Summary of Product Characteristics for Pharmaceutical Products

1. Name of the medicinal product:
Rupantel 10/10mg Film- coated Tablets

2. Qualitative and quantitative composition
Each film-coated tablet contains 10mg of Rupatadine and 10mg of Montelukast.
Excipients with known effect: Lake of ponceau (4R)

3. Pharmaceutical form
Filmcoated Tablets
A red color round shaped film-coated tablets plain on both sides.

4. Clinical particulars

4.1 Therapeutic indications
Symptomatic treatment of allergic rhinitis and urticaria in adults and adolescents (over 12 years of age).

Prophylaxis of asthma in which the predominant component is exercise-induced bronchoconstriction.

4.2 Posology and method of administration
The recommended dose for adults and adolescents 15 years of age and older with asthma, or with asthma and concomitant seasonal allergic rhinitis, is one 10 mg tablet daily to be taken in the evening.

Elderly
Rupatadine should be used with caution in elderly people

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

BLACKBOX WARNING

Serious Neuropsychiatric Events

·Serious neuropsychiatric events have been reported in patients taking MONTELUKAST

· Discuss benefits and risks of MONTELUKAST with patients and caregivers

· Monitor for neuropsychiatric symptoms in patients taking MONTELUKAST

· Discontinue MONTELUKAST immediately if neuropsychiatric symptoms occur

· **Because the benefits of MONTELUKAST may not outweigh the potential risk of neuropsychiatric symptoms in patients with allergic rhinitis, reserve use for patients who have an inadequate response or intolerance to alternative therapies.**

4.5 Interaction with other medicinal products and other forms of interaction

Interaction studies have only been performed in adults and adolescents (over 12 years of age) with rupatadine 10 mg tablets.

Effects of other drugs on rupatadine
Co-administration with potent CYP3A4 inhibitors (e.g. itraconazole, ketoconazole, voriconazole, posaconazole, HIV protease inhibitors, clarithromycin, and nefazodone) should be avoided and co-medication with moderate CYP3A4 inhibitors (erythromycin, fluconazole, diltiazem) should be used with caution.
The concomitant administration of rupatadine 20 mg and ketoconazole or erythromycin increases the systemic exposure to rupatadine 10 times and 2-3 times respectively. These modifications were not associated with an effect on the QT interval or with an increase of the adverse reactions in comparison with the drugs when administered separately.
Interaction with grapefruit: The concomitant administration of grapefruit juice increased 3.5 times the systemic exposure of rupatadine. Grapefruit juice should not be taken simultaneously.

Effects of rupatadine on other drugs
Caution should be taken when rupatadine is co-administered with other metabolised drugs with narrow therapeutic windows since knowledge of the effect of rupatadine on other drugs is limited.
Interaction with alcohol: After administration of alcohol, a dose of 10 mg of rupatadine produced marginal effects in some psychomotor performance tests although they were not significantly different from those induced by intake of alcohol only. A dose of 20 mg increased the impairment caused by the intake of alcohol.

Montelukast:
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 CYP2C8. 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 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 for an increase in adverse reactions.

4.6 Pregnancy and Lactation

Pregnancy

Animal studies do not indicate harmful effects with respect to effects on pregnancy or embryonal/ foetal development.
Available data from published prospective and retrospective cohort studies with montelukast use in pregnant women evaluating major birth defects have not established a drug-associated risk.
Available studies have methodologic limitations, including small sample size, in some cases retrospective data collection, and inconsistent comparator groups. As a precautionary measure, it is preferable to avoid the use of rupatadine during pregnancy.

Lactation

Rupatadine is excreted in animal milk. It is unknown whether rupatadine is excreted into breast milk. A decision must be made whether to discontinue breastfeeding or to discontinue/abstain from rupatadine therapy taking into account the benefit of breastfeeding for the child and the benefit of therapy for the woman.

4.7 Effects on ability to drive and use machines

Montelukast has no or negligible influence on the ability to drive and use machines. However, individuals have reported drowsiness or dizziness.
Rupatadine 10 mg had no influence on the ability to drive and use machines. Nevertheless, care should be taken before driving or using machinery until the patient's individual reaction on rupatadine has been established.

4.8 Undesirable effects

Montelukast has been evaluated in clinical studies as follows:

- 10 mg film-coated tablets in approximately 4000 adult and adolescent asthmatic patients 15 years of age and older.
- 10 mg film-coated tablets in approximately 400 adult and adolescent asthmatic patients with seasonal allergic rhinitis 15 years of age and older.
- 5 mg chewable tablets in approximately 1750 paediatric asthmatic patients 6 to 14 years of age.

The following drug-related adverse reactions in clinical studies 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:

Body System Class	Adult and Adolescent Patients 15 years and older (two 12-week studies; n=795)	Paediatric Patients 6 to 14 years old (one 8-week study; n=201) (two 56-week studies; n=615)
Nervous system disorders	headache	headache
Gastrointestinal disorders	abdominal pain	

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.

Tabulated list of Adverse Reactions
Adverse reactions reported in post-marketing use are listed by System Organ Class and specific Adverse Reactions, in the table below. Frequency Categories were estimated based on relevant clinical trials.

System Organ Class	Adverse Reactions	Frequency Category*
Infections and infestations	Upper respiratory infection†	Very Common
Blood and lymphatic system disorders	Increased bleeding tendency	Rare
	Thrombocytopenia	Very Rare
Immune system disorder	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, tremors),	Uncommon
	disturbance in attention, memory impairment, tic	Rare
	hallucinations, disorientation, suicidal thinking and behaviour (suicidality) obsessive-compulsive symptoms, dysphemia	Very Rare
Nervous system disorders	Dizziness, drowsiness, paraesthesia/hypoesthesia, seizure	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 transaminases (ALT, AST)	Common
	Hepatitis (including cholestatic, hepatocellular, and mixed-pattern liver injury).	Very Rare

4.9 Overdose

Rupatadine:

No case of overdose has been reported. In a clinical safety study rupatadine at daily dose of 100 mg during 6 days was well tolerated. The most common adverse reaction was somnolence. If accidental ingestion of very high doses occurs symptomatic treatment together with the required supportive measures should be given.

Montelukast:

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.

Symptoms of overdose
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.

Management of overdose
It is not known whether montelukast is dialyzable by peritoneal- or haemo-dialysis. No specific information is available on the treatment of overdose with montelukast.

5. Pharmacological properties

5.1 Pharmacodynamic properties

Rupatadine:
Pharmacotherapeutic group: other antihistamines for systemic use, ATC code: R06A X28. Rupatadine is a second-generation antihistamine, long-acting histamine antagonist, with selective peripheral H1-receptor antagonist activity. Some of the metabolites (desloratadine and its hydroxylated metabolites) retain an antihistaminic activity and may partially contribute to the overall efficacy of the drug.
In vitro studies with rupatadine at high concentration have shown an inhibition of the degranulation of mast cells induced by immunological and non-immunological stimuli as well as the release of cytokines, particularly of the TNFα in human mast cells and monocytes. The clinical relevance of the observed experimental data remains to be confirmed.

Clinical trials in volunteers (n= 393) and patients (n=2650) with allergic rhinitis and chronic idiopathic urticaria did not show significant effect on the electrocardiogram when rupatadine was administered at doses ranging from 2 mg to 100 mg.
Chronic idiopathic urticaria was studied as a clinical model for urticarial conditions, since the underlying pathophysiology is similar, regardless of etiology, and because chronic patients can be more easily recruited prospectively. Since histamine release is a causal factor in all urticarial diseases, rupatadine is expected to be effective in providing symptomatic relief for other urticarial conditions, in addition to chronic idiopathic urticaria, as advised in clinical guidelines. In a placebo-controlled trials in patients with Chronic Idiopathic Urticaria, rupatadine was effective reducing the mean pruritus score from baseline over the 4 week treatment period (change vs baseline: rupatadine 57.5%, placebo 44.9%) and decreasing the mean number of wheals (54.3% vs 39.7%).

Montelukast:
Harmacotherapeutic group: Leukotriene receptor antagonists ATC-code: R03D C03

Mechanism of action
The cysteinyl leukotrienes (LTC4, LTD4, and 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. 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 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.

5.2 Pharmacokinetic properties

Absorption and bioavailability

Rupatadine is rapidly absorbed after oral administration, with a tmax of approximately 0.75 hours after intake. The mean Cmax was 2.6 ng/ml after a single oral dose of 10 mg and 4.6 ng/ml after a single oral dose of 20 mg. Pharmacokinetics of rupatadine was linear for a dose between 10 and 20 mg after single and repeated doses. After a dose of 10 mg once a day for 7 days, the mean Cmax was 3.8 ng/ml. The plasma concentration followed a bi-exponential drop-off with a mean elimination half-life of 5.9 hours. The binding-rate of rupatadine to plasma proteins was 98.5-99%. As rupatadine has never been administered to humans by intravenous route, no data is available on its absolute bioavailability.

Effect of the intake of food

Intake of food increased the systemic exposure (AUC) to rupatadine by about 23%. The exposure to one of its active metabolites and to the main inactive metabolite was practically the same (reduction of about 5% and 3% respectively). The time taken to reach the maximum plasma concentration (tmax) of rupatadine was delayed by 1 hour. The maximum plasma concentration (Cmax) was not affected by food intake. These differences had no clinical significance.

5.3 Preclinical safety data

Preclinical data reveal no special hazard for humans based on conventional studies of pharmacology, repeated dose toxicity, genotoxicity, and carcinogenic potential.

More than 100 times the clinically recommended dose (10 mg) of rupatadine did neither extend the QTc or QRS interval nor produce arrhythmia in various species of animals such as rats, guinea pigs and dogs. Rupatadine and one of its main active metabolites in humans, 3-hydroxydesloratadine, did not affect the cardiac action potential in isolated dog Purkinje fibres at concentrations at least 2000 times greater than the Cmax reached after the administration of a dose of 10 mg in humans. In a study that evaluated the effect on cloned human HERG channel, rupatadine inhibited that channel at a concentration 1685 times greater than the Cmax obtained after the administration of 10 mg

of rupatadine. Desloratadine, the metabolite with the greatest activity, had no effect at a 10 micromolar concentration. Studies of tissue distribution in rats with radiolabelled rupatadine showed that rupatadine does not accumulate in heart tissue.

Montelukast:

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

6. Pharmaceutical Particulars

6.1 List of Excipients

(Microcrystalline cellulose BP, magnesium stearate BP, cross Povidones BP, purified talc BP, Aersoil BP, cross caramellose sodium BP, sodium starch Glycolate BP, Methocel E 15 BP, Ponceau 4R lake color IH, titanium dioxide BP, purified talc BP, polyethylene glycol BP, isopropyl alcohol BP, methylene dichloride BP)

6.2 Incompatibilities

Not applicable

6.3 Shelf-Life

36 Months

6.4 Special Precautions for storage

Store in a cool dry place. Store at a temperature not exceeding 30°C. Protect from light &
moisture.
Keep out of reach and sight of children.

6.5 Nature and Content of container

3 x 10 Alu-AluBlister Pack

6.6 Special precautions for disposal and other handling

No special requirements

7. Marketing Authorization Holder

EQUIVAL ENTERPRISES LTD

8. Marketing Authorization Number

CTD10184

9. Date of first authorization/renewal of the authorization
30/05/2024

10. Date of revision of the text
06/05/2024