to be taken in the evening or one packet of 4 mg granules to be taken orally once a day in the evening. No dosage adjustment within this age group is necessary.

**Special Population**
No dosage adjustment is necessary for the elderly, for patients with renal insufficiency, or mild to moderate hepatic impairment, or for patients of either gender.

**Administration of Oral Granules**
SINGULAIR® oral granules can be administered either directly in the mouth, or mixed with a spoonful of cold or room temperature soft food (e.g., applesauce). The packet should not be opened until ready to use. After opening the packet, the full dose of SINGULAIR® oral granules must be administered immediately (within 15 minutes). If mixed with food, SINGULAIR® oral granules must not be stored for future use. SINGULAIR® oral granules are not intended to be dissolved in liquid for administration. However, liquids may be taken subsequent to administration.

**Missed Dose**
SINGULAIR® should be taken as prescribed. However, if a dose is missed, the usual schedule should be resumed as prescribed.

## OVERDOSAGE

For management of a suspected drug overdose, contact your regional Poison Control Centre.

No specific information is available on the treatment of overdosage with SINGULAIR®. In chronic asthma studies, SINGULAIR® has been administered at doses up to 200 mg/day to adult patients for 22 weeks and in short-term studies, up to 900 mg/day to patients for approximately one week without clinically important adverse experiences.

There have been reports of acute overdosage in post-marketing experience and clinical studies with SINGULAIR®. These include reports in adults and children with a dose as high as 1000 mg. The clinical and laboratory findings observed were consistent with the safety profile in adults and pediatric patients. There were no adverse experiences in the majority of overdosage reports.

The adverse experiences were consistent with the safety profile of SINGULAIR® and most frequently included abdominal pain, somnolence, thirst, headache, vomiting, psychomotor hyperactivity, and less frequently convulsion.

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

## ACTION AND CLINICAL PHARMACOLOGY

### Mechanism of Action

The cysteinyl leukotrienes ($LTC_4$, $LTD_4$, $LTE_4$ ), are potent inflammatory eicosanoids released from various cells including mast cells and eosinophils. These important pro-asthmatic mediators bind to cysteinyl leukotriene (CysLT) receptors. The CysLT type-1 ($CysLT_1$) receptor is found in the human airway (including airway smooth muscle cells and airway macrophages) and on other pro-inflammatory cells (including eosinophils and certain myeloid stem cells). CysLTs have been correlated with the pathophysiology of asthma and allergic rhinitis. In asthma, leukotriene-mediated effects include a number of airway actions, including bronchoconstriction, mucous secretion, vascular permeability, and eosinophil recruitment. In allergic rhinitis, CysLTs are released from the nasal mucosa after allergen exposure during both early- and late-phase reactions and are associated with symptoms of allergic rhinitis. Intranasal challenge with CysLTs has been shown to increase nasal airway resistance and symptoms of nasal obstruction.

SINGULAIR® has not been assessed in intranasal challenge studies. The clinical relevance of intranasal challenge studies is unknown.

Montelukast is an orally active compound that improves parameters of asthmatic inflammation. Based on biochemical and pharmacological bioassays, it binds with high affinity and selectivity to the $CysLT_1$ receptor (in preference to other pharmacologically important airway receptors such as the prostanoid, cholinergic, or β-adrenergic receptor). Montelukast potently inhibits physiologic actions of $LTC_4$, $LTD_4$, and $LTE_4$ at the $CysLT_1$ receptor without any agonist activity.

### Pharmacodynamics

Montelukast causes inhibition of airway cysteinyl leukotriene receptors as demonstrated by the ability to inhibit bronchoconstriction due to inhaled $LTD_4$ in asthmatic patients. Doses as low as 5 mg cause substantial blockage of $LTD_4$-induced bronchoconstriction. In a placebo-controlled, crossover study (n=12), SINGULAIR® inhibited early- and late-phase bronchoconstriction due to antigen challenge by 75% and 57% respectively.

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

Clinical studies in adults 15 years of age and older demonstrated there is no additional clinical benefit to montelukast doses above 10 mg once daily. This was shown in two chronic asthma studies using doses up to 200 mg once daily and in one exercise challenge study using doses up to 50 mg, evaluated at the end of the once daily dosing interval.

The effect of SINGULAIR® on eosinophils in the peripheral blood was examined in clinical trials in adults and pediatric (6 to 14 years of age) asthmatic patients. SINGULAIR® decreased mean peripheral blood eosinophils approximately 13% to 15% from baseline compared with placebo over the double-blind treatment periods.

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

There have been no clinical trials evaluating the relative efficacy of morning versus evening dosing. Although the pharmacokinetics of montelukast are similar whether dosed in the morning or the evening, efficacy was demonstrated in clinical trials in adults and pediatric patients in which montelukast was administered in the evening without regard to the time of food ingestion.

**Pharmacokinetics**

**Absorption:** Montelukast is rapidly absorbed following oral administration. For the 10 mg film-coated tablet, the mean peak plasma concentration ($C_{max}$) is achieved in 3 to 4 hours ($T_{max}$) after administration in adults in the fasted state. The mean oral bioavailability is 64%. The oral bioavailability and $C_{max}$ are neither influenced by a standard meal in the morning nor by a high fat snack in the evening. Safety and efficacy were demonstrated in clinical trials where the 4 mg chewable tablet, the 5 mg chewable tablet, and the 10 mg film-coated tablet were administered in the evening without regard to the timing of food ingestion. The safety of SINGULAIR® was also demonstrated in a clinical study in which the 4 mg oral granules were administered in the evening without regard to the timing of food ingestion.

For the 5 mg chewable tablet, the $C_{max}$ is achieved 2 hours after administration in adults in the fasted state. The mean oral bioavailability is 73% in the fasted state versus 63% when administered with a standard meal in the morning. However, food does not have a clinically important influence with chronic administration of the chewable tablet. The comparative pharmacokinetics of montelukast when administered as two 5 mg chewable tablets versus one 10 mg film-coated tablet has not been evaluated.

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

The 4 mg oral granule formulation was shown to be bioequivalent to the 4 mg chewable tablet when administered to healthy adults in the fasted state. Bioequivalence was also demonstrated when the granules were administered with applesauce. The coadministration of a high fat meal decreased the rate of absorption ($C_{max}$ 112.8 versus 175.4 ng/mL with and without a high fat meal, respectively), although the extent of absorption was not affected by food ($AUC_T$ 1133.8 versus 1119.2 ng•hr/mL with and without a high fat meal, respectively).

**Distribution:** Montelukast is more than 99% bound to plasma proteins. The steady-state volume of distribution of montelukast averages 8 to 11 liters. Studies in rats with radiolabeled montelukast indicate minimal distribution across the blood-brain barrier. In addition, concentrations of radiolabeled material at 24 hours postdose were minimal in all other tissues.

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

*In vitro* studies using human liver microsomes indicate that cytochrome P450 3A4, 2C8 and 2C9 are involved in the metabolism of montelukast. CYP 2C8 appears to play a major role in the metabolism of montelukast at clinically relevant concentrations.

**Excretion:** The plasma clearance of montelukast averages 45 mL/min in healthy adults. Following an oral dose of radiolabeled montelukast, 86% of the radioactivity was recovered in 5-day fecal collections and <0.2% was recovered in urine. Coupled with estimates of montelukast oral bioavailability, this indicates montelukast and its metabolites are excreted almost exclusively *via* the bile.

In several studies, the mean plasma half-life of montelukast ranged from 2.7 to 5.5 hours in healthy young adults. The pharmacokinetics of montelukast are nearly linear for oral doses up to 50 mg. No difference in pharmacokinetics was noted between dosing in the morning or in the evening. During once-daily dosing with 10 mg montelukast, there is little accumulation of the parent drug in plasma (~14%).

**Special Populations and Conditions**

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

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

**Geriatrics:** 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.

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

**Race:** Pharmacokinetic differences due to race have not been studied. In clinical studies, there do not appear to be any differences in clinically important effects.

**Hepatic Insufficiency:** Patients with mild to moderate hepatic insufficiency and clinical evidence of cirrhosis had evidence of decreased metabolism of montelukast resulting in approximately 41% higher mean montelukast area under the plasma concentration curve (AUC) following a single 10 mg dose. The elimination of montelukast is slightly prolonged compared with that in healthy subjects (mean half-life, 7.4 hours). No dosage adjustment is required in patients with mild to moderate hepatic insufficiency. There are no clinical data in patients with hepatitis or severe hepatic insufficiency (Child-Pugh score >9).

**Renal Insufficiency:** Since montelukast and its metabolites are not excreted in the urine, the pharmacokinetics of montelukast were not evaluated in patients with renal insufficiency. No dosage adjustment is recommended in these patients.

## STORAGE AND STABILITY

Store the 10 mg film-coated tablets, and the 4 mg and 5 mg chewable tablets at room temperature (15°C–30°C), protected from moisture and light.

Store the 4 mg oral granules at room temperature (15°C–30°C), in the original package.

## DOSAGE FORMS, COMPOSITION AND PACKAGING

Each 10 mg film-coated tablet contains 10.4 mg montelukast sodium, which is the molar equivalent to 10.0 mg of free acid and the following non-medicinal ingredients: croscarmellose sodium, hydroxypropyl cellulose, lactose monohydrate (89.3 mg), magnesium stearate and microcrystalline cellulose. The film-coating consists of: carnauba wax, hydroxypropyl methylcellulose, hydroxypropyl cellulose, red ferric oxide, titanium dioxide, and yellow ferric oxide.

Each 4 mg and 5 mg chewable tablet SINGULAIR® for oral administration contains 4.2 and 5.2 mg montelukast sodium, respectively, which are the molar equivalents to 4.0 and 5.0 mg of free acid, respectively. Both chewable tablets contain the following inactive ingredients: aspartame, croscarmellose sodium, hydroxypropyl cellulose, magnesium stearate, mannitol and microcrystalline cellulose, red ferric oxide and cherry flavor.

Each 4 mg packet of oral granules contains 4.2 mg montelukast sodium, which is the molar equivalent to 4.0 mg of free acid. Each packet of 4 mg oral granules contains the following inactive ingredients: hydroxypropyl cellulose, magnesium stearate and mannitol.

SINGULAIR® Tablets 10 mg, are beige, rounded square-shaped, film-coated tablets, with the code MSD 117 on one side and SINGULAIR on the other. Available in blister packages of 30.

SINGULAIR® Chewable Tablets 5 mg, are pink, round bi-convex shaped chewable tablets with the code MSD 275 on one side and SINGULAIR on the other. Available in blister packages of 30.

SINGULAIR® Chewable Tablets, 4 mg, are pink, oval, bi-convex shaped chewable tablets with code MSD 711 on one side and SINGULAIR on the other. Available in blister packages of 30.

SINGULAIR® Oral Granules, 4 mg, are presented as a white, coarse, granular, free-flowing homogeneous solid in a foil packet. Available in packages of 30.

# PART II: SCIENTIFIC INFORMATION

## PHARMACEUTICAL INFORMATION

### Drug Substance

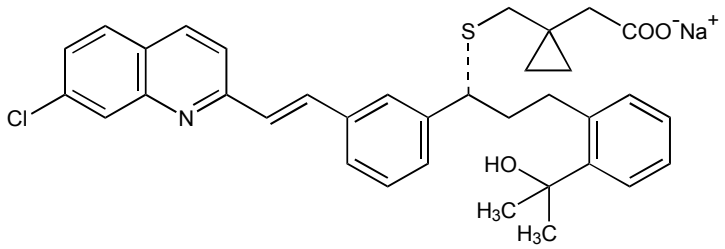
Proper name: montelukast sodium

Chemical name: [R-(E)]-1-[[[1-[3-[2-(7-chloro-2-quinolinyl)ethenyl]phenyl]-3-[2(1-hydroxy-1-methylethyl) phenyl] propyl] thio]methyl]cyclopropane acetic acid, monosodium salt.

Molecular formula: $C_{35}H_{35}ClNNaO_3S$

Molecular mass: 608.18

Structural formula:




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

## CLINICAL TRIALS

### Study Results – Asthma

#### Adults 15 Years of Age and Older

The efficacy of SINGULAIR® (montelukast sodium) for the chronic treatment of asthma in adults 15 years of age and older was demonstrated in two (US and Multinational) similarly-designed 12-week, double-blind, placebo-controlled studies in 1325 patients (795 treated with SINGULAIR® and 530 treated with placebo). Patients were symptomatic and using approximately 5 puffs of β-agonist per day on an "as-needed" basis. The mean baseline percent of predicted forced expiratory volume in 1 second ($FEV_1$) was 66% (approximate range, 40 to 90%). In these studies, asthma symptoms, asthma-related outcomes, respiratory function, and as-needed β-agonist use were measured. Endpoints were analyzed in each study and in a combined analysis according to a prespecified data analysis plan. The following clinical results were observed:

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

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

Physicians' and patients' global asthma evaluations and asthma-specific quality-of-life evaluations (in all domains, including normal daily activity and asthma symptoms) were significantly better with SINGULAIR® in each study and in the combined analysis compared with placebo.

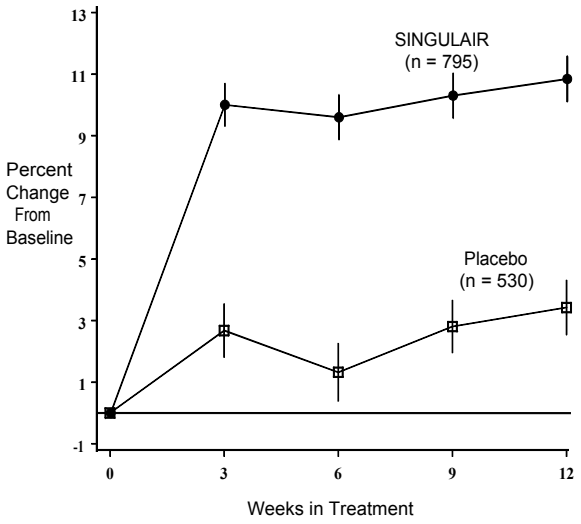
**Respiratory Function**
Compared with placebo, SINGULAIR® caused significant improvements in parameters of respiratory function ($FEV_1$, and peak expiratory flow rate, PEFR) in each study and in the combined analysis:

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

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

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

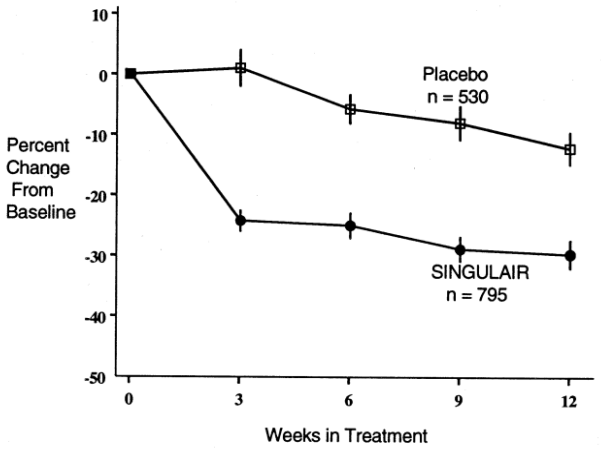
**Figure 1**
**Morning $FEV_1$ (Percent Change from Baseline)**




## β-agonist Use

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

**Figure 2**
**"As-Needed" β-agonist Use (Percent Change from Baseline)**




## Onset of Action and Maintenance of Benefits

In each study and in the combined analysis the treatment effect of SINGULAIR®, measured by daily diary card parameters, including symptom scores, "as-needed" β-agonist use and PEFR measurements, was achieved after the first dose and was maintained throughout the dosing interval (24 hours). Treatment effect also remained constant during continuous once-daily

administration in extension trials for up to one year. Withdrawal of SINGULAIR® in asthmatic patients after 12 weeks of continuous use, as with all asthma therapies, resulted in a gradual decline toward baseline. Additionally, withdrawal of SINGULAIR® did not cause rebound worsening of asthma (see also Effects on Exercise-induced Bronchoconstriction).

**Effects Relative to Inhaled Corticosteroids**
In one of the two 12-week, double-blind studies in adults (Multinational), SINGULAIR® was compared with inhaled beclomethasone (200 μg twice daily with a spacer device). SINGULAIR® demonstrated a more rapid initial response although over the full duration of the study, beclomethasone provided a greater average treatment effect. However, a high percent of patients treated with SINGULAIR® achieved similar clinical responses compared with inhaled beclomethasone (50% of patients on beclomethasone achieved an improvement in $FEV_1$ of approximately 11% or more over baseline while 42% of patients treated with SINGULAIR® achieved the same response).

**Pediatric Patients 6 to 14 Years of Age**
The efficacy of SINGULAIR® in pediatric patients 6 to 14 years of age with asthma was demonstrated in one 8-week double-blind, placebo-controlled study in 336 patients (201 treated with SINGULAIR® and 135 treated with placebo) using β-agonist on an "as-needed" basis. The mean baseline percent predicted $FEV_1$ was 72% (approximate range, 45 to 90%) and approximately 36% of the patients were on inhaled corticosteroids.

Compared with placebo, SINGULAIR®, one 5 mg chewable tablet daily at bedtime, significantly decreased the percent of days asthma exacerbations occurred. Parents' global asthma evaluations and the pediatric asthma-specific quality-of-life evaluations (in all domains, including normal daily activity and asthma symptoms) were significantly better with SINGULAIR® compared with placebo.

Compared with placebo, there was a significant improvement in morning $FEV_1$ (8.7% versus 4.2% change from baseline in the placebo group, $p<0.001$) and a significant decrease in total "as-needed" β-agonist use (11.7% decrease from baseline versus 8.2% increase from baseline in the placebo group, $p\leq0.05$).

Similar to the adult studies, the treatment effect was achieved after the first dose and remained constant during continuous once-daily administration in clinical trials for up to 6 months.

**Growth Rate in Pediatric Patients**
In a 56-week, multi-center, double-blind, randomized, placebo-controlled parallel group study, the effect of SINGULAIR® 5 mg once daily on growth rate was compared to placebo in patients aged 6 to 8 years with mild asthma. Growth rates expressed as least-squares (LS) mean (95% CI) in cm/year for the SINGULAIR® and placebo groups were 5.67 (5.46, 5.88) and 5.64 (5.42, 5.86), respectively.

**Pediatric Patients 2 to 5 Years of Age**
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®. While the primary objective was to determine the safety and tolerability of SINGULAIR®, the study included efficacy evaluations, including daytime and overnight asthma symptom scores, β-agonist use, oral corticosteroid rescue, and the physician's global evaluation. Compared with placebo, treatment with one 4-mg SINGULAIR® chewable tablet daily resulted in a significant improvement in daytime asthma symptom score [scale 0 to 5] (SINGULAIR® -0.37 vs placebo -0.25, p=0.003) and overnight asthma symptom score [scale 0 to 4] (SINGULAIR® -0.41 vs placebo -0.30, p<0.05). Both daytime and overnight asthma symptom scores were measured as a mean change from baseline with a decrease indicating improvement. There were significant decreases in the mean percentage of days of β-agonist use (SINGULAIR® 50.1% vs placebo 56.3%, p<0.001) and in the percentage of patients using oral corticosteroid rescue (SINGULAIR® 19.1% vs placebo 28.1%, p<0.01). In addition, the physicians' global evaluations were significantly better with SINGULAIR® compared with placebo (SINGULAIR® 1.2 vs placebo 1.5, p<0.01). The treatment effect for daytime asthma symptoms, as recorded on a caregiver asthma diary, was achieved after the first dose. The findings of these exploratory efficacy evaluations, along with pharmacokinetics and extrapolation of 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.

**Pediatric Patients 6 months to 2 years**
SINGULAIR® has been evaluated for safety in a 6-week, placebo-controlled clinical study in 175 asthma patients 6 months to 2 years of age receiving 4 mg as oral granules daily in the evening. There were no safety concerns compared to older pediatric patients (see ADVERSE REACTIONS, Pediatric Patients 6 Months to 2 Years of Age with Asthma). Since this study was not powered to detect between group differences in efficacy endpoints, the efficacy of SINGULAIR® could not be determined in this age group.

**Effects in Patients on Concomitant Inhaled Corticosteroids**
Separate studies in adults demonstrated the ability of SINGULAIR® to add to the clinical effect of inhaled corticosteroids, and to allow steroid tapering when used concomitantly.

Three large studies demonstrated SINGULAIR® has additional benefits in patients taking corticosteroids. In a randomized, placebo-controlled, parallel-group study (n=226), stable asthmatic patients on initial inhaled corticosteroid doses of approximately 1600 μg per day reduced their steroid use by approximately 37% during a placebo run-in period. SINGULAIR® allowed a further 47% reduction in inhaled corticosteroid dose compared with 30% for placebo over the 12-week active treatment period (p≤0.050). Approximately 40 % of the montelukast-treated patients and 29% of the placebo-treated patients could be tapered off inhaled corticosteroids and remained off inhaled corticosteroids at the conclusion of the study (p=NS). It is not known whether the results of this study are generalizable to asthmatics 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 400 μg/day), the addition of SINGULAIR® to beclomethasone resulted in statistically significant improvements in $FEV_1$ compared with those patients who were continued on beclomethasone alone or those patients who were withdrawn from beclomethasone and treated with montelukast or placebo alone over the last 10 weeks of the 16-week, blinded treatment period. Patients who were randomized to treatment arms containing beclomethasone had statistically significantly better asthma control than those patients randomized to SINGULAIR® alone or placebo alone as indicated by $FEV_1$, daytime asthma symptoms, PEFR, nocturnal awakenings due to asthma, and "as-needed" β-agonist requirements. While the dose of inhaled corticosteroid may be reduced gradually under medical supervision, SINGULAIR® should not be abruptly substituted for inhaled or oral corticosteroids.

In adult asthmatic patients with documented ASA 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 ASA-sensitive patients was similar to the effect observed in the general population of asthmatic patients studied. The effect of SINGULAIR® on the bronchoconstrictor response to ASA or other non-steroidal anti-inflammatory drugs in ASA-sensitive asthmatic patients has not been evaluated (see WARNINGS AND PRECAUTIONS).

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

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

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

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

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

Because inflammatory cell (eosinophil) infiltration is an important feature of asthma, the effects of SINGULAIR® on eosinophils in the peripheral blood and airway were examined. In Phase IIb/III clinical trials in adults, SINGULAIR® significantly decreased peripheral blood eosinophils approximately 15% from baseline, compared with placebo. In pediatric patients age 6 to 14 years of age, SINGULAIR® also significantly decreased peripheral blood eosinophils 13% over the 8-week treatment period, compared with placebo.

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

**Study Results – Seasonal Allergic Rhinitis**

The efficacy of SINGULAIR® for the treatment of seasonal allergic rhinitis was investigated in similarly designed randomized, 2-week, double-blind, placebo-controlled trials. Patients were 15 years of age and older with a history of seasonal allergic rhinitis, a positive skin test to at least one relevant seasonal allergen, and active symptoms of seasonal allergic rhinitis at study initiation.

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

## TOXICOLOGY

**Animal Toxicology**

No mortality occurred following a single oral administration of montelukast sodium at doses up to 5000 mg/kg, in mice and rats, (15,000 mg/m$^2$ and 29,500 mg/m$^2$ in mice and rats, respectively) the maximum dose tested (oral a$LD_{50}$ >5000 mg/kg). This dose is equivalent to 25,000 times the recommended daily adult human dose (determined using mg/kg/day values).*

* Based on an adult patient weight of 50 kg.

**Chronic Toxicity**
The toxic potential of montelukast sodium was evaluated in a series of repeated dose toxicity studies of up to 53 weeks in monkeys and rats and up to 14 weeks in infant monkeys and in mice. Montelukast sodium was well tolerated at doses which provide a wide margin of safety based on total dose administered. The no effect level was evaluated to be 150 mg/kg/day in female monkeys, 300 mg/kg/day in male monkeys, 50 mg/kg/day in rats, >150 mg/kg/day in infant monkeys and 50 mg/kg/day in mice. For all toxicological parameters, the no effect level was at least 125 times the recommended human dose (determined using mg/kg/day values).* There were no findings that would preclude administration at the therapeutic dosage level for both adults and pediatric patients.

**Carcinogenicity**
No evidence of tumorigenicity was seen in a 2-year carcinogenicity study in Sprague-Dawley rats, at oral (gavage) doses up to 200 mg/kg/day (approximately 160 times the maximum recommended daily oral doses in adults and 190 times the maximum recommended daily oral dose in children, on a $mg/m^2$ basis) or in a 92-week carcinogenicity study in mice at oral doses up to 100 mg/kg/day (approximately 40 times the maximum recommended daily oral dose in adults and 50 times the maximum recommended daily oral dose in children, on a $mg/m^2$ basis).

**Mutagenesis**
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 vitro* mouse bone marrow chromosomal aberration assay.

**Reproduction and Teratology**
In fertility studies in female rats, montelukast produced reductions in fertility and fecundity indices at an oral dose of 200 mg/kg (approximately 160 times the maximum recommended daily oral dose in adults on a $mg/m^2$ basis). No effects on female fertility or fecundity were observed at an oral dose of 100 mg/kg (approximately 80 times the maximum recommended daily oral dose in adults, on a $mg/m^2$ basis). Montelukast had no effects on fertility in male rats at oral doses up to 800 mg/kg (approximately 650 times the maximum recommended daily oral dose in adults, on a $mg/m^2$ basis).

No teratogenicity was observed in rats at oral doses up to 400 mg/kg/day (approximately 320 times the maximum recommended daily oral dose in adults, on a $mg/m^2$ basis) and in rabbits at oral doses up to 300 mg/kg/day (approximately 490 times the maximum recommended daily oral doses in adults, on a $mg/m^2$ basis).

Montelukast crosses the placenta following oral dosing in rats and rabbits. There are, however, no adequate and well-controlled studies in pregnant women. Because animal reproduction

* Based on an adult patient weight of 50 kg.

studies are not always predictive of human response, SINGULAIR® should be used during pregnancy only if clearly needed.

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**PART III: CONSUMER INFORMATION**

# ℞SINGULAIR®

**montelukast tablets**
**montelukast chewable tablets**
**montelukast granules for oral use**
**(as montelukast sodium)**

This leaflet is part III of a three-part "Product Monograph" published when SINGULAIR® was approved for sale in Canada and is designed specifically for Consumers. This leaflet is a summary and will not tell you everything about SINGULAIR®. Contact your physician or pharmacist if you have any questions about the drug.

Please read this leaflet carefully before you or your child start to take this medicine, even if you have just refilled the prescription. Some of the information in the previous leaflet may have changed.

## ABOUT THIS MEDICATION

**What the medication is used for:**
**Asthma (for adults, adolescents and children 2 to 14 years old):**
Your physician has prescribed SINGULAIR® to treat your asthma or your child's asthma, including preventing your asthma symptoms during the day and night. When taken as prescribed, SINGULAIR® also prevents the narrowing of airways triggered by exercise.

SINGULAIR® can be used alone or together with other medications to help with the treatment and prevention of you or your child's asthma. Your physician will decide which combination of medicines will work best for you or your child.

**Seasonal Allergic Rhinitis (for adults and adolescents 15 years and older):**
Your physician has prescribed SINGULAIR® to treat your seasonal allergies, including daytime and nighttime symptoms, including nasal congestion, runny nose, nasal itching, and sneezing; nasal congestion upon awakening; tearing, itchy, red, and puffy eyes.

**What it does:**
SINGULAIR® is a leukotriene receptor antagonist that blocks substances in your lungs called leukotrienes. Leukotrienes cause narrowing and swelling of airways in your lungs. Blocking leukotrienes improves asthma symptoms and helps prevent asthma attacks. Leukotrienes also can contribute to the development of allergy symptoms. Blocking leukotrienes improves seasonal allergy symptoms (also known as hay fever or seasonal allergic rhinitis).

**When it should not be used:**
Do not take SINGULAIR® if you or your child are allergic to any of its ingredients. See what the non-medicinal ingredients are.

**What the medicinal ingredient is:**
montelukast sodium

**What the non-medicinal ingredients are:**
10 mg film-coated tablet: carnauba wax, croscarmellose sodium, hydroxypropyl cellulose, hydroxypropyl methylcellulose, lactose monohydrate (89.3 mg), magnesium stearate, microcrystalline cellulose, red ferric oxide, titanium dioxide, and yellow ferric oxide.

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

4 mg packet of oral granules: hydroxypropyl cellulose, magnesium stearate and mannitol.

**Phenylketonurics:** SINGULAIR® 4 mg and 5 mg chewable tablets contain 0.674 and 0.842 mg phenylalanine, respectively.

**What dosage forms it comes in:**
SINGULAIR® film-coated tablet 10 mg.

SINGULAIR® chewable tablet 4 mg, 5 mg.

SINGULAIR® oral granules 4 mg.

## WARNINGS AND PRECAUTIONS

**SINGULAIR® is not for the treatment of acute asthma attacks.** If an attack occurs, you or your child should follow the instructions your physician has given you for that situation.

Behavior and mood-related changes have been reported in patients taking SINGULAIR®. If you or your child experience these changes while taking SINGULAIR® (see "SERIOUS SIDE EFFECTS, HOW OFTEN THEY HAPPEN AND WHAT TO DO ABOUT THEM"), tell your physician.

**BEFORE** using SINGULAIR®, tell your physician if you or your child:
- have phenylketonuria;
- suffer from liver problems;
- are using any other medicines;
- have or have had any medical problems or allergies.

You should immediately inform your doctor if you or your child start to have any:

- agitation, including aggressive behaviour or hostility (such as temper tantrums in children),
- suicidal thoughts and actions,
- anxiousness, depression (sad mood),
- disorientation (inability to know correct time, place or person), dream abnormalities, hallucinations (seeing or hearing things that are not there),
- insomnia, irritability, restlessness, sleep walking,
- tremors,
- disturbance in attention, memory impairment.

**Use in pregnancy**
Women who are pregnant or intend to become pregnant should consult their physician before taking SINGULAIR®.

**Use in breast-feeding**
It is not known if SINGULAIR® appears in breast milk. You should consult your physician before taking SINGULAIR® if you are breast-feeding or intend to breast-feed.

SINGULAIR® is not expected to affect your ability to drive a car or operate machinery. However, individual responses to medication may vary. Certain side effects (such as dizziness and drowsiness) that have been reported very rarely with SINGULAIR® may affect some patients' ability to drive or operate machinery.

If your or your child's asthma symptoms get worse, you should contact your physician immediately.

If your asthma is made worse by exercise, you should continue to use the medicines your physician has prescribed for you to use before exercise, unless your physician tells you otherwise. You should always have your inhaled rescue medicine for asthma attacks with you in case you need it.

If your asthma is made worse by acetylsalicylic acid (ASA) (e.g., Aspirin*), you should continue to avoid ASA or other non-steroidal anti-inflammatory drugs.

## INTERACTIONS WITH THIS MEDICATION

In general, SINGULAIR® does not interfere with other medicines that you may be taking. However, some medicines may affect how SINGULAIR® works, or SINGULAIR® may affect how your other medicines work. It is important to tell your physician about all drugs that you are using or plan to use, including those obtained without a prescription.

## PROPER USE OF THIS MEDICATION

**Usual dose:**
**Asthma (for adults, adolescents and children 2 to 14 years old):**
Take SINGULAIR® once a day in the evening with or without food, as your physician has prescribed.

SINGULAIR® oral granules for children 2 to 5 years old can be given either:

- directly in the mouth;
  OR
- all contents mixed with a spoonful of cold or room temperature soft food (for example, applesauce), taking care to see that the entire dose is mixed with the food.

Do not open the packet until ready to use.

Be sure the child is given the entire spoonful of the oral granule/food mixture immediately (within 15 minutes). IMPORTANT: Never store any oral granule/food mixture for use at a later time.

SINGULAIR® oral granules are not intended to be dissolved in liquid. However, your child may take liquids after swallowing the SINGULAIR® oral granules.

Take SINGULAIR® daily for as long as your physician prescribes it in order to maintain control of your or your child's asthma. SINGULAIR® can treat your or your child's asthma only if you or your child continue to take it.

It is important that you or your child **continue taking SINGULAIR® daily as prescribed by your physician, even when you or your child has no symptoms or if you or your child has an asthma attack**.

If you are taking other medications along with SINGULAIR® your physician will instruct you how and when to take each medication. Your physician will increase or decrease the doses of these medications as needed.

**Seasonal Allergic Rhinitis (for adults and adolescents 15 years and older):**

Take SINGULAIR® once a day in the evening with or without food, as your physician has prescribed.

Remember that your physician has prescribed this medicine only for you or your child. Never give it to anyone else.

Follow up with your physician to ensure your continued health and safety.

**Overdose:**

In case of drug overdose, contact a health care practitioner, hospital emergency department or regional Poison Control Centre immediately, even if there are no symptoms.

**Missed Dose:**
Try to take SINGULAIR® as prescribed. However, if you miss a dose, just resume the usual schedule of one tablet or packet once daily.

## SIDE EFFECTS AND WHAT TO DO ABOUT THEM

Any medicine may have unintended or undesirable effects, so-called side effects. SINGULAIR® is generally well-tolerated. The most common side effects reported were:

- abdominal pain
- headache
- thirst
- diarrhea
- hyperactivity
- asthma
- scaly and itchy skin
- rash

These were usually mild.

Additionally, the following have been reported:

- upper respiratory tract infection (common cold)
- feeling anxious, irritability, disturbance in attention
- memory impairment, restlessness, sleep walking
- sleep disorders including dream abnormalities and insomnia, uncontrolled muscle movements
- dizziness, drowsiness, pins and needles/numbness
- nose bleed
- joint pain, muscle aches and muscle cramps
- tender red lumps under the skin, most commonly on your shins
- weakness/tiredness, fatigue
- swelling
- fever
- bedwetting in children

Tell your physician or pharmacist if you develop any of the above symptoms, any unusual symptom, or if any known symptom continues or worsens.

## SERIOUS SIDE EFFECTS, HOW OFTEN THEY HAPPEN AND WHAT TO DO ABOUT THEM

| Symptoms / Effects | Talk with your physician or pharmacist | | Stop taking drug and seek immediate emergency medical attention |
|---|---|---|---|
| | Only if severe | In all cases | |
| **Rare** | | | |
| symptoms of allergic reactions such as swelling of the face, lips, tongue, and/or throat (which may cause difficulty in breathing or swallowing), hives, rash, and itching | | | ✓ |
| **Very Rare** | | | |
| symptoms of liver problems: nausea, vomiting, fatigue, jaundice (yellowing of the skin and eyes), dark urine, flu-like symptoms, loss of appetite, and pain in your abdomen | | | ✓ |
| increased bleeding tendency, bruising, low blood platelet count | | ✓ | |
| severe skin reactions ( erythema multiforme) that may occur without warning | | ✓ | |
| behavior and mood related changes [agitation including aggressive behavior or hostility (such as temper tantrums in children)] | | ✓ | |
| depression | | ✓ | |
| disorientation (inability to know correct time, place or person) | | ✓ | |
| suicidal thoughts and actions | | | ✓ |
| tremor | | ✓ | |
| hallucinations (seeing or hearing things that are not there) | | ✓ | |
| seizure (convulsions or fits) | | | ✓ |
| palpitations (heart skips a beat) | ✓ | | |
| Churg-Strauss syndrome: a flu-like illness, rash, pins and needles or numbness of arms or legs, joint pain and severe sinusitis | | | ✓ |
| swelling (inflammation) of the lungs: breathing problems that continue to get worse | | | ✓ |

***This is not a complete list of side effects. For any unexpected effects while taking* SINGULAIR®*, contact your physician or pharmacist.***

## HOW TO STORE IT

Store the 10 mg film-coated tablets, and the 4 mg and 5 mg chewable tablets at room temperature (15°C–30°C). Protect from moisture and light.

Store the 4 mg oral granules at room temperature (15°C–30°C), in the original package.

**Keep all medicines safely away from children.**

### REPORTING SIDE EFFECTS

You can help improve the safe use of health products for Canadians by reporting serious and unexpected side effects to Health Canada. Your report may help to identify new side effects and change the product safety information.

**3 ways to report**:

- Online at MedEffect;
- By calling 1-866-234-2345 (toll-free);
- By completing a Consumer Side Effect Reporting Form and sending it by:
  - Fax to 1-866-678-6789 (toll-free), or
  - Mail to: Canada Vigilance Program
    Health Canada, Postal Locator 0701E
    Ottawa, ON
    K1A 0K9

    Postage paid labels and the Consumer Side Effect Reporting Form are available at MedEffect.

*NOTE: Contact your health professional if you need information about how to manage your side effects. The Canada Vigilance Program does not provide medical advice.*

## MORE INFORMATION

**If you want more information about SINGULAIR®:**

- Talk to your healthcare professional
- Find the full product monograph that is prepared for healthcare professionals and includes this Consumer Information by visiting the Health Canada website, www.merck.ca or by calling 1-800-567-2594

To report an adverse event related to SINGULAIR®, please contact 1-800-567-2594.

This leaflet was prepared by Merck Canada Inc.

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