

Name of Medicine

SINGULAIR®

montelukast sodium
10 mg tablet
5 mg chewable tablet
4 mg chewable tablet

Presentation

10 mg tablet: A beige rounded square film-coated tablet engraved with SINGULAIR on one side and MSD117 on the other, containing 10.4 mg of montelukast sodium which is the molar equivalent of 10.0 mg of free acid. Dimensions: 7.87 x 7.87 mm.

5 mg chewable tablet: A pink round biconvex chewable tablet with a cherry flavour engraved SINGULAIR on one side and MSD275 on the other, containing 5.2 mg of montelukast sodium which is the molar equivalent of 5.0 mg of free acid. Dimensions: 9.525 mm diameter.

4 mg chewable tablet: A pink round biconvex tablet with a cherry flavour engraved SINGULAIR on one side and MSD 711 on the other, containing 4.2 mg montelukast sodium which is the molar equivalent of 4.0 mg of free acid. (Currently not available in New Zealand.)

Therapeutic Class

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

Indications

SINGULAIR is indicated in adult and paediatric patients 2 years of age and older for the prophylaxis and chronic treatment of asthma, including the prevention of day- and night-time symptoms and the prevention of exercise-induced bronchospasm.

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

Dosage and Administration

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

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

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

The dosage for adults 15 years of age and older is one 10 mg tablet daily.

Paediatric Patients 6 to 14 Years of Age with Asthma and/or Allergic Rhinitis

The dosage for paediatric patients 6 to 14 years of age is one 5 mg chewable tablet daily.

Paediatric Patients 2 to 5 Years of Age with Asthma and/or Allergic Rhinitis

The dosage for paediatric patients 2 to 5 years of age is one 4 mg chewable tablet daily.

General Recommendations

The therapeutic effect of SINGULAIR on parameters of asthma control occurs within one day. SINGULAIR may be taken with or without food. Patients should be advised to continue taking SINGULAIR while their asthma is controlled, as well as during periods of worsening asthma.

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

Therapy with SINGULAIR in Relation to Other Treatments for Asthma

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

Reduction in Concomitant Therapy

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

Inhaled Corticosteroids: Treatment with SINGULAIR provides additional clinical benefit to patients treated with inhaled corticosteroids. A reduction in the corticosteroid dose can be made as tolerated. The dose should be reduced gradually with medical supervision. In some patients, the dose of inhaled corticosteroids can be tapered off completely. SINGULAIR should not be abruptly substituted for inhaled corticosteroids.

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

Contraindications

Hypersensitivity to any component of this product.

Warnings and Precautions

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

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

Neuropsychiatric events have been reported in patients taking SINGULAIR (see Adverse Effects). Since other factors may have contributed to these events, it is not known if they are related to SINGULAIR. 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.

The reduction in systemic corticosteroid dose in patients receiving anti-asthma agents including leukotriene receptor antagonists has been followed in rare cases by the occurrence of one or more of the following: eosinophilia, vasculitic rash, worsening

pulmonary symptoms, cardiac complications, and/or neuropathy sometimes diagnosed as Churg-Strauss syndrome, a systemic eosinophilic vasculitis. Although a causal relationship with leukotriene receptor antagonism has not been established, caution and appropriate clinical monitoring are recommended when systemic corticosteroid reduction is considered in patients receiving SINGULAIR.

Pregnancy

SINGULAIR has not been studied in pregnant women. SINGULAIR should be used during pregnancy only if clearly needed.

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

Nursing Mothers

It is not known if SINGULAIR is excreted in human milk. Because many medicines are excreted in human milk, caution should be exercised when SINGULAIR is given to a nursing mother.

Paediatric Use

SINGULAIR has been studied in paediatric patients 2 to 14 years of age (see Dosage and Administration). Safety and effectiveness in paediatric patients younger than 2 years of age have not been studied. Studies have shown that SINGULAIR does not affect the growth rate of paediatric patients.

Use in the Elderly

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

Renal/Hepatic Impairment

No dosage adjustment is required for patients with renal insufficiency or mild to moderate hepatic impairment. (See Pharmacokinetics; *Hepatic Insufficiency & Renal Insufficiency*.)

Carcinogenicity and Mutagenicity

There were no significant results seen with montelukast sodium in carcinogenicity or mutagenicity studies.

Reproduction

In pre-clinical studies, there were no significant results in reproduction studies conducted with montelukast sodium.

Development

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

Effect on and Ability to Drive and use Machines

There is no evidence that SINGULAIR affects the ability to drive and use machines.

Adverse Effects

SINGULAIR has been generally well tolerated. Adverse effects, which usually were mild, generally did not require discontinuation of therapy. The overall incidence of adverse effects (including laboratory adverse effects) reported with SINGULAIR was comparable to placebo.

Adults 15 Years of Age and Older with Asthma

SINGULAIR has been evaluated 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 medicine-related in $\geq 1\%$ 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.

Cumulatively, 544 patients were treated with SINGULAIR for at least 6 months, 253 for one year and 21 for 2 years in clinical studies. With prolonged treatment, the adverse experience profile did not change.

Paediatric Patients 6 to 14 Years of Age with Asthma

SINGULAIR has been evaluated in approximately 475 paediatric patients 6 to 14 years of age. The safety profile in paediatric patients is generally similar to the adult safety profile and to placebo.

In an 8-week, placebo-controlled clinical study, the only adverse experience reported as medicine-related in $>1\%$ of patients treated with SINGULAIR and at a greater incidence than in patients treated with placebo was headache. The incidence of headache was not significantly different in the two treatment groups.

In studies evaluating the growth rate, the safety profile in these paediatric patients was consistent with the safety profile previously described for SINGULAIR.

Cumulatively, 263 paediatric patients 6 to 14 years of age were treated with SINGULAIR for at least 3 months and 164 for 6 months or longer. With prolonged treatment, the adverse experience profile did not change.

Paediatric Patients 2 to 5 Years of Age with Asthma

SINGULAIR has been evaluated in 573 paediatric patients 2 to 5 years of age. In a 12-week, placebo-controlled clinical study, the only adverse experience reported as medicine-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, 426 paediatric patients 2 to 5 years of age were treated with SINGULAIR for at least 3 months, 230 for 6 months or longer, and 63 patients for 12 months or longer. With prolonged treatment, the adverse experience profile did not change.

Adults 15 Years of Age and Older with Seasonal Allergic Rhinitis

SINGULAIR has been evaluated in 2199 adult patients 15 years of age and older for the treatment of seasonal allergic rhinitis in clinical studies. SINGULAIR administered once daily in the morning or in the evening was generally well tolerated with a safety profile similar to that of placebo. In placebo-controlled clinical studies, no adverse experiences reported as drug related in $\geq 1\%$ of patients treated with SINGULAIR and at a greater incidence than in patients treated with placebo were observed. 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.

Paediatric Patients 2 to 14 Years of Age with Seasonal Allergic Rhinitis

SINGULAIR has been evaluated in 280 paediatric patients 2 to 14 years of age for the treatment of seasonal allergic rhinitis in a 2-week, placebo-controlled, clinical study. SINGULAIR administered once daily in the evening was generally well tolerated with a safety profile similar to that of placebo. In this study, no adverse experiences reported as drug related in $\geq 1\%$ of patients treated with SINGULAIR and at a greater incidence than in patients treated with placebo were observed.

Adults 15 Years of Age and Older with Perennial Allergic Rhinitis

SINGULAIR has been evaluated in 3235 adult and adolescent patients 15 years of age and older with perennial allergic rhinitis (defined as a history of symptoms for at least two years and positive skin tests for at least two perennial allergens) in two, 6 week, placebo-controlled, clinical studies. SINGULAIR administered once daily was generally well tolerated, with a safety profile consistent with that observed in patients with seasonal allergic rhinitis and similar to that of placebo. In these two studies, no adverse experiences reported as drug related in $\geq 1\%$ 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.

Pooled Analyses of Clinical Trials Experience

A pooled analysis of 41 placebo-controlled clinical studies (35 studies in patients 15 years of age and older; 6 studies in paediatric patients 6 to 14 years of age) was performed using a validated assessment method of suicidality. Among the 9929 patients who received SINGULAIR and 7780 patients who received placebo in these studies, there was one patient with suicidal ideation in the group taking SINGULAIR. There were no completed suicides, suicide attempts or preparatory acts toward suicidal behaviour in either treatment group.

A separate pooled analysis of 46 placebo-controlled clinical studies (35 studies in patients 15 years of age and older; 11 studies in paediatric patients 3 months to 14 years of age) assessing behaviour-related adverse experiences (BRAEs) was performed. Among the 11,673 patients who received SINGULAIR and 8827 patients who received placebo in these studies, the frequency of patients with at least one BRAE was 2.73% in patients who received SINGULAIR and 2.27% in patients who received placebo; the odds ratio was 1.12 (95% CI [0.93; 1.36]).

The clinical trials included in these pooled analyses were not designed specifically to examine suicidality or BRAEs.

Post-Marketing Experience

The following adverse reactions have been reported in post-marketing use:

Infections and infestations: upper respiratory infection

Blood and lymphatic system disorders: increased bleeding tendency

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

Psychiatric disorders: agitation including aggressive behaviour or hostility, anxiousness, depression, disorientation, dream abnormalities, hallucinations, insomnia, irritability, restlessness, somnambulism, suicidal thinking and behaviour (suicidality), tremor

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

Cardiac disorders: palpitations

Respiratory, thoracic and mediastinal disorders: epistaxis

Gastrointestinal disorders: diarrhoea, dyspepsia, nausea, vomiting

Hepatobiliary disorders: increased ALT and AST, very rarely hepatitis (including cholestatic, hepatocellular, and mixed-pattern liver injury)

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

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

General disorders and administration site conditions: asthenia/fatigue, oedema, pyrexia

Interactions

SINGULAIR may be administered with other therapies routinely used in the prophylaxis and chronic treatment of asthma, and in the treatment of allergic rhinitis. In medicine-interactions studies, the recommended clinical dose of montelukast did not have clinically important effects on the pharmacokinetics of the following medicines: theophylline, prednisone, prednisolone, oral contraceptives (ethinyl estradiol/norethindrone 35/1), terfenadine, digoxin and warfarin.

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

The area under the plasma concentration-time curve (AUC) for montelukast was decreased approximately 40% in subjects with co-administration of phenobarbital. No dosage adjustment for SINGULAIR is recommended.

In vitro studies have shown that montelukast is an inhibitor of CYP2C8. However, data from a clinical drug-drug interaction study involving montelukast and rosiglitazone (a probe substrate representative of drugs primarily metabolised by CYP2C8 demonstrated that montelukast does not inhibit CYP2C8 *in vivo*. Therefore, montelukast is not anticipated to alter the metabolism of drugs metabolised by this enzyme (e.g., paclitaxel, rosiglitazone, repaglinide).

SINGULAIR may be taken with or without food. There are no data available on the use of SINGULAIR and alcohol.

Overdosage

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

approximately one week without clinically important adverse experiences.

There have been reports of acute overdose 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 paediatric patients. There were no adverse experiences in the majority of overdose reports. The most frequently occurring adverse experiences were consistent with the safety profile of SINGULAIR and included abdominal pain, somnolence, thirst, headache, vomiting, and psychomotor hyperactivity.

It is not known whether montelukast is dialysable by peritoneal- or haemodialysis.

Actions

Mechanism of Action

The cysteinyl leukotrienes (LTC₄, LTD₄, LTE₄), 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 (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 a number of airway actions, including bronchoconstriction, mucous secretion, vascular permeability, and eosinophil recruitment. In allergic rhinitis, CysLTs are released from the nasal mucosa after allergen exposure during both early- and late-phase reactions and are associated with symptoms of allergic rhinitis. Intranasal challenge with CysLTs has been shown to increase nasal airway resistance and symptoms of nasal obstruction.

Montelukast is a potent, orally active compound that significantly improves parameters of asthmatic inflammation. Based on biochemical and pharmacological bioassays, it 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 potently inhibits physiologic actions of LTC₄, LTD₄, and LTE₄ at the CysLT₁ receptor without any agonist activity.

Pharmacokinetics

Absorption

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

For the 5 mg chewable tablet, the C_{max} is achieved 2 hours after administration in adults in the fasted state. The mean oral bioavailability is 73%. Food does not have a clinically important influence with chronic administration.

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

Safety and efficacy were demonstrated in clinical studies where the 4 mg chewable tablet, 5 mg chewable tablet, and 10 mg film-coated tablet were administered without regard to the timing of food ingestion.

Distribution

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

Metabolism

Montelukast is extensively metabolised. In studies with therapeutic doses, plasma concentrations of metabolites of montelukast are undetectable at steady state in adults and paediatric patients.

In vitro studies using human liver microsomes indicate that cytochrome P450 3A4 and 2C9 are involved in the metabolism of montelukast. Based on further *in vitro* results in human liver microsomes, therapeutic plasma concentrations of montelukast do not inhibit cytochromes P450 3A4, 2C9, 1A2, 2A6, 2C19, or 2D6.

Elimination

The plasma clearance of montelukast averages 45 mL/min in healthy adults. Following an oral dose of radiolabelled montelukast, 86% of the radioactivity was recovered in 5-day faecal 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 medicine in plasma (~14%).

Characteristics in Patients

Gender

The pharmacokinetics of montelukast are similar in males and females.

Elderly

The pharmacokinetic profile and the oral bioavailability of a single 10 mg oral dose of montelukast are similar in elderly and younger adults. The plasma half-life of montelukast is slightly longer in the elderly. No dosage adjustment in the elderly is required.

Race

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

Hepatic Insufficiency

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

Renal Insufficiency

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

Adolescents and Paediatric Patients

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

Pharmacokinetic studies using either the chewable tablet or film-coated tablet show that the plasma profile of the 5 mg chewable tablet in paediatric patients 6 to 14 years of age is similar to that of the 10 mg film-coated tablet in adults. In a pharmacokinetic study in paediatric patients 2 to 5 years of age, the plasma profile of the 4 mg chewable tablet was also similar to that of the 10 mg film-coated tablet in adults. The 5 mg chewable tablet should be used in paediatric patients 6 to 14 years of age and the 4 mg chewable tablet in paediatric patients 2 to 5 years of age.

Pharmaceutical Precautions

Store the 10 mg film-coated tablets and the 4 mg and 5 mg chewable tablets at room temperature 15-30°C (59-86°F), protected from moisture and light.

Medicine Classification

Prescription Medicine

Package Quantities

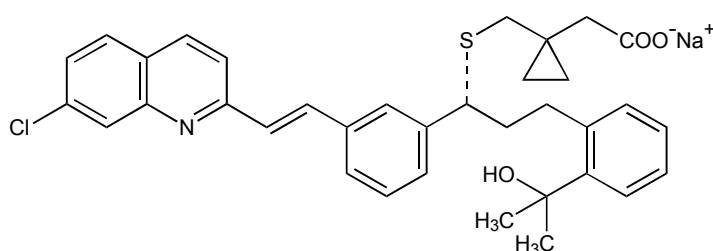
SINGULAIR Tablets/Chewable Tablets are available in blister packs of 28 tablets.

Further Information

Chemistry

SINGULAIR, (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]cyclopropane acetic acid, monosodium salt.

The empirical formula is $C_{35}H_{35}ClNaO_3S$, and its molecular weight is 608.18. The structural formula is:



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

Composition

Active Ingredients

Each 10 mg film-coated tablet contains 10.4 mg montelukast sodium, which is the molar equivalent to 10.0 mg of free acid. Each 5 mg chewable tablet contains 5.2 mg montelukast sodium, which is the molar equivalent to 5.0 mg of free acid. Each 4 mg chewable tablet contains 4.2 mg montelukast sodium, which is the molar equivalent to 4.0 mg of free acid.

Inactive Ingredients

Each 10 mg film-coated tablet contains the following inactive ingredients: microcrystalline cellulose, lactose monohydrate, croscarmellose sodium, hydroxypropyl cellulose, and magnesium stearate. The film coating consists of: hydroxypropyl methylcellulose, hydroxypropyl cellulose, titanium dioxide, red ferric oxide, yellow ferric oxide, and carnauba wax.

Each 4 mg and 5 mg chewable tablet contains the following inactive ingredients: mannitol, microcrystalline cellulose, hydroxypropyl cellulose, red ferric oxide, croscarmellose sodium, cherry flavour, aspartame, and magnesium stearate.

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