SUMMARY PRODUCT OF CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

ZESPİRA 5 mg chewable tablet

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Active Substance:
Montelukast : 5 mg (as 5.2 mg montelukast sodium)

Excipients:
Aspartame (E951) : 1.7 mg
Croscarmellose sodium: 20.0 mg
Mannitol (E421) : 126.0 mg

See section 6.1 for excipients.

3. PHARMACEUTICAL FORM

Chewable Tablet.
Pink coloured, round, biconvex tablet.

4. CLINICAL PARTICULARS

4.1. Therapeutic indications

ZESPİRA 5 mg chewable tablet is indicated in the treatment of persistent asthma (to prevent symptoms seen whole day and night, to treat asthma patients who are sensitive to aspirin, to prevent exercise-induced bronchoconstriction) for 6 to 14 years of age pediatric patients.

ZESPİRA 5 mg chewable tablet is indicated for relief of symptoms of perennial allergic rhinitis, seasonal allergic rhinitis (year-long) in 6 to 14 years of age pediatric patients.

4.2. Posology and method of administration

Dosage / Frequency and duration of application:
The dosage for paediatric patients 6-14 years of age is one 5 mg chewable tablet daily to be taken.

Persistent asthma for pediatric patients 6-14 years of age
ZESPİRA should be taken once daily in the evening.

Allergic rhinitis
Seasonal allergic rhinitis and perennial allergic rhinitis in pediatric patients 6-14 years of age

ZESPİRA for allergic rhinitis should be taken once daily. Application time can be customized according to the requirements of the patient.

Asthma and allergic rhinitis in pediatric patients 6-14 years of age
Patients with both asthma and allergic rhinitis should take only one 4 mg chewable tablet daily in the evening.

Method of administration
The therapeutic effect of ZESPİRA on parameters of asthma control occurs within one day. Patients should be advised to continue taking ZESPİRA even if their asthma is under control, as well as during periods of worsening asthma. If taken in connection with food, ZESPİRA should be taken 1 hour before or 2 hours after food.

Additional information on special populations:
Renal impairment:
No dosage adjustment is necessary for patients with renal insufficiency, (see section 5.2).

Hepatic impairment:
No dosage adjustment is necessary for patients with mild-to-moderate hepatic impairment, (see section 5.2.). There are no data on patients with severe hepatic impairment.

Pediatric population:
Safety and efficacy of Montelukast in 6-14 years of age pediatric patients with asthma, has been revealed by adequate, well-controlled studies. Safety and efficacy profiles in this age group are similar with adults.

Effectiveness of Montelukast in allergic rhinitis treatment for 2 to14 years old pediatric patients and perennial allergic rhinitis treatment for 6 months to 14 years old pediatric patients are supported by the extrapolation of the effectiveness in 15 years old and older patients with allergic rhinitis and course of disease, pathophysiology and similarity of the drug's effect in these populations.

Safety of Montelukast in 2-14 years of age patients with allergic rhinitis is supported by the studies conducted in 2-14 years of age pediatric patients with asthma. Safety study conducted for seasonal allergic rhinitis in 2 to 14 years old pediatric patients showed a similar safety profile (see section 4.8.).

Geriatric population:
3.5% of total number of subjects in Montelukast clinical studies includes 65 years old and over patients and 0.4% includes 75 years old and over patients. Overall difference was not observed between these people and the younger ones in terms of safety or efficacy, reported other experiences did not result in differences between elderly and young patients.

Therapy with Montelukast in relation to other treatments for asthma
Inhaled corticosteroids: ZESPİRA is indicated in the treatment of asthma as add-on therapy of patients who are inadequately controlled on inhaled corticosteroids and in whom 'as-needed' short-acting β-agonists provide inadequate clinical control of asthma. Where necessary, the dose of inhaled corticosteroid may be reduced gradually. ZESPİRA should not be abruptly taken after stopping steroids.

4.3. Contraindications
Hypersensitivity to the active substance or to any of the excipients in this product.

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 beta-agonist should be used. Patients should seek their doctor's advice as soon as possible if they need more inhalations of short-acting beta-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.

Neuropsychiatric events
Adolescents and neuropsychiatric events have been reported in pediatric patients and adults who use Montelukast. Post-marketing data in the montelukast during the agitation, aggressive behavior or hostility, feeling of anxiety, depression, disorientation 's, dream abnormalities, hallucinations, insomnia, restlessness, mobility, sleepwalking, suicidal thoughts and behavior (suicide attempts included) and tremor disorders have been reported. The existence of a relationship between the clinical characteristics of some reports annouced post-marketing and advers effects is determined.

Patients and physicians should be careful in terms of neuropsychiatric events. Patients in case of these types of changes should be warned to inform their doctor. Doctors in such cases should evaluate the risk and benefit ratio to continue treatment with ZESPİRA (see section 4.8.).

Eosinophilic Conditions
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.

Excipients:
Each dose of ZESPİRA contains less than 1 mmol (23 mg) sodium; there is not any unexpected adverse effect concerning sodium in this dose.

ZESPİRA contains aspartame (E951) (source of phenylalanine) may be harmful for people with phenylketonuria.

Each dose of ZESPİRA contains less than 10 g mannitol (E421); there is not any unexpected adverse effect concerning mannitol in this dose.

4.5. Interaction with other medicinal products and other forms of interaction

Montelukast may be administered with other therapies routinely used in the prophylaxis and chronic treatment of asthma. In drug-interactions studies, the recommended clinical dose of montelukast did not have clinically important effects on the pharmacokinetics of the following drugs: theophylline, prednisone, prednisolone, oral contraceptives (ethinyl oestradiol/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, caution should be exercised, particularly in children, when montelukast is co-administered with inducers of CYP 3A4, 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 drugs primarily metabolised by CYP 2C8) demonstrated that montelukast does not inhibit CYP 2C8 *in vivo.* Therefore, montelukast is not anticipated to markedly alter the metabolism of drugs metabolised by this enzyme (e.g., paclitaxel, rosiglitazone, and repaglinide).

In vitro studies have shown that montelukast is a substrate of CYP 2C8, 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. Co-administration of montelukast with itraconazole , a strong inhibitor of CYP 3A4, resulted in no significant increase in the systemic exposure of montelukast. In adults, approved 10 mg dose at the higher doses (e.g., adult patients 22 weeks of 200 mg per day for about one week, a day for 900 mgA) clinically significant adverse events have been observed, based gemfibrozil montelukast systemic exposure their effects on the clinical aspects is not considered to be significant. Therefore, when coadministered with gemfibrozil, montelukast do not require dosage adjustment. However, due to the potential for an increase in adverse reactions should be careful. According to in vitro data , other known inhibitors of CYP 2C8 (e.g., trimethoprim) with clinically significant drug interactions can be expected. In addition, administration of montelukast only with itraconazole in systemic exposures did not result in a significant increase.

4.6. Pregnancy and lactation

General advise
Pregnancy Category is B.

Women of childbearing potential / birth control (contraception)

Not enough data about fertility effects on women of childbearing potential.

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.

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

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.

ZESPİRA may be used in breast feeding only if it is considered to be clearly essential.

Fertility
At fertility studies in female rats, montelukast 200 mg/ kg oral dose (calculated exposure maximum recommended daily oral dose was about 70 times of adults's AUC) caused reductions in fertility and fecundity (fertility) results. There was no effect on fertility or fecundity observed with 100 mg / kg (calculated exposure at the maximum recommended daily oral dose was about 20 times of adults's AUC) in females. There was no effect on fertility with Montelukast 800 mg / kg oral doses (calculated exposure at the maximum recommended daily oral dose was about 160 times of adult's AUC) in male rats.

There is not adequate data on ZESPİRA's ability on fertility of people.

4.7. Effects on ability to drive and use machines

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

4.8. Undesirable effects

Montelukast has been evaluated in clinical studies as follows:

- 10 mg film-coated tablets in approximately 4000 adult patients and adolescents 15 years of age and older

- 5 mg chewable tablets in approximately 1,750 paediatric patients 6 to 14 years of age

For 15 years of age and older patients (two 12 week studies n =795), 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:

Nervous system disorders:
Common: Headache

Gastrointestinal disorders:
Common: Abdominal pain

For 6 to 14 years of age paediatric patients (one 8 week study n =201), (two 56 week studies, n=615), 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:

Nervous system disorders:
Common: Headache

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.

Postmarketing experience

Adverse reactions reported in post-marketing are listed, by System Organ Class and specific Adverse Experience term, in the table below. Frequency Categories were estimated based on relevant clinical trials. Frequencies are defined as: very common (≥1/10), common (≥1/100, <1/10), uncommon (≥1/1,000, <1/100), rare (≥1/10,000, <1/1000) and very rare (<1/10,000).

Infections and infestations:
Very Common: Upper respiratory infection*

Blood any lymphatic system disorders:
Rare: Increased bleeding tendency

Immune system disorders:
Uncommon: Hypersensitivity reactions including anaphylaxis
Very Rare: Hepatic eosinophilic infiltration

Psychiatric disorders:
Uncommon: Dream abnormalities including nightmares, insomnia, somnambulism, irritability, anxiety, restlessness, agitation including aggressive behaviour or hostility, depression
Rare: Tremor
Very rare: Hallucinations, disorientation, suicidal thinking and behaviour (suicidality)

Nervous system disorders:
Uncommon: Dizziness, drowsiness, Paraesthesia/hypoesthesia, seizure

Cardiac disorders:
Rare: Palpitations

Respiratory, thoracic and mediastinal disorders:
Uncommon: Epistaxis
Very Rare: Churg-Strauss Syndrome (CSS) (see section 4.4)

Gastrointestinal disorders:
Common: Diarrhoea**, nausea**, vomiting**
Uncommon: Dry mouth, dyspepsia

Hepatobiliary disorders:
Common: Elevated levels of serum transaminases (ALT, AST)
Very rare: Hepatitis (including cholestatic, hepatocellular and mixed-pattern liver injury).

Skin and subcutaneous tissue disorders:
Common: Rash**
Uncommon: Bruising, urticaria, pruritus
Rare: Angiooedema
Very rare: Erythrema nodosum, erythrema multiforme

Muscoskeletal and connective tissue disorders:
Uncommon: Arthralgia, myalgia, including muscle cramps

General disorders and administration site conditions:
Common: Pyrexia **
Uncommon: Asthenia/fatigue, malaise, oedema

*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

4.9. Overdose

No specific information is available on the treatment of overdosage 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 overdosage 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 overdosage 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 haemo-dialysis.

5. PHARMACOLOGICAL PROPERTIES

5.1. Pharmacodynamic properties

Pharmacotherapeutic group: Leukotriene receptor antagonists
ATC code: R03DC03

The cysteinyl leukotrienes (LTC_4, LTD_4, LTE_4) are potent inflammatory eicosanoids released from various cells including mast cells and eosinophils. These important pro-asthmatic mediators bind to cysteinyl leukotriene receptors (CysLT).

CysLT type 1 (CysLT) receptor is found in human respiratory tract (airway smooth muscle cells and airway macrophages) and other pro-inflammatory cells (eosinophils and certain myeloid stem cells). CysLT has been associated with the pathophysiology of asthma and allergic rhinitis. Effects of leukotrienes in asthma include bronchoconstriction, mucous secretion, vascular permeability, and eosinophil recruitment. CysLT allergens in allergic rhinitis matches with both early and late phase reactions after released from the nasal mucosa, and are associated with allergic rhinitis symptoms. By intranasal administration of CysLT nasal airway resistance and nasal congestion shows to improve symptoms.

5.2. Pharmacokinetic properties
General 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 three 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 two 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 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 metabolised. In studies with therapeutic doses, plasma concentrations of metabolites of montelukast are undetectable at steady state in adults and children.

In vitro studies using human liver microsomes indicate that cytochromes P450 3A4, 2A6 and 2C9 are involved in the metabolism of montelukast. 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 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.

Linearity / non-linearity:
Up to 50 mg of montelukast oral dose pharmacokinetic data are close to linear. During use single daily dose of 10 mg of montelukast in very small amounts accumulated the parent drug in plasma (about 14%).

Additional data regarding special populations
Elderly:
No dosage adjustment is necessary for the elderly patients.

Hepatic Impairment:
No dosage adjustment is necessary for mild to moderate hepatic impairment.

Renal impairment:
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 of 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, gastro-intestinal 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

Mannitol (E421)
Microcrystalline cellulose
Croscarmellose sodium
Hydroxypropyl cellulose
Aspartame (E951)
Flavour cherry black
Red iron oxide
Magnesium steratae

6.2. Incompatibilities

Not applicable.

6.3. Shelf life

24 months

6.4. Special precautions for storage

Store below 30°C at room temperature, in packaging, prevent from humidity and light.

6.5. Nature and contents of container

Packed 28 or 84 chewable tablets in Al/Al foil blister packaging with leaflet in the cartoon box.

6.6. Special precautions for disposal and other handling

Unused product or waste materials "Medical Waste Control Regulation" and "Packaging and Packaging Waste must be disposed of in accordance with the Regulation on Control.

7. MARKETING AUTHORISATION HOLDER

BİLİM PHARMACEUTICALS
34440 Beyoğlu – İSTANBUL-TURKEY

8. MARKETING AUTHORISATION NUMBER(S)

05340/07443/REN/2020

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

First Authorisation:
Renewal of the Authorisation:
Sep 23, 2020

10. DATE OF REVISION OF THE TEXT : -