1. Name of the Medicinal Product:

Product Name: Kipel 10 [Montelukast Tablets 10 mg]

2. Qualitative and quantitative composition

Qualitative Declaration:

Ingredients	**Specification**
Montelukast sodium	Ph.Eur/USP
Lactose Sodium	USP-NF
Maize Starch	USP-NF
Hydroxy propyl cellulose	USP-NF
Sodium Starch glycollate	USP-NF
Colloidal silicon dioxide	USP-NF
Magnesium stearate	USP-NF
CoatingInstacoat universal yellow IC-U-5855	IH
Purified water	USP

Quantitative Declaration:

Ingredients	**Specification**	**Quantity per 10 mg**
Montelukast sodium	Ph.Eur/USP	10.38
Lactose Sodium	USP-NF	149.12
Maize Starch	USP-NF	20.00
Hydroxy propyl cellulose	USP-NF	5.00
Sodium Starch glycollate	USP-NF	10.00
Colloidal silicon dioxide	USP-NF	3.00
Magnesium stearate	USP-NF	2.50
CoatingInstacoat universal yellow IC-U-5855	IH	6.00
Purified water	USP	Q.S

3. Pharmaceutical Form

Pale yellow colored round shaped biconvex, smooth film coated tablets having bisecting line on one side of the tablet, with white to off white colored core.

4. Clinical Particulars

4.1 Therapeutic Indications

Asthma - Montelukast is indicated for the prophylaxis and chronic treatment of asthma in adults and pediatric patients 12 months of age and older.

Exercise-Induced Bronchoconstriction - Montelukast is indicated for prevention of exercise-induced bronchoconstriction in patients 15 years of age and older.

Allergic Rhinitis - Montelukast is indicated for the relief of symptoms of allergic rhinitis (seasonal allergic rhinitis in adults and pediatric patients 2 years of age and older, & perennial allergic rhinitis in adults and pediatric patients 6 months of age & older).

4.2 Posology and method of administration

Asthma

Montelukast should be taken once daily in the evening. The following doses are recommended:

For adults and adolescents 15 years of age and older: one 10-mg tablet.

For pediatric patients 6 to 14 years of age: one 5-mg chewable tablet.

For pediatric patients 2 to 5 years of age: one 4-mg chewable tablet.

Safety and effectiveness in pediatric patients less than 12 months of age with asthma have not been established.

There have been no clinical trials in patients with asthma to evaluate the relative efficacy of morning versus evening dosing. The pharmacokinetics of montelukast are similar whether dosed in the morning or evening. Efficacy has been demonstrated for asthma when montelukast was administered in the evening without regard to time of food ingestion.

Exercise-Induced Bronchoconstriction (EIB) in Patients 15 Years of Age and Older

For prevention of EIB, a single 10 mg dose of montelukast should be taken at least 2 hours before exercise. An additional dose should not be taken within 24 hours of a previous dose. Patients already taking montelukast daily for another indication (including chronic asthma) should not take an additional dose to prevent EIB. All patients should have available for rescue a short-acting β-agonist. Safety and effectiveness in patients younger than 15 years of age have not been established. Daily administration of montelukast for the chronic treatment of asthma has not been established to prevent acute episodes of EIB.

Allergic Rhinitis

For allergic rhinitis, montelukast should be taken once daily. Efficacy was demonstrated for seasonal allergic rhinitis when montelukast was administered in the morning or the evening without regard to time of food ingestion. The time of administration may be individualized to suit patient needs.

The following doses for the treatment of symptoms of seasonal allergic rhinitis are recommended:

For adults and adolescents 15 years of age and older: one 10-mg tablet.

For pediatric patients 6 to 14 years of age: one 5-mg chewable tablet.

For pediatric patients 2 to 5 years of age: one 4-mg chewable tablet.

Safety and effectiveness in pediatric patients younger than 2 years of age with seasonal allergic rhinitis have not been established.

The following doses for the treatment of symptoms of perennial allergic rhinitis are recommended:

For adults and adolescents 15 years of age and older: one 10-mg tablet.

For pediatric patients 6 to 14 years of age: one 5-mg chewable tablet.

For pediatric patients 2 to 5 years of age: one 4-mg chewable tablet.

Safety and effectiveness in pediatric patients younger than 6 months of age with perennial allergic rhinitis have not been established.

Asthma and Allergic Rhinitis

Patients with both asthma and allergic rhinitis should take only one montelukast dose daily in the evening.

4.3 Contraindications

Hypersensitivity to any component of this product.

4.4 Special Warnings and Precautions for Use

Precautions:

General

Montelukast is not indicated for use in the reversal of bronchospasm in acute asthma attacks, including status asthmaticus.

Patients should be advised to have appropriate rescue medication available. Therapy with Montelukast can be continued during acute exacerbations of asthma. Patients who have

exacerbations of asthma after exercise should have available for rescue a shortacting inhaled -β-agonist.

While the dose of inhaled corticosteroid may be reduced gradually under medical supervision, Montelukast should not be abruptly substituted for inhaled or oralcorticosteroids.

Patients with known aspirin sensitivity should continue avoidance of aspirin or nonsteroidal anti-inflammatory agents while taking Montelukast. Although Montelukast is effective in improving airway function in asthmatics with documented aspirin sensitivity, it has not been shown to truncate bronchoconstrictor response to aspirin and other non-steroidal anti-inflammatory drugs in aspirin sensitive asthmatic patients.

Neuropsychiatric Events

Neuropsychiatric events have been reported in adult, adolescent, and pediatric patients taking Montelukast. Events reported are agitation, aggressive behavior or hostility, anxiousness, depression, dream abnormalities, hallucinations, insomnia, irritability, restlessness, somnambulism, suicidal thinking and behavior (including suicide), and tremor.

Patients and prescribers should be alert for neuropsychiatric events. Patients should be instructed to notify their prescriber if these changes occur. Prescribers should carefully evaluate the risks and benefits of continuing treatment with Montelukast if such events occur.

Eosinophilic Conditions

In rare cases, patients with asthma on therapy with 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.

Phenylketonuria

Phenylketonuric patients should be informed that the 4-mg and 5-mg chewable tablets contain phenylalanine (a component of aspartame), 2.0mg/table and 2.5mg/tablet per 4-mg and 5-mg chewable tablet, respectively.

Information for Patients

- Patients should be advised to take Montelukast daily as prescribed, even when they are asymptomatic, as well as during periods of worsening asthma, and to contact their physicians if their asthma is not well controlled.
- Patients should be advised that oral Montelukast is not for the treatment of acute asthma attacks.
- They should have appropriate short-acting inhaled β-agonist medication available to treat asthma exacerbations. Patients who have exacerbations of asthma after exercise should be instructed to have available for rescue a short-acting inhaled β-agonist.

Daily administration of Montelukast for the chronic treatment of asthma has not been established to prevent acute episodes of exercise induced bronchoconstriction.

- Patients should be advised that, while using Montelukast, medical attention should be sought if short-acting inhaled bronchodilators are needed more often than usual, or if more than the maximum number of inhalations of short-acting bronchodilator treatment prescribed for a 24-hour period are needed.
- Patients receiving Montelukast should be instructed not to decrease the dose or stop taking any other anti-asthma medications unless instructed by a physician.
- Patients should be instructed to notify their physician if neuropsychiatric events occur while using Montelukast.
- Patients with known aspirin sensitivity should be advised to continue avoidance of aspirin or nonsteroidal anti-inflammatory agents while taking Montelukast.

4.5 Drug Interactions

No dose adjustment is needed when montelukast is co-administered with theophylline, prednisone, prednisolone, oral contraceptives, terfenadine, digoxin, warfarin, thyroid hormones, sedative hypnotics, non-steroidal anti-inflammatory agents, benzodiazepines, decongestants, and Cytochrome P450 (CYP) enzyme inducers .

Carcinogenesis, Mutagenesis, Impairment of Fertility

Montelukast demonstrated no evidence of mutagenic or clastogenic activity.

4.6 Pregnancy and Lactation

Pregnancy Category B:

There are no adequate and well-controlled studies in pregnant women.

Montelukast should be used during pregnancy only if clearly needed.

Nursing mother

It is not known if montelukast is excreted in human milk. Caution should be exercised when Montelukast is given to a nursing mother.

Pediatric Use

Safety and efficacy of Montelukast have been established in adequate and well controlled studies in pediatric patients with asthma 6 to 14 years of age. Safety and efficacy profiles in this age group are similar to those seen in adults.

The safety of Montelukast 4-mg chewable tablets in pediatric patients 2 to 5 years of age with asthma has been demonstrated by adequate and well-controlled data.

The safety and effectiveness in pediatric patients below the age of 12 months with asthma and 6 months with perennial allergic rhinitis have not been established.

4.7 Effects on Ability to Drive and Use Machines

There is no evidence that Montelukast affects the ability to drive and use machines.

4.8 Undesirable Effects

Common adverse reactions are headache, influenza, abdominal pain, cough, dyspepsia, increase in ALT, asthenia/fatigue, dizziness, fever, gastroenteritis, dental pain, nasal congestion, rash, increase in AST, pyuria.

The following additional adverse reactions have been reported:

Blood and lymphatic system disorders: increased bleeding tendency

Immune system disorders: hypersensitivity reactions including anaphylaxis, very rarely hepatic eosinophilic infiltration

Psychiatric disorders: agitation including aggressive behavior or hostility, anxiousness, depression, dream abnormalities, hallucinations, insomnia, irritability, restlessness, somnambulism, suicidal thinking and behavior (including suicide), tremor.

Nervous system disorders: drowsiness, paraesthesia/hypoesthesia, seizures

Cardiac disorders: palpitations

Respiratory, thoracic and mediastinal disorders: epistaxis

Gastrointestinal disorders: diarrhea, dyspepsia, nausea, very rarely pancreatitis, Vomiting

Hepatobiliary disorders: Rare cases of cholestatic hepatitis, hepatocellular liver injury, and mixed-pattern liver injury have been reported in patients treated with montelukast. Most of these occurred in combination with other confounding factors, such as use of other medications, or when montelukast was administered to patients who had underlying potential for liver disease such as alcohol use or other forms of hepatitis.

Skin and subcutaneous tissue disorders: angioedema, bruising, erythema nodosum, pruritus, urticarial.

Musculoskeletal and connective tissue disorders: arthralgia, myalgia including muscle cramps.

General disorders and administration site conditions: edema

In rare cases, patients with asthma on therapy with 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 events usually, but not always, have been associated with the reduction of oral corticosteroid therapy. Physicians should be alert to eosinophilia, vasculitic rash, worsening pulmonary symptoms, cardiac complications, and/or neuropathy presenting in their patients. A causal association between montelukast and these underlying conditions has not been established.

4.9 Overdose

No specific information is available on the treatment of overdosage with montelukast. 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 removed by peritoneal dialysis or hemodialysis.

5. Pharmacological properties

5.1 Pharmacodynamic Properties

Mechanism of action:

The cysteinyl leukotrienes (LTC4, LTD4, and LTE4) are products of arachidonic acid metabolism and are released from various cells, including mast cells and eosinophils.

These eicosanoids bind to cysteinyl leukotriene (CysLT) receptors. The CysLT type-1 (CysLT1) receptor is found in the human airway (including airway smooth muscle cells and airway macrophages) and on other pro-inflammatory cells (including eosinophils and certain myeloid stem cells). CysLTs have been correlated with the pathophysiology of asthma and allergic rhinitis. In asthma, leukotriene-mediated effects include airway edema, smooth muscle contraction, and altered cellular activity associated with the inflammatory process. 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 that binds with high affinity and selectivity to the CysLT1 receptor (in preference to other pharmacologically important airway receptors, such as the prostanoid, cholinergic, or β-adrenergic receptor). Montelukast inhibits physiologic actions of LTD4 at the CysLT1 receptor without any agonist activity.

Montelukast causes inhibition of airway cysteinyl leukotriene receptors as demonstrated by the ability to inhibit bronchoconstriction due to inhaled LTD4 in asthmatics.

5.2 Pharmacokinetics

Absorption

Montelukast is rapidly absorbed following oral administration. After administration of the 10-mg film-coated tablet to fasted adults, the mean peak montelukast plasma concentration (Cmax) is achieved in 3 to 4 hours (Tmax). The mean oral bioavailability is 64%. The oral bioavailability and Cmax are not influenced by a standard meal in the morning.

For the 4-mg chewable tablet, the mean Cmax is achieved 2 hours after administration in pediatric patients 2 to 5 years of age in the fasted state.

For the 5-mg chewable tablet, the mean Cmax is achieved in 2 to 2.5 hours after administration to adults in the fasted state. The mean oral bioavailability is 73% in the fasted state versus 63% when administered with a standard meal in the morning.

Distribution

Montelukast is more than 99% bound to plasma proteins. The steady state volume of distribution of montelukast averages 8 to 11 liters.

Metabolism

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

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.

In several studies, the mean plasma half-life of montelukast ranges from 2.7 to 5.5 hours in healthy young adults. The pharmacokinetics of montelukast are nearly linear for oral doses up to 50 mg. During once-daily dosing with 10-mg montelukast, there is little accumulation of the parent drug in plasma (14%).

Special Population:

Gender: The pharmacokinetics of montelukast is similar in males and females.

Elderly: The plasma half-life of montelukast is slightly longer in the elderly. No dosage adjustment in the elderly is required.

Race: Pharmacokinetic differences due to race have not been studied.

Hepatic Insufficiency: No dosage adjustment is required in patients with mild-to moderate hepatic insufficiency. The pharmacokinetics of Montelukast in patients with more severe hepatic impairment or with hepatitis has not been evaluated.

Renal Insufficiency: Since montelukast and its metabolites are not excreted in the urine, no dosage adjustment is recommended in these patients.

Adolescents and Pediatric Patients:

The plasma concentration profile of montelukast following administration of the 10-mg film-coated tablet is similar in adolescents 15 years of age and young adults. The 10-mg film-coated tablet is recommended for use in patients ≥ 15 years of age.

The mean systemic exposure of the 4-mg chewable tablet in pediatric patients 2 to 5 years of age and the 5-mg chewable tablets in pediatric patients 6 to 14 years of age is similar to the mean systemic exposure of the 10-mg film-coated tablet in adults. The 5-mg chewable tablet should be used in pediatric patients 6 to 14 years of age and the 4-mg chewable tablet should be used in pediatric patients 2 to 5 years of age.

In children 6 to 11 months of age, the systemic exposure to montelukast and the variability of plasma montelukast concentrations were higher than those observed in adults.

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 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 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

Core Tablet

Lactose Anhydrous, Maize Starch, Hydroxy Propyl Cellulose, Sodium Starch Glycolate, Colloidal silicon dioxide, Magnesium stearate.

Coating Tablet

Instacoat Universal Yellow IC-U-5855: Hypromellose, Polyethylene Glycol, Talc, Titanium Dioxide, Iron oxide yellow.

6.2 Incompatibilities

Not applicable.

6.3 Shelf Life

24 months from date of manufacture.

6.4 Storage

Store below 30°C. Protect from light and moisture.

6.5 Nature and Contents of Container

Alu-Alu Blister pack of 10 Tablets

Pack Size: 3 x 10's

6.6 Special precautions for disposal and other handling

No special requirements for disposal.

7. Marketing Authorization Holder: MEGA LIFESCIENCES (AUSTRALIA) PTY. LTD

8. Marketing Authorization Numbers: No. 20/1534/DGCS/PH/2015

9. Date of first authorization / renewal of the authorization: April 2016

10. Date of revision of the text: April 2020

11. Dosimetry (If Applicable)--NA

12. Instructions for Preparation of Radiopharmaceuticals (If Applicable)—NA