SUMMARY OF PRODUCT CHARACTERISTICS

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1. NAME OF THE MEDICINAL PRODUCTS

Denk-Air Junior 4 mg
Denk-Air Junior 5 mg
Denk-Air 10 mg

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Active substance: montelukast

Denk-Air Junior 4 mg:
Each chewable tablet contains 4 mg of montelukast (as montelukast sodium).
Excipient with known effect: aspartame
For the full list of excipients, see section 6.1.

Denk-Air Junior 5 mg:
Each chewable tablet contains 5 mg of montelukast (as montelukast sodium).
Excipient with known effect: aspartame
For the full list of excipients, see section 6.1.

Denk-Air 10 mg:
Each film-coated tablet contains 10 mg of montelukast (as montelukast sodium).
Excipient with known effect: aspartame
For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Denk-Air Junior 4 mg:
Chewable tablet.
Pink, flat, round, chewable tablets with bevelled edges, with embossing “4” on one side and plain on the other.

Denk-Air Junior 5 mg:
Chewable tablet.
Pink, flat, round, chewable tablets with bevelled edges.

Denk-Air 10 mg:
Film-coated tablet.
Beige, round, biconvex film-coated tablets.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Denk-Air* is indicated in the treatment of asthma as add-on therapy in patients 2 years of age and over with mild to moderate persistent asthma who are inadequately controlled on inhaled corticosteroids and in whom “as-needed” short acting β-symphatomimetics provide inadequate clinical control of asthma.

***All statements made under "Denk-Air" apply - where not otherwise apparent from the context - to Denk-Air 10 mg, Denk-Air Junior 4 mg and Denk-Air Junior 5 mg.**

Denk-Air may also be an alternative treatment option to low-dose inhaled corticosteroids for 2 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).

In patients 15 years of age and over for whom Denk-Air° is indicated in asthma, Denk-Air 10 mg film-coated tablets can also alleviate the symptoms of seasonal allergic rhinitis.

Denk-Air is also indicated in the prophylaxis of asthma in patients from 2 years of age in which the predominant component is exercise-induced bronchoconstriction.

4.2 Posology and method of administration

Denk-Air Junior 4 mg
This medicinal product is to be given to a child under adult supervision. The dosage for paediatric patients 2-5 years of age is one 4 mg chewable tablet daily to be taken in the evening. Denk-Air Junior 4 mg chewable tablets should not be taken with food. The chewable tablets should be taken at least 1 hour before or 2 hours after eating. No dosage adjustment within this age group is necessary.

Denk-Air Junior 4 mg is not recommended below 2 years of age.

Denk-Air Junior 4 mg 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.

Denk-Air Junior 5 mg
This medicinal product is to be given to a child under adult supervision. The dosage for paediatric patients 6-14 years of age is one 5 mg chewable tablet daily to be taken in the evening. Denk-Air Junior 5 mg chewable tablets should not be taken with food. The chewable tablets should be taken at least 1 hour before or 2 hours after eating. No dosage adjustment within this age group is necessary.

Denk-Air 10 mg
The dosage for adults and adolescents 15 years of age and older with asthma or with allergic rhinitis and asthma is one 10-mg film-coated tablet daily in the evening. Denk-Air 10 mg film-coated tablets can be taken with or without food.

General recommendations
The effect of Denk-Air on asthma symptoms occurs within one day. Patients should be advised to continue treatment with Denk-Air both when they are asymptomatic and during a worsening of the asthmatic symptoms. Denk-Air should not be used concomitantly with other medicinal products containing the same active ingredient (montelukast).

No dosage adjustment is necessary in elderly patients. No dosage adjustments should be made also in patients with renal insufficiency or mild to moderate hepatic impairment. There is no experience for patients with severe hepatic impairment. The dosage is the same for male and female patients.

Denk-Air Junior 4 mg and Denk-Air Junior 5 mg 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 aged 2 to 14 years 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). In mild persistent asthma, asthma symptoms occur more than once a week but less than once a day, nocturnal symptoms more than twice a month but less than once a week, while lung function is normal between episodes. If satisfactory control of asthma symptoms cannot be achieved by the next follow-up (usually within one month), the need for an additional or different anti-inflammatory therapy based on the step system recommended for asthmatic therapy should be evaluated. The efficacy of the asthma treatment should be reviewed at regular intervals.

Therapy with Denk-Air in relation to other treatments for asthma
Denk-Air can be added to an existing treatment regimen.

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

Strengths and dosage forms
4 mg chewable tablets are intended for children 2 to 5 years of age.
5 mg chewable tablets are intended for paediatric patients 6 to 14 years of age.
10 mg film-coated tablets are available for adults and adolescents 15 years of age and older.

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.

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.

Patients with aspirin intolerance syndrome must also avoid taking acetylsalicylic acid and other non-steroidal anti-inflammatory drugs during treatment with Denk-Air.

Denk-Air contains aspartame as a source of phenylalanine. May be harmful for people with phenylketonuria.

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 Cytochrome P450 (CYP3A4, 2C8 and 2C9), caution should be exercised, particularly in children, when montelukast is coadministered with inducers of CYP 3A4, 2C8 and 2C9, such as phenytoin, phenobarbital and rifampicin.

In vitro studies have shown that montelukast is a potent inhibitor of CYP 2C8. However, data from a clinical drug-drug interaction study involving montelukast and rosiglitazone (a probe substrate representative of medicinal products primarily metabolized by CYP 2C8) demonstrated that montelukast does not inhibit CYP 2C8 *in vivo*. Therefore, montelukast is not anticipated to markedly alter the metabolism of medicinal products metabolized by this enzyme (e.g., paclitaxel, rosiglitazone, and repaglinide.)

In vitro studies have shown that montelukast is a substrate of CYP 2C8 and to a less significant extent of 2C9 and 3A4. In a clinical 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 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.

Denk-Air 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.

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

4.7 Effects on ability to drive and use machines

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

4.8 Undesirable effects

Montelukast has been evaluated in clinical studies in patients with persistent asthma as follows:
- 10 mg film-coated tablets in approximately 4000 adults and adolescents 15 years of age and older with asthma
- 10 mg film-coated tablets in approximately 400 adults and adolescents 15 years of age and older with seasonal allergic rhinitis and asthma
- 5 mg chewable tablets in approximately 1750 paediatric asthma patients 6 to 14 years of age
- 4 mg chewable tablets in 851 paediatric asthma patients 2 to 5 years of age.

Montelukast has been evaluated in a clinical study in 1038 patients with intermittent asthma as follows:
- 4 mg granules and 4 mg chewable tablets in 1038 paediatric asthma patients 6 months to 5 years of age.

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

Organ system	**Adults and adolescent patients 15 years and older** (two 12-week studies, n=795)	**Paediatric patients 6-14 years old** (one 8-week study, n=201) (two 56-week studies, n=615)	**Paediatric patients 2-5 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 children 2 to 5 years of age were treated with montelukast for at least 3 months, 338 children for 6 months or longer and 534 children for 12 months or longer. With prolonged treatment, the safety profile did not change in this age group either.

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

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

System organ class	Adverse experience term	Frequency*
Infections and infestations	Upper respiratory infection†	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§)	Uncommon
	Disturbance in attention, memory impairment	Rare
	Hallucinations, disorientation, suicidal thinking and behaviour (suicidality)	Very rare
Nervous system disorders	Dizziness, drowsiness, paraesthesia/hypoesthesia, seizures	Uncommon
Cardiac disorders	Palpitations	Rare
Respiratory, thoracic and mediastinal disorders	Epistaxis	Uncommon
	Churg-Strauss syndrome (CSS) (see section 4.4)	Very rare
	Pulmonary eosinophilia	Very rare
Gastrointestinal disorders	Diarrhoea‡, nausea‡, vomiting‡	Common
	Dry mouth, dyspepsia	Uncommon
Hepatobiliary disorders	Elevated levels of serum transaminase (ALT [GPT] and AST [GOT])	Common
	Hepatitis (including cholestatic, hepatocellular and mixed-pattern liver injury)	Very rare
Skin and subcutaneous tissue disorders	Rash‡	Common
	Bruising, urticaria, pruritus	Uncommon
	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	Pyrexia‡	Common
	Asthenia/fatigue, malaise, oedema	Uncommon

*Frequency category: defined for each adverse experience by the incidence reported in clinical trials databases:
Very common (≥1/10), Common (≥1/100 to <1/10), Uncommon (≥1/1000 to <1/100), Rare (≥1/10,000 to <1/1,000), Very rare (<1/10,000).

† 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.

‡ 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.

§ Frequency category: rare

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare

professionals are asked to report any suspected adverse reactions via the national reporting system.

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 hemodialysis.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Leukotriene receptor antagonist
ATC-code: R03D C03

Mechanism of action

Asthma
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.

Seasonal allergic rhinitis (Denk-Air 10 mg)
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 present in the human airway. The CysLT type-1 (CysLT1) receptor is found in the human airway (including smooth muscle cells and 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 $CysLT_1$ receptor.

Clinical studies

Asthma
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 FEV_1 (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 FEV_1: 5.43% vs 1.04%; β-agonist use: -8.70% vs 2.64%). Compared with inhaled beclomethasone (200 µg 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 FEV_1: 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 FEV_1 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 (FEV_1 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 [Last Square] 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:
FEV_1 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 FEV_1 was -0.02 L with a 95% CI of -0.06, 0.02. The mean increase from baseline in % predicted FEV_1 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 FEV_1 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.

In a 12-week, placebo-controlled study in children 2 to 5 years of age, an improvement in asthma-specific endpoints was obtained with a single daily dose of 4 mg montelukast compared with placebo, irrespective of concomitant therapy with other medicinal products (controllers) for long-term therapy (inhaled/nebulised corticosteroids or cromoglicic acid). Sixty percent of patients received no controller. Montelukast improved both daytime asthma symptoms (with cough, wheezing, trouble breathing and activity limitation) and night-time symptoms compared with placebo. Montelukast also decreased 'as needed' ß-agonist use and corticosteroid rescue for worsening asthma compared with placebo. Patients receiving montelukast had more days without asthma symptoms 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, 4 mg montelukast once daily significantly ($p \leq 0.001$) reduced the yearly rate of asthmatic exacerbation episodes (EE) compared with placebo (1.60 EE vs. 2.34 EE) (EE defined as $\geq$ 3 successive days with daytime symptoms requiring ß-agonist use or corticosteroids [oral or inhaled] or hospitalisation for asthma). The percentage reduction in the yearly EE rate was 31.9% (95% CI: 16.9; 44.1).

In a placebo-controlled study in paediatric patients 6 months to 5 years of age with intermittent but not persistent asthma, treatment with montelukast was administered over a 12-month period. Montelukast was used either as a once daily 4-mg dose 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 utilisation of health-care resources such as an unscheduled visit to a doctor's surgery, emergency department or hospital or treatment with oral, intravenous, or intramuscular corticosteroids.

Efficacy of montelukast is supported in children 6 months to 2 years of age by extrapolation from the efficacy data in patients 2 years of age and over with asthma and is based on similar pharmacokinetic data. It is assumed that the disease course, pathophysiology and the medicinal product's effect are similar among these populations.

Significant reduction of exercise-induced bronchoconstriction (EIB) was demonstrated in a 12-week study in adults (maximal fall in FEV_1 22.33% for montelukast vs 32.40% for placebo; time to recovery to within 5% of baseline FEV_1 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 FEV_1 18.27% vs 26.11%; time to recovery to within 5% of baseline FEV_1 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 (FEV_1 8.55% vs -1.74% change from baseline and decrease in total β-agonist use -27.78% vs 2.09% change from baseline).

Seasonal allergic rhinitis (clinical trials with 10-mg film-coated tablets)
In a clinical study, montelukast 10-mg tablets administered once daily in adult asthmatic patients 15 years of age and older with seasonal allergic rhinitis produced a statistically significant improvement in the Daily Rhinitis Symptoms score compared with placebo. The Daily Rhinitis Symptom score is the average of the Daytime Nasal Symptoms Score (mean of nasal congestion, rhinorrhoea, sneezing and nasal itching) and the Night-Time Symptoms Score (mean of nasal congestion upon awakening,

difficulty going to sleep and night-time awakenings). 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.

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 to metabolism, although itraconazole, an inhibitor of CYP 3A4, was shown not to change pharmacokinetic variables of montelukast in healthy trial subjects who 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 breast 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/m^2 and 30,000 mg/m^2 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

Denk-Air Junior 4 mg and **Denk-Air Junior 5 mg:**
Mannitol
Microcrystalline cellulose
Hydroxypropyl cellulose
Iron oxide red
Croscarmellose sodium
Cherry flavour (contains: flavouring substances, arabic gum, maltodextrin, propylene glycol)
Aspartame
Magnesium stearate

Denk-Air 10 mg:

Tablet core
Mannitol
Microcrystalline cellulose
Hydroxypropyl cellulose
Croscarmellose sodium
Banana flavour (contains: flavouring substances, maltodextrin, modified starch, propylene glycol)
Aspartame
Magnesium stearate

Film-coating
Hypromellose
Hydroxypropyl cellulose

Talc
Titanium dioxide
Iron oxide yellow
Iron oxide red

6.2 Incompatibilities

Not applicable.

6.3 Shelf-life

3 years

6.4 Special precautions for storage

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

6.5 Nature and contents of container

Aluminium/Aluminium blisters
Pack size: 28 tablets

6.6 Special precautions for disposal

No special requirements.
Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7. MARKETING AUTHORIZATION HOLDER

DENK PHARMA GmbH & Co. KG
Prinzregentenstr. 79
81675 München
Germany

8. MARKETING AUTHORISATION NUMBERS IN GERMANY

93825.00.00
93826.00.00
93824.00.00

9. DATE OF FIRST AUTHORISATION IN GERMANY

08.05.2015

10. DATE OF REVISION OF THE TEXT

05/2015

11. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription