Summary of Product Characteristics

1. NAME OF THE MEDICINAL PRODUCT (FPP)

Alukon 10 mg.

Montelukast

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each One film-coated tablet contains montelukast sodium equivalent to 10 mg of montelukast.

Excipient with known effect: each film-coated tablet contains 89.3 mg of lactose (see Section 4.3).
For a full list of excipients, please see Section 6.1.

3. PHARMACEUTICAL FORM

Film-coated tablets.

Light yellow, round, biconvex film-coated tablet.

Box with 28 tablets.

4. CLINICAL PARTICULARS

4.1. Therapeutic indications

Alukon 10 mg is indicated in the treatment of asthma as add-on therapy in those patients with mild to moderate persistent asthma who are inadequately controlled on inhaled corticosteroids and in whom 'as-needed' short acting beta-agonists provide inadequate clinical control of asthma.
In those asthmatic patients in whom Alukon 10 mg is indicated in asthma, Alukon can also provide symptomatic relief of seasonal allergic rhinitis.

Alukon 10 mg is also indicated in patients 15 years of age and older in the prophylaxis of asthma in which the predominant component is exercise-induced bronchoconstriction.

4.2. Posology and mode of administration

4.2.1. Posology

The recommended dose for adults and adolescents 15 years of age and older with asthma, with or without associated seasonal allergic rhinitis, is one 10 mg film coated tablet daily to be taken in the evening.

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.

Administration of Alukon with other treatments for asthma
Alukon can be added to an existing anti-asthmatic treatment regimen.

Inhaled corticosteroids
Treatment with Alukon can be used as add-on therapy when inhaled corticoids and an 'as needed' short-acting beta-mimetic provide inadequate symptom control. When Alukon is used as add-on therapy to inhaled corticosteroids, it should not be abruptly substituted for inhaled corticosteroids.

4.2.2. Special populations

Geriatric population
No dosage adjustment is necessary.

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.

Gender
The dosage is the same regardless of patient gender.

4.2.3. Pediatric population

Use of Alukon 10 mg film-coated tablets is not recommended in children less than 15 years of age due to the absence of efficacy and safety data.

For children from 6 months to 5 years of age: Alukon is available in sachets of granules. Alukon should not be used in children under 6 months of age.
For children from 6 to 14 years of age: Alukon is available in chewable tablets

4.2.4. Method of administration

Oral use.
Alukon can be taken independently of meals.

4.3. Contraindications

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

This medicine contains lactose. Patients with rare hereditary problems of fructose intolerance, galactose intolerance, galactosaemia or glucose-galactose malabsorption should not take this medicine.

4.4. Special warning 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 readily available. If an acute attack occurs, a short-acting inhaled beta-agonist should be used. Patients should seek their doctors' advice as soon as possible if they need more inhalations of short-acting beta-agonists 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 present with systemic eosinophilia, sometimes presenting with clinical features of vasculitis consistent with Churg-Strauss syndrome, a condition which is often treated with systemic corticosteroid therapy. These cases have been sometimes associated with the reduction or withdrawal of oral corticosteroid therapy. Although a causal relationship with leukotriene receptor antagonism has not been established, physicians should be alert to eosinophilia, vasculitic rash, worsening pulmonary symptoms, cardiac

complications, and/or neuropathy presenting in their patients. Patients who develop these symptoms should be reassessed and their treatment regimens evaluated.

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.

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

4.5.1. General information

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.

4.5.2. Additional information on special populations

No study on interaction with special populations has been reported.

4.5.3. Paediatric population

No study on the paediatric population has been reported.

4.6. Pregnancy, lactation and fertility

4.6.1. 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.

4.6.2. Lactation

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

4.6.3. 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)	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, pulmonary eosinophilia	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
General disorders and administration site conditions	Pyrexie[2]	Common
	Asthaenia/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 ($LTCs_4$, $LTDs_4$, $LTEs_4$) 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 5mg. Bronchodilatation was observed within 2 hours of oral administration. The bronchodilation effect caused by a beta-agonist 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.

Clinical efficacy and safety

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% versus 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.

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-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 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. Reduction in EIB was also demonstrated in a short-term study in children 6 to 14 years of age (maximum fall in FEV: 18.27% vs 26.11%; time to recovery close to at least 5% of initial 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.

In aspirin-intolerant asthmatic patients receiving concomitant inhaled and/or oral corticoid therapy, treatment with montelukast, compared with placebo, resulted in significant improvement in asthma control (FEV: 8.55% vs -1.74% change from baseline and decrease in total beta-mimetic 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 (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.

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

Nucleus of the tablet

- Lactose (anhydrous)
- Microcrystalline cellulose
- Low-substituted hydroxypropyl cellulose
- Croscarmellose sodium
- Magnesium stearate

Coating

- Opadry orange 20A23503 containing:
- Hydroxypropyl cellulose (E463)
- Hypromellose (E464)
- Titanium dioxide (E171)
- Yellow ferric oxide (E172)
- Red ferric oxide (E172)

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

Aluminium/aluminium blister package with 14 tablets per package.
Cardboard box containing 2 blister packages.

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 Pharmaceuticals

GOSB 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

May 2019.