

SINGULAIR™ - Local Prescribing Information

SINGULAIR PAEDIATRIC 4 mg GRANULES

1. NAME OF THE MEDICINAL PRODUCT SINGULAIR® Paediatric 4 mg Granules

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

One sachet of granules contains montelukast sodium, which is equivalent to 4 mg montelukast.
For excipients, see 6.1.

3. PHARMACEUTICAL FORM

Granules.
White granules.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

'Singulair' is indicated in the treatment of asthma as add-on therapy in those patients with mild to moderate persistent asthma who are inadequately controlled on inhaled corticosteroids and in whom 'as-needed' short acting β -agonists provide inadequate clinical control of asthma.
'Singulair' is also indicated in the prophylaxis of asthma in which the predominant component is exercise-induced bronchoconstriction.

4.2 Posology and method of administration

The dosage for paediatric patients 6 months to 5 years of age is one sachet of 4-mg granules daily to be taken in the evening. No dosage adjustment within this age group is necessary. The experience in use in paediatric patients 6 to 12 months of age is limited. Safety and efficacy below 6 months of age have not been established.

Administration of 'Singulair' granules

'Singulair' granules can be administered either directly in the mouth, or mixed with a spoonful of cold or room temperature soft food (e.g. applesauce, ice cream, carrots and rice). The sachet should not be opened until ready to use. After opening the sachet, the full dose of 'Singulair' granules must be administered immediately (within 15 minutes). If mixed with food, 'Singulair' granules must not be stored for future use. 'Singulair' granules are not intended to be dissolved in liquid for administration. However, liquids may be taken subsequent to administration. 'Singulair' granules can be administered without regard to the timing of food ingestion.

General recommendations: The therapeutic effect of 'Singulair' on parameters of asthma control occurs within one day. Patients should be advised to continue taking 'Singulair' even if their asthma is under control, as well as during periods of worsening asthma.

No dosage adjustment is necessary for patients with renal insufficiency, or mild to moderate hepatic impairment. There are no data on patients with severe hepatic impairment. The dosage is the same for both male and female patients.

Therapy with 'Singulair' in relation to other treatments for asthma.

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

β -agonist therapy: 'Singulair' can be added to the treatment regimen of patients who are not adequately controlled on 'as-needed' short acting β -agonist. When a clinical response is evident (usually after the first dose), the patient may be able to decrease the use of 'as-needed' short acting β -agonist.

Inhaled corticosteroids: Treatment with 'Singulair' can be used as add-on therapy in patients when other agents, such as inhaled corticosteroids, provide inadequate clinical control. 'Singulair' should not be substituted for inhaled corticosteroids. (See section 4.4 'Special warnings and precautions for use'.)

10-mg tablets are available for adults 15 years of age and older.

5-mg chewable tablets are available for paediatric patients 6 to 14 years of age.

4-mg chewable tablets are available as an alternative formulation for paediatric patients 2 to 5 years of age.

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients.

4.4 Special warnings and special precautions for use

Patients should be advised never to use oral montelukast to treat acute asthma attacks and to keep their usual appropriate rescue medication for this purpose readily available. If an acute attack occurs, a short-acting inhaled β -agonist should be used. Patients should seek their doctors' advice as soon as possible if they need more inhalations of short-acting β -agonists than usual.

Montelukast should not be substituted for inhaled or oral corticosteroids.

There are no data demonstrating that oral corticosteroids can be reduced when montelukast is given concomitantly.

In rare cases, patients on therapy with anti-asthma agents including montelukast 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 cases usually, but not always, have been associated with the reduction or withdrawal of oral corticosteroid therapy. The possibility that leukotriene receptor antagonists may be associated with emergence of Churg-Strauss syndrome can neither be excluded nor established. Physicians should be alert to eosinophilia, vasculitic rash, worsening pulmonary symptoms, cardiac complications, and/or neuropathy presenting in their patients. Patients who develop these symptoms should be reassessed and their treatment regimens evaluated.

Safety and efficacy have not yet been established in the paediatric population below 6 months of age.

4.5 Interaction with other medicinal products and other forms of interaction

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

The area under the plasma concentration curve (AUC) for montelukast was decreased approximately 40% in subjects with co-administration of phenobarbital. Since montelukast is metabolised by CYP 3A4, caution should be exercised, particularly in children, when montelukast is coadministered with inducers of CYP 3A4, such as phenytoin, phenobarbital and rifampicin.

4.6 Pregnancy and lactation

Since there are no controlled studies in pregnant or nursing women, montelukast should not be used during pregnancy or in nursing mothers unless it is considered to be clearly essential. (See section 5.3 'Preclinical safety data'.)

4.7 Effects on ability to drive and use machines

Montelukast is not expected to affect a patient's ability to drive a car or operate machinery. However, in very rare cases, individuals have reported drowsiness.

4.8 Undesirable effects

Montelukast has been evaluated in clinical studies as follows:

- 10-mg film-coated tablets in approximately 4,000 adult patients 15 years of age and older
- 5-mg chewable tablets in approximately 1,100 paediatric patients 6 to 14 years of age.
- 4-mg chewable tablets in 573 paediatric patients 2 to 5 years of age, and
- 4-mg granules in 170 paediatric patients 6 months to 2 years of age.

The following drug-related adverse reactions in placebo-controlled clinical studies were reported commonly (>1/100, <1/10) in patients treated with montelukast and at a greater incidence than in patients treated with placebo:

Body System Class	Adult Patients 15 years and older (two 12-week studies; n=795)	Paediatric Patients 6 to 14 years old (one 8-week study; n=201)	Paediatric Patients 2 to 5 years old (one 8-week study; n=461)	Paediatric Patients 6 months up to 2 years old (one 6-week study; n=175)
Body as a whole	abdominal pain			
Digestive system disorders			thirst	diarrhoea
Nervous system /psychiatric	headache	headache		hyperkinesia
Respiratory system disorders				asthma
Skin/skin appendages disorder				eczematous dermatitis, rash

With prolonged treatment in clinical trials with a limited number of patients for up to 2 years for adults, and up to 6 months for paediatric patients 6 to 14 years of age, the safety profile did not change.

Cumulatively, 502 paediatric patients 2 to 5 years of age were treated with montelukast for at least 3 months, 338 for 6 months or longer, and 256 patients for 12 months or longer. With prolonged treatment, the safety profile did not change in these patients either.

The safety profile in paediatric patients 6 months to 2 years of age did not change with treatment up to 3 months.

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

Body as a whole: asthenia/fatigue, malaise, oedema, hypersensitivity reactions including anaphylaxis, angioedema, urticaria, pruritus, rash and one isolated report of hepatic eosinophilic infiltration.

Nervous system/psychiatric: dizziness, dream abnormalities including nightmares, hallucinations, drowsiness, insomnia, paraesthesia/hypoesthesia, irritability, agitation including aggressive behaviour, restlessness, seizure.

Musculo-skeletal disorders: arthralgia, myalgia including muscle cramps.

Digestive system disorders: diarrhoea, dry mouth, dyspepsia, nausea, vomiting.

Hepato-biliary disorders: elevated levels of serum transaminases (ALT, AST), cholestatic hepatitis.

Cardiovascular disorders: increased bleeding tendency, bruising, palpitations.

Very rare cases of Churg-Strauss Syndrome (CSS) have been reported during montelukast treatment in asthmatic patients. (see Section 4.4 'Special warnings and precautions for use').

4.9 Overdose

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

There have been reports of acute overdose in children in post-marketing experience and clinical studies of up to at least 150 mg/day with montelukast. The clinical and laboratory findings observed were consistent with the safety profile in adults and older paediatric patients. There were no adverse experiences reported in the majority of overdose reports. The most frequent adverse experiences observed were thirst, somnolence, mydriasis, hyperkinesia, and abdominal pain.

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

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Anti-Asthmatics for systemic use, Leukotriene receptor antagonist

ATC-code: R03D C03

The cysteinyl leukotrienes (LTCA, LTD4, LTE4) are potent inflammatory eicosanoids released from various cells including mast cells and eosinophils. These important pro-asthmatic mediators bind to cysteinyl leukotriene receptors (CysLT) found in the human airway and cause airway actions, including bronchoconstriction, mucous secretion, vascular permeability, and eosinophil recruitment.

Montelukast is an orally active compound which binds with high affinity and selectivity to the CysLT1 receptor. In clinical studies, montelukast inhibits bronchoconstriction due to inhaled LTD4 at doses as low as 5 mg. Bronchodilation was observed within 2 hours of oral administration. The bronchodilation effect caused by β -agonist was additive to that caused by montelukast. Treatment with montelukast inhibited both early- and late-phase bronchoconstriction due to antigen challenge. Montelukast, compared with placebo, decreased peripheral blood eosinophils in adult and paediatric patients. In a separate study, treatment with montelukast significantly decreased eosinophils in the airways (as measured in sputum). In adult and paediatric patients 2 to 14 years of age, montelukast, compared with placebo, decreased peripheral blood eosinophils while improving clinical asthma control.

In studies in adults, montelukast, 10 mg once daily, compared with placebo, demonstrated significant improvements in morning FEV1 (10.4% vs 2.7% change from baseline), AM peak expiratory flow rate (PEFR) (24.5 L/min vs 3.3 L/min change from baseline), and significant decrease in total β -agonist use (-26.1% vs -4.6% change from baseline). Improvement in patient-reported daytime and night-time asthma symptoms scores was significantly better than placebo.

Studies in adults demonstrated the ability of montelukast to add to the clinical effect of inhaled corticosteroid (% change from baseline for inhaled beclomethasone plus montelukast vs beclomethasone, respectively for FEV1: 5.43% vs 1.04%; β -agonist use: -3.70% vs 2.54%). Compared with inhaled beclomethasone (200 μ g twice daily with a spacer device), montelukast demonstrated a more rapid initial response, although over the 12-week study, beclomethasone provided a greater average treatment effect (% change from baseline for montelukast vs beclomethasone, respectively for FEV1: 7.49% vs 13.3%; β -agonist use: -28.28% vs -43.89%). However, compared with beclomethasone, a high percentage of patients treated with montelukast achieved similar clinical responses (e.g. 50% of patients treated with beclomethasone achieved an improvement in FEV1 of approximately 11% or more over baseline while approximately 42% of patients treated with montelukast achieved the same response).

In an 8-week study in paediatric patients 6 to 14 years of age, montelukast 5 mg once daily, compared with placebo, significantly improved respiratory function (FEV1 8.71% vs 4.16% change from baseline; AM PEFR 27.9 L/min vs 17.8 L/min change from baseline) and decreased 'as-needed' β -agonist use (-11.7% vs -8.2% change from baseline).

In a 12-week, placebo-controlled study in paediatric patients 2 to 5 years of age, montelukast 4 mg once daily improved parameters of asthma control compared with placebo irrespective of concomitant controller therapy (inhaled/nebulised corticosteroids or inhaled/nebulised sodium cromoglycate). Sixty percent of patients were not on any other controller therapy. Montelukast improved daytime symptoms (including coughing, wheezing, trouble breathing and activity limitation) and nighttime symptoms compared with placebo. Montelukast also decreased 'as-needed' β -agonist use and corticosteroid rescue for worsening asthma compared with placebo. Patients receiving montelukast had more days without asthma than those receiving placebo. A treatment effect was achieved after the first dose.

Efficacy of montelukast is supported in paediatric patients 6 months to 2 years of age by extrapolation from the demonstrated efficacy in patients 2 years of age and older with asthma, and is based on similar pharmacokinetic data, as well as the assumption that the disease course, pathophysiology and the drug's effect are substantially similar among these populations.

Significant reduction of exercise-induced bronchoconstriction (EIB) was demonstrated in a 12-week study in adults (maximal fall in FEV1 22.33% for montelukast vs 32.40% for placebo; time to recovery to within 5% of baseline FEV1 44.22 min vs 60.64 min). This effect was consistent throughout the 12-week study period. Reduction in EIB was also demonstrated in a short term study in paediatric patients 6 to 14 years of age (maximal fall in FEV1 18.27% vs 26.11%; time to recovery to within 5% of baseline FEV1 17.76 min vs 27.38 min). The effect in both studies was demonstrated at the end of the once-daily dosing interval.

In aspirin-sensitive asthmatic patients receiving concomitant inhaled and/or oral corticosteroids, treatment with montelukast, compared with placebo, resulted in significant improvement in asthma control (FEV1 8.55% vs -1.74% change from baseline and decrease in total β -agonist use -27.78% vs 2.09% change from baseline).

5.2 Pharmacokinetic properties

Absorption: Montelukast is rapidly 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 and C_{max} are not influenced by a standard meal. Safety and efficacy were demonstrated in clinical trials where the 10mg film-coated tablet was administered without regard to the timing of food ingestion.

For the 5-mg chewable tablet, the C_{max} is achieved in 2 hours after administration in adults in the fasted state. The mean oral bioavailability is 73% and is decreased to 63% by a standard meal.

After administration of the 4-mg chewable tablet to paediatric patients 2 to 5 years of age in the fasted state, C_{max} is achieved 2 hours after administration. The mean C_{max} is 66% higher while mean C_{min} is lower than in adults receiving a 10-mg tablet.

The 4-mg granule formulation is bioequivalent to the 4-mg chewable tablet when administered to adults in the fasted state. In paediatric patients 6 months to 2 years of age, C_{max} is achieved 2 hours after administration of the 4-mg granules formulation. C_{max} is nearly 2-fold greater than in adults receiving a 10-mg tablet. The co-administration of applesauce or a high-fat standard meal with the granule formulation did not have a clinically meaningful effect on the pharmacokinetics of montelukast as determined by AUC (1225.7 vs 1223.1 ng.hr/mL with and without applesauce, respectively, and 1191.8 vs 1148.5 ng.hr/mL with and without a high-fat standard meal, respectively).

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

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

In vitro studies using human liver microsomes indicate that cytochrome P450 3A4, 2A6 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. The contribution of metabolites to the therapeutic effect of montelukast is minimal.

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

Characteristics in patients: No dosage adjustment is necessary for the elderly or mild to moderate hepatic insufficiency. Studies in patients with renal impairment have not been conducted. Because montelukast and its metabolites are eliminated by the biliary route, no dose adjustment is anticipated to be necessary in patients with renal impairment. There are no data on the pharmacokinetics of montelukast in patients with severe hepatic insufficiency (Child-Pugh score=9). With high doses of montelukast (20- and 60-fold the recommended adult dose), a decrease in plasma theophylline concentration was observed. This effect was not seen at the recommended dose of 10 mg once daily.

5.3 Preclinical safety data

In animal toxicity studies, minor serum biochemical alterations in ALT, glucose, phosphorus and triglycerides were observed which were transient in nature. The signs of food intake increased excretion of saline, gastro-intestinal symptoms, loose stools and ion imbalance. These occurred at doses which provided 17-fold the systemic exposure seen at the clinical dosage. In monkeys, the adverse effects appeared at doses from 150 mg/kg/day (>232-fold the systemic exposure seen at the clinical dose). In animal studies, montelukast did not affect fertility or reproductive performance at systemic exposure exceeding the clinical systemic exposure by greater than 24-fold. A slight decrease in pup body weight was noted in the female fertility study in rats at 200 mg/kg/day (>69-fold the clinical systemic exposure). In studies in rabbits, a higher incidence of incomplete ossification, compared with concurrent control animals, was seen at systemic exposure-24-fold the clinical systemic exposure seen at the clinical dose. No abnormalities were seen in rats. Montelukast has been shown to cross the placental barrier and is excreted in breast milk of animals.

No deaths occurred following a single oral administration of montelukast sodium at doses up to 5,000 mg/kg in mice and rats (15,000 mg/m² and 30,000 mg/m² in mice and rats, respectively) the maximum dose tested. This dose is equivalent to 25,000 times the recommended daily adult human dose (based on an adult patient weight of 50 kg).

Montelukast was determined not to be phototoxic in mice for UVA, UVB or visible light spectra at doses up to 500 mg/kg/day (approximately 200-fold based on adult systemic exposure).

Montelukast was neither mutagenic in vitro nor in vivo tests nor tumorigenic in rodent species.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Mannitol, hydroxypropyl cellulose, and magnesium stearate.

6.2 Incompatibilities

Not applicable.

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6.3 Shelf life

2 years

6.4 Special precautions for storage

Store in the original package.

6.5 Nature and contents of container

Packaged in polyethylene/aluminium/polyester sachet in: Cartons of 7, 20, 28 and 30 sachets. Not all pack sizes may be marketed.

6.6 Instructions for use and handling

No special requirements.

7. MARKETING AUTHORISATION HOLDER

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Hertfordshire EN11 9BU, UK

8. MARKETING AUTHORISATION NUMBER(S)

PL 0025/0440

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

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10. DATE OF REVISION OF THE TEXT

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LEGAL CATEGORY

POM

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