Summary of Product Characteristics

1. NAME OF THE MEDICINAL PRODUCT (FPP)

ALUKON®

Montelukast

1.1 Strength 4 mg

1.2 Pharmaceutical form granules

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

One sachet of granules contains montelukast sodium equivalent to 4 mg of montelukast.

For a full list of excipients, please see Section 6.1.

3. PHARMACEUTICAL FORM

Granules.

White, homogeneous granules, one dose per sachet.

4. CLINICAL PARTICULARS

4.1. Therapeutic indications

Alukon is indicated in the treatment of asthma as add-on therapy in patients 6 months to 5 years of age with mild to moderate persistent asthma who are inadequately controlled on inhaled corticosteroids and in whom 'as-needed' short acting beta-agonists provide inadequate clinical control of asthma.

Alukon can also be an alternative to low-dose inhaled corticoids in patients 2 to 5 years of age with mild persistent asthma with no recent history of severe asthma attacks requiring oral corticoid therapy, and who have demonstrated inability to adhere to inhaled corticoid therapy (see section 4.2).

Alukon 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 mode of administration

4.2.1. Posology

This medicinal product is to be given to a child under adult supervision.
In patients 6 months to 5 years of age, the posology is one sachet of 4 mg granules per day, to be taken in the evening.
No dosage adjustment is necessary in this age group. There is limited efficacy data from clinical studies conducted on paediatric patients 6 months to 2 years of age with persistent asthma.
The response to treatment with montelukast should be assessed after 2 to 4 weeks, and treatment should be discontinued in the absence of a response.
Alukon should not be used in children under 6 months of age.

General recommendations

The therapeutic effect of Alukon on parameters of asthma control occurs within one day. Patients should be advised to continue taking Alukon even if their asthma has become stable, as well as during periods of symptom exacerbation.
Alukon should not be used concomitantly with other products containing the same active ingredient, montelukast.

Alukon used as an alternative to low-dose inhaled corticoid therapy in mild persistent asthma

Montelukast is not recommended as single treatment in patients with moderate persistent asthma. Montelukast should only be considered as an alternative to low-dose inhaled corticoids in children 2 to 5 years of age with mild persistent asthma, with no recent history of severe asthma attacks requiring oral corticoid therapy, and who have demonstrated inability to adhere to inhaled corticoid therapy (see section 4.1). Mild persistent asthma is characterised by daytime symptoms appearing more than once weekly, but less than once daily, night-time symptoms more than twice monthly, but less than once weekly, and normal lung function between attacks. If asthma control is found to be insufficient during monitoring (typically within a month), an additional or different anti-inflammatory therapy should be considered based on a step-by-step treatment scheme. Asthma control in these patients should be evaluated at regular intervals.

Alukon used in the prophylaxis of exercise-induced asthma in children 2 to 5 years of age.

In children 2 to 5 years of age, exercise-induced bronchoconstriction can be the main manifestation of persistent asthma requiring inhaled corticosteroid therapy.

Response to treatment with montelukast should be evaluated after 2 to 4 weeks. If the effect is insufficient, an additional or different therapy should be considered.

Administration of Alukon with other asthma treatments
When Alukon is used as add-on therapy to inhaled corticoids, it should not be abruptly substituted for inhaled corticoids (see section 4.4).

4.2.2. Special populations

Renal impairment or hepatic insufficiency
No dosage adjustment is necessary in patients with mild to moderate renal impairment or hepatic insufficiency.
There are no data available in patients with severe hepatic insufficiency.

4.2.3. Pediatric population

No dosage adjustment is necessary in this age group.
Alukon 4 mg should not be used in children under 6 months of age. The safety and efficacy of Alukon 4 mg in patients under 6 months of age have not been established.

Alukon 5 mg chewable tablets are available for children 6 to 14 years of age.

4.2.4. Method of administration

Oral use

- Alukon 4 mg granules may be administered directly into the mouth or mixed with one spoonful of food, preferably half-liquid, either cold or at room temperature (for example, apple sauce, ice-cream, carrots and rice). Only open the sachet at the time of taking the medicine.
- After opening, the full dose of Alukon 4 mg granules must be administered within 15 minutes and may not be store for later use if mixed with food.
- Alukon 4 mg granules are not intended to be dissolved in a drink; however, drinks may be taken after administration.
- Alukon 4 mg granules can be administered without regard to the timing of food ingestion.

4.3. Contraindications

Hypersensitivity to the active ingredient or to any of the excipients listed in Section 6.1.

4.4. Special warning and precautions for use

In very young children (6 months to 2 years of age), the diagnosis of persistent asthma must be determined by a paediatrician or a pulmonologist.

Patients should be advised never to use oral montelukast to treat acute asthma attacks and to keep their usual appropriate rescue medication readily available. If an acute attack occurs, a short-acting inhaled beta-2-mimetics should be used. Patients should seek their doctors' advice as soon as possible if they need more inhalations of short-acting beta-2-mimetics than usual.

Alukon should not be substituted abruptly for inhaled or oral corticoids.

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 develop systemic eosinophilia, sometimes associated 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.

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.

Neuropsychiatric events have been reported in adults, adolescents and children taken a medicine with montelukast. Patients and doctors should be alert for neuropsychiatric events. Patients and/or caregivers should be instructed to notify their doctor of these changes occur. Prescribers should evaluate the risks and benefits of continuing treatment with Alukon if such events occur.

4.5. Interactions with other medicinal products and other forms of interactions

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 co-administered 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 cytochrome CYP 2C8. However, data from a clinical drug-drug interaction study involving montelukast and rosiglitazone (a probe substrate representative of medicinal products primarily metabolised by CYP 2C8) demonstrated that montelukast does not inhibit CYP 2C8 in vivo. Therefore, it is unlikely that montelukast would alter the metabolism of medicinal products metabolised 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 risk 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. Fertility, pregnancy and lactation

4.6.1. Fertility

No data available on human fertility. In animal studies, montelukast did not affect fertility or reproductive performance at systemic exposure exceeding the clinical systemic exposure by greater than 24-fold.

4.6.2. Pregnancy

Animal studies do not indicate harmful effects on gestation 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 rarely been reported in worldwide post-marketing experience.

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

4.6.3. Lactation

Studies in rats have shown that montelukast is excreted in milk. It is unknown whether montelukast and metabolites are excreted in human milk (see section 5.3). Alukon may only be used in breast-feeding if necessary.

4.6.4. Fertility

No data available on human fertility. In animal studies, montelukast did not affect fertility or reproductive performance at systemic exposure exceeding the clinical systemic exposure by greater than 24-fold.

4.7. Effects on the ability to drive and use machines

Montelukast has no or negligible influence on the ability to drive and use machines. However, patients 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 adult and adolescent asthmatic patients 15 years of age and older.
- 5 mg chewable tablets in approximately 1,750 paediatric asthmatic patients 6 to 14 years of age.
- 4 mg chewable tablets in 851 paediatric patients 2 to 5 years of age.
- 4 mg granules in 175 paediatric patients aged 6 months to 2 years.

Montelukast was evaluated in a clinical study on patients with intermittent asthma, as follows:

- 4 mg granules and chewable tablets in 1,038 paediatric patients 6 months to 5 years of age.

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

System Organ Class	**Adults and adolescents 15 years of age and over** *(2 studies of 12 weeks; n = 795)*	**Children 6 to 14 years of age** *(1 study of 8 weeks; n = 201) (2 studies of 56 weeks; n = 615)*	**Children 2 to 5 years of age** *(1 study of 12 weeks; n = 461) (1 study of 48-weeks; n = 278)*	**Children 6 months to 2 years of age** *(1 study of 6 weeks; 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, Skin rash
General disorders and administration site conditions			Thirst	

In clinical studies on a limited number of patients who had received an extended treatment for up to 2 years for adults and up to 12 months for paediatric patients 6 to 14 years of age, the safety profile remained unchanged.
In total, 502 children 2 to 5 years of age were treated with montelukast for at least 3 months, 338 for 6 months or more, and 534 patients for 12 months or more. The safety profile also remained unchanged in those patients who had received an extended treatment.
In paediatric patients aged 6 months to 2 years, the safety profile did not change with treatments up to 3 months.

Tabulated list of adverse reactions

Adverse reactions reported in post-marketing use are listed below by System Organ Class and per adverse reaction. Frequency categories were estimated based on relevant

clinical studies: Very common (≥1/10), common (≥1/100, <1/10), uncommon (≥1/1,000, <1/100), rare (≥1/10,000, <1/1,000), very rare (<1/10,000).

System Organ Class	Undesirable effects	Frequency
Infections and infestations	Upper respiratory infection[1]	Very common
Blood and lymphatic system disorders	Increased bleeding tendency	Rare
Immune system disorders	Hypersensitivity reactions, including anaphylaxis	Uncommon
	Hepatic eosinophilic infiltration	Very rare
Psychiatric disorders	Dream abnormalities including nightmares, insomnia, somnambulism, anxiety, agitation including aggressive behaviour or hostility, depression, psychomotor hyperactivity (including irritability, restlessness, tremor[3])	Uncommon
	Disturbance in attention, memory impairment	Rare
	Hallucinations, disorientation, suicidal thinking and behaviour (suicidality) ,obsessive-compulsive symptom, dysphemia	Very rare
Nervous system disorders	Dizziness, drowsiness, paraesthesia/hypoaesthesia, seizure	Uncommon
Cardiac disorders	Palpitations	Rare
Respiratory, thoracic and mediastinal disorders	Epistaxis	Uncommon
	Churg-Strauss syndrome, (see section 4.4)	Very rare
	Pulmonary eosinophilia	Very rare
Gastro-intestinal disorders	Diarrhoea[2], nausea[2], vomiting[2]	Common
	Dry mouth, dyspepsia	Uncommon
Hepatobiliary disorders	Elevated serum transaminase levels (ALT, AST)	Common
	Hepatitis (including cholestatic, hepatocellular and mixed-pattern liver injury).	Very rare
Skin and subcutaneous tissue disorders	Skin rash[2]	Common
	Bruising, urticaria, pruritus	Uncommon

System Organ Class	Undesirable effects	Frequency
	Angio-oedema	Rare
	Erythema nodosum, erythema multiforme	Very rare
Musculoskeletal and connective tissue disorders	Arthralgia, myalgia, including muscle cramps	Uncommon
Renal and urinary disorders	Enuresis in children	Uncommon
General disorders and administration site conditions	Pyrexie[2]	Common
	Asthenia/fatigue, malaise, oedema	Uncommon

1. This adverse reaction, 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.
2. This adverse effect, reported as Common in the patients who received montelukast, was also reported as Common in the patients who received placebo in clinical trials.
3. Frequency category: Rare.

4.9. Overdose

In chronic asthma studies, montelukast has been administered at doses up to 200 mg/day to patients for 22 weeks, and in short term studies up to 900 mg/day for approximately one week without clinically important adverse events.
There have been reports of acute overdose in post-marketing experience and clinical studies with montelukast. These included reports in adults and children who had absorbed doses as high as 1,000 mg (approximately 61 mg/kg in a 42-month-old child). The clinical and laboratory findings observed were consistent with the safety profile described in adults and in children. There were no adverse effects in the majority of overdose reports.

Symptoms of overdose
The most commonly reported adverse events were consistent with the known safety profile of montelukast, including abdominal pain, somnolence, thirst, headache, vomiting and psychomotor hyperactivity.

Treatment of overdose
No specific information is available on the treatment of overdose with montelukast. It is not known whether montelukast is dialysable by peritoneal- or haemodialysis.

5. PHARMACOLOGICAL PROPERTIES

5.1. Pharmacodynamic properties

Pharmacotherapeutic group: Other systemic medicines for obstructive respiratory diseases, leukotriene receptor antagonists.
ATC code: R03D C03.

Mechanism of action
The cysteinyl-leukotrienes (LTCs4, LTDs4, LTEs4) are potent inflammatory eicosanoids released from various cells including mast cells and eosinophils. These important pro-asthmatic mediators bind to cysteinyl-leukotriene (CysLT) receptors. Cysteine-rich type-1 receptors ($CysLT_1$) are found in human respiratory airways (in the airway smooth muscle cells and airway macrophages) and in other pro-inflammatory cells (including eosinophils and certain myeloid stem cells). CysLTs have been correlated with the physiopathology 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.

Pharmacodynamic effects
Montelukast is an orally active compound which binds with high affinity and selectivity to the $CysLT_1$ receptor. In clinical studies, montelukast inhibits bronchoconstriction induced by LTD_4 inhalation at doses as low as 5 mg. Bronchodilatation was observed within 2 hours of oral administration. The bronchodilation effect caused by a beta-mimetic was additive to that caused by montelukast. Treatment with montelukast inhibited both early- and late-phase bronchoconstriction induced by antigenic 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 asthma control.

Studies on clinical efficacy and safety in adolescents and adults
In studies in adults, montelukast, 10 mg once daily, compared with placebo, demonstrated significant improvements in morning forced expiratory volume (FEV) per second (10.4% vs 2.7% change from baseline), morning peak expiratory flow rate (PEFR) (24.5L/min vs 3.3L/min change from baseline), and significant decrease in total beta-2-

mimetic use (-26.1% vs -4.6% change from baseline). Improvement in patient-reported daytime and night-time asthma symptom scores was significantly better than placebo.

Studies in adults demonstrated that montelukast adds to the clinical effect of inhaled corticoids (% change compared to study start time for inhaled beclomethasone plus montelukast vs beclomethasone, respectively, for: FEV, 5.43% vs 1.04%; beta-mimetic use: -8.70% vs 2.64%). Compared with inhaled beclomethasone (200µg twice daily with a spacer device), montelukast induced a more rapid initial response, although after 12 weeks beclomethasone provided a greater average treatment effect (percentage of change compared to study start time for montelukast vs beclomethasone, respectively, for: FEV, 7.49% vs 13.3%; beta-mimetic use: -28.8% versus -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 FEV 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 asthmatic patients 15 years of age and older with seasonal allergic rhinitis. In this study, montelukast 10 mg tablets administered once daily induced a statistically significant improvement of the daily rhinitis symptom score compared with placebo. The daily rhinitis symptom score is the average of the daytime nasal symptoms score (mean of nasal congestion, rhinorrhoea, sneezing, nasal itching) and the night-time symptoms score (mean of nasal congestion upon awakening, difficulty going to sleep, and night-time 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.

Significant reduction compared to placebo of exercise-induced bronchoconstriction (EIB) was demonstrated in a 12-week study in adults (maximal fall in FEV 22.33% for montelukast vs 32.40% for placebo; time to recovery to within 5% of baseline FEV: 44.22 minutes vs 60.64 minutes). This effect was consistent throughout the 12-week study period.

In aspirin-intolerant asthmatic patients receiving concomitant inhaled and/or oral corticoid therapy, treatment with montelukast, compared with the placebo, resulted in a significant improvement in asthma control (FEV: +8.55% vs. -1.74% compared to baseline, and a decrease in total beta-mimetic use: -27.78% vs. 2.09% variation compared to baseline), compared to the placebo.

Pediatric population

Studies on clinical efficacy and safety in children

In an 8-week study in children 6 to 14 years of age, montelukast 5 mg once daily, compared with placebo, significantly improved respiratory function (FEV 8.71% vs 4.16% change from baseline; morning PEFR 27.9L/min vs 17.8L/min change from baseline) and decreased 'as-needed' beta-2-mimetic use (-11.7% vs +8.2% change from baseline).

A 12-month study compared the efficacy of montelukast with that of inhaled fluticasone for asthma control in children 6 to 14 years of age with mild persistent asthma. On the primary study endpoint, percentage of days without using a symptomatic rescue treatment, the results analysis found non-inferiority of montelukast compared to fluticasone. On average, over the 12-month treatment period, the percentage of days without using a symptomatic rescue treatment increased from 61.6% to 84.0% in the montelukast group and from 60.9% to 86.7% in the fluticasone group. The difference between the two groups in terms of increase in the percentage of days without using the rescue treatment was statistically significant (-2.8%, with a 95% CI of [-4.7; -0.9]) according to the method of least squares, but remained within the predefined limits of clinical non-inferiority. Both montelukast and fluticasone also improved the secondary endpoints for asthma control during the 12-month treatment period: FEV increased from 1.83L to 2.09L in the montelukast group and from 1.85L to 2.14L in the fluticasone group. The difference between the two groups in terms of FEV increase was -0.02L, with a 95% CI of [-0.06; 0.02], according to the method of least squares. These average increases in FEV compared to baseline, expressed as percentages of theoretical individual values, were of 0.6% in the montelukast group and 2.7% in the fluticasone group. The difference found for this endpoint between the two groups: –2.2% compared to baseline (95% CI = [-3.6%; -0.7%]), was significant (method of least squares). The percentage of days of beta-2-mimetic use decreased from 38.0% to 15.4% in the montelukast group and from 38.5% to 12.8% in the fluticasone group. The difference between the two groups in terms of the percentage of days requiring beta-mimetic use was significant according to the method of least squares: 2.7% with a 95% CI of [0.9; 4.5]. The percentage of patients who suffered an asthma attack (defined as being a period of worsening of the asthma requiring oral corticoid therapy, an unscheduled visit to the doctor or to an emergency room, or hospitalisation) was 32.2% in the montelukast group and 25.6% in the fluticasone group; the odds ratio (95% CI) was significant: equal to 1.38 [1.04; 1.84]. The percentage of patients who used systemic corticosteroids (primarily oral) during the study period was 17.8% in the montelukast group and 10.5% in the fluticasone group. The difference between the two groups was significant: 7.3% (95% CI = [2.9; 11.7]).

In a 12-week, placebo-controlled study conducted in children 2 to 5 years of age, montelukast 4 mg administered once daily improved the asthma control evaluation parameters compared to the placebo, regardless of concomitant treatments (corticoid

therapy, or inhaled or sprayed sodium cromoglycate treatment); 60% of the patients did not take any other treatments. Compared to the placebo, montelukast improved daytime symptoms (including: cough, wheezing, difficulty breathing and restricted activity) as well as night-time symptoms. Compared to the placebo, montelukast also decreased 'as needed' beta-mimetic use and corticosteroid use in cases of worsening asthma. Patients treated with montelukast had more days without asthma than those receiving the placebo. The effect of the treatment was achieved after taking the first dose.

In a 12-month, placebo-controlled study conducted in children 2 to 5 years of age showing mild asthma with exacerbation periods, montelukast 4 mg administered once daily significantly decreased ($p \leq 0.01$) the annual rate of exacerbation periods compared to the placebo (respectively, 1.60 vs. 2.34), the rate of exacerbation periods being defined as ≥3 consecutive days with daytime symptoms requiring beta-mimetic use, corticosteroid administration (oral or inhaled), or hospitalisation due to asthma. The percentage decrease in the annual rate of periods of asthma exacerbation was 31.9%, with a 95% CI of [16.9; 44.1].

In a placebo-controlled study conducted in children 6 months to 5 years of age with intermittent asthma, but no persistent asthma, montelukast treatment was administered for 12 months, either in a single dose of 4 mg once daily, or in 12-day periods, with each period beginning at the onset of symptoms of an intermittent asthma episode. No difference was observed between patients treated with a single dose of 4 mg montelukast or with the placebo in terms of number of asthma episodes developing into an asthma attack, defined as an asthma episode requiring healthcare such as an unscheduled visit to the doctor, an emergency room or hospital, or using an oral, intravenous or intramuscular corticosteroid treatment.

in paediatric patients 6 months to 2 years of age, montelukast efficacy is based on extrapolating from the efficacy demonstrated in asthmatic patients at least 2 years of age and similar pharmacokinetic data, but also on assuming that disease development, pathophysiology and the effect of the medicine are practically similar among these populations.

Reduction of exercise-induced bronchoconstriction was also demonstrated in a short-term study conducted in paediatric patients 6 to 14 years of age (maximal fall in FEV: 18.27% vs. 26.11%; time to recovery to within 5% of baseline FEV: 17.76 minutes vs 27.98 minutes). This effect, found in both studies, was observed at the end of the 24-hour interval between each dose.

5.2. Pharmacokinetic properties

Absorption
Montelukast is rapidly absorbed following oral administration. For the 10 mg film-coated tablet, the mean peak plasma concentration (Cmax) is achieved 3 hours (Tmax) 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 studies 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 fasted-state administration of one 4 mg chewable tablet in children 2 to 5 years of age, C_{max} was reached two hours after administration. Average C_{max} was greater by 66% compared to that measured in adults receiving a 10 mg tablet, while C_{min} was lower.

When administered to fasting adults, the 4 mg granule formulation was bioequivalent to the 4 mg chewable tablet. in children 6 months to 2 years of age, C_{max} was reached 2 hours after administration of the 4 mg granule form. C_{max} was nearly twice higher than in adults receiving a 10 mg tablet. Concomitant administration of apple sauce or a standard high-fat meal with the granule formulation had no clinically significant effect on montelukast pharmacokinetics, as shown by AUC [Area Under Curve] measurements (respectively, 1,225.7 vs. 1,223.1 ng.h/mL, with and without apple sauce, and respectively 1,191.8 vs. 1,148.5 ng.h/ml, with and without a standard high-fat meal).

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

Metabolism
Montelukast is extensively metabolised. In studies with therapeutic doses, plasma concentrations of metabolites of montelukast are undetectable at steady state in adults and children. Cytochrome P450 2C8 is the major enzyme in the metabolism of

montelukast. Additionally, P450 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 the 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 radiolabelled montelukast, 86% of the radioactivity was recovered in 5-day faecal collections and <0.2% was recovered in urine. Coupled with estimates of montelukast oral bioavailability, this indicates that montelukast and its metabolites are excreted almost exclusively via the bile.

Characteristics in special patients

- No dosage adjustment is necessary for elderly patients or patients with 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 therapeutic dosage. In monkeys, adverse effects appeared at doses from 150 mg/kg/day (>232-fold the systemic exposure seen at the therapeutic dose).

In animal studies, montelukast did not affect fertility or reproductive performance at systemic exposure exceeding the clinical systemic exposure more than 24-fold. A

slight decrease in pup body weight was shown in the female fertility study in rats at 200 mg/kg/day (>69-fold the clinical therapeutic systemic exposure).

In studies in rabbits, a higher incidence of incomplete ossification, compared with the control group, was recorded at systemic exposure >24-fold the systemic exposure seen at the clinical therapeutic dose. No abnormalities were seen in rats. Montelukast crosses the placenta barrier and is excreted in breast milk of animals. No deaths occurred following a single oral administration of montelukast sodium at doses up to 5,000 mg/kg in mice and rats (15,000 mg/m2 and 30,000 mg/m2 in mice and rats, respectively), the maximum dose tested. This dose is equivalent to 25,000 times the recommended daily 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 the systemic exposure).

Montelukast did not prove mutagenic during in vitro and in vivo tests, nor tumorigenic in rodent species.

6. PHARMACEUTICAL PARTICULARS

6.1. List of excipients

- Mannitol (200 SD granules)
- Hydroxypropylcellulose (type SSL)
- Magnesium stearate

6.2. Incompatibilities

Not applicable.

6.3. Shelf life

3 years.

6.4. Special precautions for storage

Store below 30°C in the original package to protect from light and moisture.

6.5. Nature and contents of container

Sachet made of Polyester/Aluminium/Polyethylene foil.

Cardboard box containing 14 sachets.

6.6. Special precautions for disposal and other handlings

No special requirements.

Any unused product or waste material should be disposed of in accordance with the regulations in force.

7. MARKETING AUTHORISATION HOLDER AND MANUFACURING SITE ADDRESS

7.1. Marketing Authorisation Holder

Dafra Pharma GmbH

Mühlenberg 7, 4052 Basel, Switzerland.

7.2. Manufacturer

Bilim Ilaç San.ve Tic. A.Ş
GOSB 1900 Sokak1904
41480 Gebze, Kocaeli, Turkey.

8. MARKETING AUHORISATION NUMBER

See list of MAs per country

9. DATE OF FIRST REGISTRATION

See list of MAs per country

10. DATE OF REVISION OF TEXT

April 2021 (section 4.8/5.1/lay-out).