

SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Montelukast 4 mg chewable tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each Montelukast 4 mg chewable tablet contains 4.16 mg montelukast sodium which corresponds to 4 mg montelukast.

Excipients:

Aspartame 0.3 mg per tablet

For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Chewable tablet

Pink coloured, oval biconvex shaped, uncoated tablets, with breakline on both sides.

The tablet can be divided into equal halves.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Montelukast is indicated in the treatment of asthma as add-on therapy in those 2 to 5 year old 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.

Montelukast may also be an alternative treatment option to low-dose inhaled corticosteroids for 2 to 5 year old patients with mild persistent asthma 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 4.2).

Montelukast is also indicated in the prophylaxis of asthma from 2 years of age and older in which the predominant component is exercise-induced bronchoconstriction.

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 2 to 5 years of age is one 4 mg chewable tablet daily to be taken in the evening. If taken in connection with food, Montelukast chewable tablets should be taken 1 hour before or 2 hours after food. The tablet can be chewed or swallowed. No dosage adjustment within this age group is necessary.

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

Method of administration:

For oral use.

The tablet can be chewed or swallowed. If swallowed it should be taken with sufficient amount of fluid (e.g. a glass of water).

General recommendations. The therapeutic effect of Montelukast on parameters of asthma control occurs within one day. Patients should be advised to continue taking Montelukast 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 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 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 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 in relation to other treatments for asthma

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

Other available strengths and pharmaceutical forms:

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

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

4.3 Contraindications

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

4.4 Special warnings and 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 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 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.

Montelukast 4 mg chewable tablets contain aspartame, a source of phenylalanine. May be harmful for patients with phenylketonuria. Each 4 mg tablet contains phenylalanine in an amount equivalent to 0.169 mg phenylalanine per dose.

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 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 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 and malformations (i.e. limb defects) that have been rarely reported in worldwide post marketing experience.

Montelukast 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 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 4,000 adults and adolescent patients 15 years of age and older.
- 5 mg chewable tablets in approximately 1,750 paediatric patients 6 to 14 years of age.
- 4 mg chewable tablets in 851 paediatric patients 2 to 5 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	Adults and 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)
Nervous system disorders	headache	headache	
Gastrointestinal disorders	abdominal pain		abdominal pain
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.

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 thinking and behaviour	Very Rare

	(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	diarrhoe [‡] , 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.

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

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmaco-therapeutic group: Other systemic drugs for obstructive airway diseases, Leukotriene receptor antagonists

ATC-code: R03D C03

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 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 a 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 nighttime 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: -8.70 % vs 2.64 %). 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 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/nebulized corticosteroids or inhaled/nebulized 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.

In a 12-month, placebo-controlled study in paediatric patients 2 to 5 years of age with mild asthma and episodic exacerbations, montelukast 4 mg once daily significantly ($p \leq 0.001$) reduced the yearly rate of asthma exacerbation episodes (EE) compared with placebo (1.60 EE vs. 2.34 EE, respectively), [EE defined as ≥ 3 consecutive days with daytime symptoms requiring β -agonist use, or corticosteroids (oral or inhaled), or hospitalization for asthma]. The percentage reduction in yearly EE rate was 31.9 %, with a 95 % CI of 16.9, 44.1.

In a placebo-controlled study in paediatric patients 6 months to 5 years of age who had intermittent asthma but did not have persistent asthma, treatment with montelukast was administered over a 12-month period, either as a once-daily 4 mg regimen or as a series of 12-day courses that each were started when an episode of intermittent symptoms began. No significant difference was observed between patients treated with montelukast 4 mg or placebo in the number of asthma episodes culminating in an asthma attack, defined as an asthma episode requiring utilization of health-care resources such as an unscheduled visit to a doctor's office, emergency room, or hospital or treatment with oral, intravenous, or intramuscular corticosteroid.

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 PEF 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-month study comparing the efficacy of montelukast to inhaled fluticasone on asthma control in paediatric patients 6 to 14 years of age with mild persistent asthma, montelukast was non-inferior to fluticasone in increasing the percentage of asthma rescue-free days (RFDs), the primary endpoint. Averaged over the 12-month treatment period, the percentage of asthma RFDs increased from 61.6 to 84.0 in the montelukast group and from 60.9 to 86.7 in the fluticasone group. The between group difference in LS mean increase in the percentage of asthma RFDs was statistically significant (- 2.8 with a 95 % CI of -4.7, -0.9), but within the limit pre-defined to be clinically not inferior. Both montelukast and fluticasone also improved asthma control on secondary variables assessed over the 12 month treatment period:

FEV₁ increased from 1.83 L to 2.09 L in the montelukast group and from 1.85 L to 2.14 L in the fluticasone group. The between-group difference in LS mean increase in FEV₁ was -0.02 L with a 95 % CI of -0.06, 0.02. The mean increase from baseline in % predicted FEV₁ was 0.6 % in the montelukast treatment group, and 2.7 % in the

fluticasone treatment group. The difference in LS means for the change from baseline in the % predicted FEV₁ was significant: -2.2 % with a 95 % CI of -3.6, -0.7.

The percentage of days with β -agonist use decreased from 38.0 to 15.4 in the montelukast group, and from 38.5 to 12.8 in the fluticasone group. The between group difference in LS means for the percentage of days with β -agonist use was significant: 2.7 with a 95 % CI of 0.9, 4.5.

The percentage of patients with an asthma attack (an asthma attack being defined as a period of worsening asthma that required treatment with oral steroids, an unscheduled visit to the doctor's office, an emergency room visit, or hospitalization) was 32.2 in the montelukast group and 25.6 in the fluticasone group; the odds ratio (95 % CI) being significant: equal to 1.38 (1.04, 1.84).

The percentage of patients with systemic (mainly oral) corticosteroid use during the study period was 17.8 % in the montelukast group and 10.5% in the fluticasone group. The between group difference in LS means was significant: 7.3 % with a 95 % CI of 2.9; 11.7.

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 27.98 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 is 64 %. The oral bioavailability and C_{max} are not influenced by a standard meal. Safety and efficacy were demonstrated in clinical trials where the 10 mg 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.

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

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

Cytochrome P450 2C8 is the major enzyme in the metabolism of montelukast. Additionally CYP 3A4 and 2C9 may have a minor contribution, although itraconazole, an inhibitor of CYP 3A4, was shown not to change pharmacokinetic variables of montelukast in healthy subjects that received 10 mg montelukast daily. 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 fecal collections and <0.2 % was recovered in urine. Coupled with estimates of montelukast oral bioavailability, this indicates that montelukast and its metabolites are excreted almost exclusively via the bile.

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 undertaken. 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 toxicity in animals were increased excretion of saliva, gastrointestinal symptoms, loose stools and ion imbalance. These occurred at dosages 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 milk of animals.

No deaths occurred following a single oral administration of montelukast sodium at doses up to 5000 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 systemic exposure).

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

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Mannitol (E421)
Cellulose, Microcrystalline
Croscarmellose Sodium
Magnesium Stearate
Aspartame (E951)
Iron Oxide Red (E172)
Cherry Flavour (Firmenich CHERRY 501027 AP0551)

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

5 years

6.4 Special precautions for storage

This medicinal product does not require any special temperature storage conditions. Store in the original package in order to protect from light and moisture.

6.5 Nature and contents of container

Tablets are packed into a cold forming blister foil sealed with aluminium foil (Alu/Alu blister). The blisters are packed into cartons.

Pack sizes of: 10, 14, 20, 28, 50, 56, 98, 100 tablets

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

No special requirements.

Any unused product or waste material should be disposed of in accordance with local requirements.

7 MARKETING AUTHORISATION HOLDER

Torrent Pharma (UK) Ltd
Unit 4, Charlwood Court
County Oak Way, Crawley
West Sussex RH11 7XA
United Kingdom

8 MARKETING AUTHORISATION NUMBER(S)

PL 36687/0047

**9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE
AUTHORISATION**

22/11/2010

10 DATE OF REVISION OF THE TEXT

25/02/2013

SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

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2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each Montelukast 5 mg chewable tablet contains 5.2 mg montelukast sodium which corresponds to 5 mg montelukast.

Excipients:

Aspartame 0.375 mg per tablet

For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Chewable tablet

Pink coloured, round, uncoated tablets, with breakline on both sides.

The tablet can be divided into equal halves.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Montelukast is indicated in the treatment of asthma as add-on therapy in those 6 to 14 year old 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.

Montelukast may also be an alternative treatment option to low-dose inhaled corticosteroids for 6 to 14 year old patients with mild persistent asthma 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 4.2).

Montelukast is also indicated in the prophylaxis of asthma in which the predominant component is exercise-induced bronchoconstriction.

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 to 14 years of age is one 5 mg chewable tablet daily to be taken in the evening. If taken in connection with food, Montelukast chewable tablets should be taken 1 hour before or 2 hours after food. The tablet can be chewed or swallowed. No dosage adjustment within this age group is necessary.

Method of administration:

For oral use.

The tablet can be chewed or swallowed. If swallowed it should be taken with sufficient amount of fluid (e.g. a glass of water).

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

Therapy with Montelukast in relation to other treatments for asthma.

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

Other available strengths and pharmaceutical forms:
4 mg chewable tablets are available for paediatric patients 2 to 5 years of age.
10 mg tablets are available for adolescents and adults 15 years of age and older.

4.3 Contraindications

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

4.4 Special warnings and 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 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 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.

Montelukast 5 mg chewable tablets contain aspartame, a source of phenylalanine. May be harmful for patients with phenylketonuria. Each 5 mg tablet contains phenylalanine in an amount equivalent to 0.211 mg phenylalanine per dose.

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 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 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 and malformations (i.e. limb defects) that have been rarely reported in worldwide post marketing experience.

Montelukast 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 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 as follows:

- 10 mg film-coated tablets in approximately 4,000 adults and adolescent patients 15 years of age and older.
- 5 mg chewable tablets in approximately 1,750 paediatric patients 6 to 14 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	Adults and 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)
Nervous system disorders	headache	headache
Gastrointestinal disorders	abdominal pain	
General disorders and administration site conditions		

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.

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 thinking and behaviour (suicidality)	Very Rare
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.

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

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Other systemic drugs for obstructive airway diseases, Leukotriene receptor antagonists

ATC-code: R03D C03

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 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 a 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 nighttime 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: -8.70 % vs 2.64 %). 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-month study comparing the efficacy of montelukast to inhaled fluticasone on asthma control in paediatric patients 6 to 14 years of age with mild persistent asthma, montelukast was non-inferior to fluticasone in increasing the percentage of asthma rescue-free days (RFDs), the primary endpoint. Averaged over the 12-month treatment period, the percentage of asthma RFDs increased from 61.6 to 84.0 in the montelukast group and from 60.9 to 86.7 in the fluticasone group. The between group difference in LS mean increase in the percentage of asthma RFDs was statistically significant (-2.8 with a 95 % CI of -4.7, -0.9), but within the limit pre-defined to be clinically not inferior. Both montelukast and fluticasone also improved asthma control on secondary variables assessed over the 12 month treatment period:

FEV₁ increased from 1.83 L to 2.09 L in the montelukast group and from 1.85 L to 2.14 L in the fluticasone group. The between-group difference in LS mean increase in FEV₁ was -0.02 L with a 95 % CI of -0.06, 0.02. The mean increase from baseline in % predicted FEV₁ was 0.6 % in the montelukast treatment group, and 2.7 % in the fluticasone treatment group. The difference in LS means for the change from baseline in the % predicted FEV₁ was significant: -2.2 % with a 95 % CI of -3.6, -0.7.

The percentage of days with β -agonist use decreased from 38.0 to 15.4 in the montelukast group, and from 38.5 to 12.8 in the fluticasone group. The between

group difference in LS means for the percentage of days with β -agonist use was significant: 2.7 with a 95 % CI of 0.9, 4.5.

The percentage of patients with an asthma attack (an asthma attack being defined as a period of worsening asthma that required treatment with oral steroids, an unscheduled visit to the doctor's office, an emergency room visit, or hospitalization) was 32.2 in the montelukast group and 25.6 in the fluticasone group; the odds ratio (95 % CI) being significant: equal to 1.38 (1.04, 1.84).

The percentage of patients with systemic (mainly oral) corticosteroid use during the study period was 17.8 % in the montelukast group and 10.5% in the fluticasone group. The between group difference in LS means was significant: 7.3 % with a 95 % CI of 2.9; 11.7.

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 27.98 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 is 64 %. The oral bioavailability and C_{max} are not influenced by a standard meal. Safety and efficacy were demonstrated in clinical trials where the 10 mg 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.

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

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

Cytochrome P450 2C8 is the major enzyme in the metabolism of montelukast. Additionally CYP 3A4 and 2C9 may have a minor contribution, although itraconazole, an inhibitor of CYP 3A4, was shown not to change pharmacokinetic variables of montelukast in healthy subjects that received 10 mg montelukast daily. Based on *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 fecal collections and <0.2 % was recovered in urine. Coupled with estimates of montelukast oral bioavailability, this indicates that montelukast and its metabolites are excreted almost exclusively via the bile.

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 undertaken. 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 toxicity in animals were increased excretion of saliva, gastrointestinal symptoms, loose stools and ion imbalance. These occurred at dosages 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 milk of animals.

No deaths occurred following a single oral administration of montelukast sodium at doses up to 5000 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 systemic exposure).

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

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Mannitol (E421)
Cellulose, Microcrystalline

Croscarmellose Sodium
Magnesium Stearate
Aspartame (E951)
Iron Oxide Red (E172)
Cherry Flavour (Firmenich CHERRY 501027 AP0551)

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

5 years

6.4 Special precautions for storage

This medicinal product does not require any special temperature storage conditions. Store in the original package in order to protect from light and moisture.

6.5 Nature and contents of container

Tablets are packed into a cold forming blister foil sealed with aluminium foil (Alu/Alu blister). The blisters are packed into cartons.

Pack sizes of: 10, 14, 20, 28, 50, 56, 98, 100 tablets

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

No special requirements.

Any unused product or waste material should be disposed of in accordance with local requirements.

7 MARKETING AUTHORISATION HOLDER

Torrent Pharma (UK) Ltd
Unit 4, Charlwood Court
County Oak Way, Crawley
West Sussex RH11 7XA
United Kingdom

8 MARKETING AUTHORISATION NUMBER(S)

PL 36687/0048

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

22/11/2010

10 DATE OF REVISION OF THE TEXT

25/02/2013

SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Montelukast 10 mg tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains 10.4 mg montelukast sodium which corresponds to 10 mg montelukast.

Excipients:

Aspartame 0.75 mg per tablet

For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Tablet

Light brown coloured, round biconvex shaped, uncoated tablet, with breakline on both sides.

The tablet can be divided into equal halves.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Montelukast is indicated in the treatment of asthma as add-on therapy in adolescents and adults from 15 years of age 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.

In those asthmatic patients in whom Montelukast is indicated in asthma, Montelukast can also provide symptomatic relief of seasonal allergic rhinitis.

Montelukast 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 adults and adolescents 15 years of age and older with asthma, or with asthma and concomitant seasonal allergic rhinitis, is one 10-mg tablet daily to be taken in the evening. Montelukast tablets may be taken with or without food.

Method of administration:

For oral use.

The tablet should be swallowed with a sufficient amount of fluid (e.g. a glass of water).

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

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

No dosage adjustment is necessary for the elderly, or 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 Montelukast in relation to other treatments for asthma.

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

Inhaled corticosteroids: Treatment with Montelukast can be used as add-on therapy in patients when inhaled corticosteroids plus "as needed" short acting β -agonists provide inadequate clinical control. Montelukast should not be abruptly substituted for inhaled corticosteroids (see section 4.4).

Other available strengths/pharmaceuticals form:

4 mg chewable tablets are available for paediatric patients 2 to 5 years of age.

5 mg chewable tablets are available for paediatric patients 6 to 14 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

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.

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

Montelukast 10 mg tablets contain aspartame, a source of phenylalanine. May be harmful for patients with phenylketonuria. Each 10 mg tablet contains phenylalanine in an amount equivalent to 0.421 mg phenylalanine per dose.

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 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 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 and malformations (i.e. limb defects) that have been rarely reported in worldwide post marketing experience.

Montelukast 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 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 as follows:

- 10 mg film-coated tablets in approximately 4,000 adults and adolescent patients 15 years of age and older.
- 10 mg film-coated tablets in approximately 400 adult and adolescent patients from 15 years of age and older with seasonal allergic rhinitis.
- 5 mg chewable tablets in approximately 1,750 paediatric patients 6 to 14 years of age.

The following drug-related adverse reactions in clinical studies were reported commonly ($\geq 1/100$ to $< 1/10$) in asthmatic 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)
Nervous system disorders	headache	headache
Gastro-intestinal disorders	abdominal pain	

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.

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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.

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	hepatic eosinophilic infiltration	Very Rare
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	tremor	Rare
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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	diarrhoe [‡] , 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
	angiooedema	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.

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

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Other systemic drugs for obstructive airway diseases, Leukotriene receptor antagonists

ATC-code: R03D C03

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 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 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 a 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 and in peripheral blood) 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 nighttime 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: -8.70% vs 2.64%). 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).

A clinical study was conducted to evaluate montelukast for the symptomatic treatment of seasonal allergic rhinitis in adult asthmatic patients 15 years of age and older with concomitant seasonal allergic rhinitis. In this study, montelukast 10-mg tablets administered once daily demonstrated a statistically significant improvement in the Daily Rhinitis Symptoms score, compared with placebo. The Daily Rhinitis Symptoms score is the average of the Daytime Nasal Symptoms score (mean of nasal congestion, rhinorrhea, sneezing, nasal itching) and the Nighttime Symptoms score (mean of nasal congestion upon awakening, difficulty going to sleep, and nighttime awakenings scores). Global evaluations of allergic rhinitis by patients and physicians were significantly improved, compared with placebo. The evaluation of asthma efficacy was not a primary objective in this study.

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 PEF 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).

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 27.98 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 is 64%. The oral bioavailability and C_{max} are not influenced by a standard meal. Safety and efficacy were demonstrated in clinical trials where the 10-mg 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.

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

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

Cytochrome P450 2C8 is the major enzyme in the metabolism of montelukast. Additionally CYP 3A4 and 2C9 may have a minor contribution, although itraconazole, an inhibitor of CYP 3A4, was shown not to change pharmacokinetic variables of montelukast in healthy subjects that received 10 mg montelukast daily. 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 fecal collections and < 0.2% was recovered in urine. Coupled with estimates of montelukast oral bioavailability, this indicates that montelukast and its metabolites are excreted almost exclusively via the bile.

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 undertaken. 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 toxicity in animals were increased excretion of saliva, gastrointestinal symptoms, loose stools and ion imbalance. These occurred at dosages 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 milk of animals.

No deaths occurred following a single oral administration of montelukast sodium at doses up to 5000 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 systemic exposure).

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

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Mannitol (E421)

Cellulose, Microcrystalline

Croscarmellose Sodium

Magnesium Stearate

Aspartame (E951)

Cherry Flavour (Firmenich CHERRY 501027 AP0551)

Iron oxide yellow (E172)

Iron Oxide Red (E172)

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

5 years

6.4 Special precautions for storage

This medicinal product does not require any special temperature storage conditions. Store in the original package in order to protect from light and moisture.

6.5 Nature and contents of container

Tablets are packed into a cold forming blister foil sealed with aluminium foil (Alu/Alu blister). The blisters are packed into cartons.

Pack sizes of: 10, 14, 20, 28, 50, 56, 98, 100 tablets

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

No special requirements.

Any unused product or waste material should be disposed of in accordance with local requirements.

7 MARKETING AUTHORISATION HOLDER

Torrent Pharma (UK) Ltd
Unit 4, Charlwood Court
County Oak Way, Crawley
West Sussex RH11 7XA
United Kingdom

8 MARKETING AUTHORISATION NUMBER(S)

PL 36687/0046

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

22/11/2010

10 DATE OF REVISION OF THE TEXT

25/02/2013