

EUROPEAN UNION CORE SAFETY PROFILE**Montelukast Sodium 4 mg Oral Granules****4.2 Posology and method of administration**

This medicinal product is to be given to a child under adult supervision. 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. Efficacy data from clinical trials in paediatric patients 6 months to 2 years of age with persistent asthma are limited. Patients should be evaluated after 2 to 4 weeks for response to montelukast treatment. Treatment should be discontinued if a lack of response is observed. The montelukast sodium 4 mg granules formulation is not recommended below 6 months of age.

Montelukast Sodium 4 mg Chewable Tablets:

For children who have problems consuming a chewable tablet, a granule formulation is available (see montelukast sodium 4 mg granule SPC).

The montelukast sodium 4 mg chewable tablet formulation is not recommended below 2 years of age.

Administration of montelukast sodium granules:

Montelukast sodium 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 montelukast sodium granules must be administered immediately (within 15 minutes). If mixed with food, montelukast sodium granules must not be stored for future use. Montelukast sodium granules are not intended to be dissolved in liquid for administration. However, liquids may be taken subsequent to administration. Montelukast sodium granules can be administered without regard to the timing of food ingestion.

Montelukast Sodium 10 mg Film-coated Tablets:

Montelukast sodium should not be used concomitantly with other products containing the same active ingredient, montelukast.

General recommendations. The therapeutic effect of montelukast sodium on parameters of asthma control occurs within one day. Patients should be advised to continue taking montelukast sodium 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.

Montelukast sodium as an alternative treatment option to low-dose inhaled corticosteroids for mild, persistent asthma:

Montelukast is not recommended as monotherapy in patients with moderate persistent asthma. The use of montelukast as an alternative treatment option to low-dose inhaled corticosteroids for children 2 to 5 years old with mild persistent asthma should only be considered for patients who do not have a recent history of serious asthma attacks that required oral corticosteroid use and who have demonstrated that they are not capable of using inhaled corticosteroids (see section 4.1). Mild persistent asthma is defined as asthma symptoms more than once a week but less than once a day, nocturnal symptoms more than twice a month but less than once a week, normal lung function between episodes. If satisfactory control of asthma is not achieved at follow-up (usually within one month), the need for an additional or different

anti-inflammatory therapy based on the step system for asthma therapy should be evaluated. Patients should be periodically evaluated for their asthma control.

Montelukast sodium as prophylaxis of asthma for 2 to 5 year old patients in whom the predominant component is exercise-induced bronchoconstriction:

In 2 to 5 year old patients, exercise-induced bronchoconstriction may be the predominant manifestation of persistent asthma that requires treatment with inhaled corticosteroids. Patients should be evaluated after 2 to 4 weeks of treatment with montelukast. If satisfactory response is not achieved, an additional or different therapy should be considered.

Therapy with montelukast sodium in relation to other treatments for asthma.

When treatment with montelukast sodium is used as add-on therapy to inhaled corticosteroids, montelukast sodium should not be abruptly substituted for inhaled corticosteroids (see section 4.4).

10 mg film-coated 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 precautions for use

The diagnosis of persistent asthma in very young children (6 months – 2 years) should be established by a paediatrician or pulmonologist.

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 abruptly 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 have been sometimes associated with the reduction or withdrawal of oral corticosteroid therapy. Although a causal relationship with leukotriene receptor antagonism has not been 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.

Montelukast Sodium 10 mg Film-coated Tablets:

Treatment with montelukast does not alter the need for patients with aspirin-sensitive asthma to avoid taking aspirin and other non-steroidal anti-inflammatory drugs.

Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicine.

Montelukast sodium 5 mg and 4 mg Chewable Tablets:

Montelukast sodium contains aspartame, a source of phenylalanine. Patients with phenylketonuria should take into account that each 5 mg chewable tablet contains phenylalanine in an amount equivalent to 0.842 mg phenylalanine per dose.

Montelukast sodium contains aspartame, a source of phenylalanine. Patients with phenylketonuria should take into account that each 4 mg chewable tablet contains phenylalanine in an amount equivalent to 0.674 mg phenylalanine per dose.

4.5 Interactions 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 medicinal products: 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, 2C8, and 2C9, caution should be exercised, particularly in children, when montelukast is coadministered with inducers of CYP 3A4, 2C8, and 2C9, such as phenytoin, phenobarbital and rifampicin.

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 medicinal products primarily metabolized by CYP 2C8) demonstrated that montelukast does not inhibit CYP 2C8 *in vivo*. Therefore, montelukast is not anticipated to markedly alter the metabolism of medicinal products metabolized by this enzyme (e.g., paclitaxel, rosiglitazone, and repaglinide.)

In vitro studies have shown that montelukast is a substrate of CYP 2C8, and to a less significant extent, of 2C9, and 3A4. In a clinical drug-drug interaction study involving montelukast and gemfibrozil (an inhibitor of both CYP 2C8 and 2C9) gemfibrozil increased the systemic exposure of montelukast by 4.4-fold. No routine dosage adjustment of montelukast is required upon co-administration with gemfibrozil or other potent inhibitors of CYP 2C8, but the physician should be aware of the potential for an increase in adverse reactions.

Based on *in vitro* data, clinically important drug interactions with less potent inhibitors of CYP 2C8 (e.g., trimethoprim) are not anticipated. Co-administration of montelukast with itraconazole, a strong inhibitor of CYP 3A4, resulted in no significant increase in the systemic exposure of montelukast.

4.6 Pregnancy and lactation

Use during pregnancy

Animal studies do not indicate harmful effects with respect to effects on pregnancy or embryonal/foetal development.

Limited data from available pregnancy databases do not suggest a causal relationship between montelukast sodium and malformations (i.e. limb defects) that have been rarely reported in worldwide post marketing experience.

Montelukast sodium may be used during pregnancy only if it is considered to be clearly essential.

Use during lactation

Studies in rats have shown that montelukast is excreted in milk (see section 5.3). It is not known if montelukast is excreted in human milk.

Montelukast sodium may be used in breast-feeding mothers only if it is considered to be clearly essential.

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 or dizziness.

4.8 Undesirable effects

Montelukast has been evaluated in clinical studies in patients with persistent asthma as follows:

- 10 mg film-coated tablets in approximately 4000 adult patients 15 years of age and older
- 5 mg chewable tablets in approximately 1750 paediatric patients 6 to 14 years of age
- 4 mg chewable tablets in 851 paediatric patients 2 to 5 years of age, and
- 4 mg granules in 175 paediatric patients 6 months to 2 years of age.

Montelukast has been evaluated in a clinical study in patients with intermittent asthma as follows:

- 4 mg granules and chewable tablets in 1038 paediatric patients 6 months to 5 years of age

The following drug-related adverse reactions in clinical studies were reported commonly ($\geq 1/100$ to $< 1/10$) 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) (two 56-week studies; n=615)	Paediatric Patients 2 to 5 years old (one 12-week study; n=461) (one 48-week study; n=278)	Paediatric Patients 6 months up to 2 years old (one 6-week study; n=175)

Nervous system disorders	headache	headache		hyperkinesia
Respiratory, thoracic, and mediastinal disorders				asthma
Gastrointestinal disorders	abdominal pain		abdominal pain	diarrhoea
Skin and subcutaneous tissue disorders				eczematous dermatitis, rash
General disorders and administration site conditions			thirst	

With prolonged treatment in clinical trials with a limited number of patients for up to 2 years for adults, and up to 12 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 534 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.

Post-marketing Experience

Adverse reactions reported in post-marketing use are listed, by System Organ Class and specific Adverse Experience Term, in the table below. Frequency Categories were estimated based on relevant clinical trials.

System Organ Class	Adverse Experience Term	Frequency Category*
Infections and infestations	upper respiratory infection†	Very Common
Blood and lymphatic system disorders	increased bleeding tendency	Rare
Immune system disorder	hypersensitivity reactions including anaphylaxis	Uncommon
	hepatic eosinophilic infiltration	Very Rare
Psychiatric disorders	dream abnormalities including nightmares, insomnia, somnambulism, irritability, anxiety, restlessness, agitation including aggressive behaviour or hostility, depression	Uncommon
	tremor	Rare
	hallucinations, disorientation, suicidal	Very Rare

	thinking and behaviour (suicidality)	
Nervous system disorder	dizziness, drowsiness, paraesthesia/hypoesthesia, seizure	Uncommon
Cardiac disorders	palpitations	Rare
Respiratory, thoracic and mediastinal disorders	epistaxis	Uncommon
	Churg-Strauss Syndrome (CSS) (see section 4.4)	Very Rare
Gastrointestinal disorders	diarrhoea [†] , nausea [†] , vomiting [†]	Common
	dry mouth, dyspepsia	Uncommon
Hepatobiliary disorders	elevated levels of serum transaminases (ALT, AST)	Common
	hepatitis (including cholestatic, hepatocellular, and mixed-pattern liver injury).	Very Rare
Skin and subcutaneous tissue disorders	rash [†]	Common
	bruising, urticaria, pruritus	Uncommon
	angioedema	Rare
	erythema nodosum, erythema multiforme	Very Rare
Musculoskeletal, connective tissue and bone disorders	arthralgia, myalgia including muscle cramps	Uncommon
General disorders and administration site conditions	pyrexia [†]	Common
	asthenia/fatigue, malaise, oedema,	Uncommon
<p>*Frequency Category: Defined for each Adverse Experience Term by the incidence reported in the clinical trials data base: Very Common ($\geq 1/10$), Common ($\geq 1/100$ to $< 1/10$), Uncommon ($\geq 1/1000$ to $< 1/100$), Rare ($\geq 1/10,000$ to $< 1/1000$), Very Rare ($< 1/10,000$).</p> <p>[†]This adverse experience, reported as Very Common in the patients who received montelukast, was also reported as Very Common in the patients who received placebo in clinical trials.</p> <p>[‡]This adverse experience, reported as Common in the patients who received montelukast, was also reported as Common in the patients who received placebo in clinical trials.</p>		

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 post-marketing experience and clinical studies with montelukast. These include reports in adults and children with a dose as high as 1000 mg (approximately 61 mg/kg in a 42 month old child). 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 montelukast and included abdominal pain, somnolence, thirst, headache, vomiting, and psychomotor hyperactivity.

EUCSP-MK0476-OG-FI/H/0104/01-04/070/WS-2
(montelukast sodium, MSD)

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