Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

SINGULAIR ALLERGY 10mg film-coated tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

One film-coated tablet contains montelukast sodium, which is equivalent to 10 mg montelukast.

Excipients with known effect: This medicine contains 89.3 mg lactose monohydrate per tablet.

This medicine contains less than 1 mmol sodium (23 mg) per tablet, that is to say essentially 'sodium-free'.

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Film-coated tablet
Beige, rounded square, film-coated, size 7.9 mm x 7.9 mm with 117 engraved on one side.

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

The relief of symptoms of seasonal allergic rhinitis.

4.2 Posology and method of administration

Posology
The recommended dose for adults and adolescents 15 years of age and older is one 10 mg tablet daily.

General recommendations
Singulair Allergy contains montelukast, the same active ingredient in Singulair. Singulair Allergy should not be used concomitantly with other products containing the same active ingredient, montelukast. Singulair Allergy may be taken with or without food. Singulair Allergy should be taken once daily each day for the duration of prescribed therapy. The time of administration for seasonal allergic rhinitis may be individualized to suit patient needs.

No dosage adjustment is necessary for the elderly, or for patients with renal insufficiency, or mild to moderate hepatic impairment. There are no data on patients with severe hepatic impairment. The dosage is the same for both male and female patients.

Paediatric population
Do not give Singulair Allergy 10 mg film-coated tablets to children and adolescents less than 15 years of age. The safety and efficacy of Singulair Allergy 10 mg film-coated tablets in patients younger than 15 years of age have not been established.

5 mg chewable tablets are available for paediatric patients 6 to 14 years of age.
4 mg chewable tablets are available for paediatric patients 2 to 5 years of age.

Method of administration
Oral use.

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

Oral montelukast is not for treatment of acute asthma (see Singulair SmPC).

There are reports of rare cases of systemic eosinophilia, sometimes presenting with clinical features of vasculitis consistent with Churg-Strauss syndrome, in asthmatic patients treated with anti-asthma agents including leukotriene receptor antagonists. These cases have been sometimes associated with the reduction or withdrawal of oral corticosteroid therapy in patients with asthma. Although a causal relationship with leukotriene receptor antagonism has not been established, physicians should be alert to eosinophilia, vasculitic rash, worsening pulmonary symptoms, cardiac complications, and/or neuropathy presenting in their patients treated with montelukast. Patients who develop these symptoms should be reassessed and their treatment regimens evaluated.

Treatment with montelukast does not alter the need for patients with aspirin-sensitive asthma to avoid taking aspirin and other non-steroidal anti-inflammatory drugs.

For pharmacokinetics of montelukast in patients with severe hepatic insufficiency (Child-Pugh score >9), see section 5.2.

Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicine.

Neuropsychiatric events have been reported in adults, adolescents, and children taking Singulair Allergy (see section 4.8). Patients and physicians should be alert for neuropsychiatric events. Patients and/or caregivers should be instructed to notify their physician if these changes occur. Prescribers should carefully evaluate the risks and benefits of continuing treatment with Singulair Allergy if such events occur.

4.5 Interaction with other medicinal products and other forms of interactions

Montelukast may be administered with other therapies routinely used in the treatment of allergic rhinitis. 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 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 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.

Based on *in vitro* data, clinically important drug interactions with less potent inhibitors of CYP 2C8 (e.g., trimethoprim) are not anticipated. Co-administration of montelukast with itraconazole, a strong inhibitor of CYP 3A4, resulted in no significant increase in the systemic exposure of montelukast.

4.6 Fertility, pregnancy and lactation

<u>Pregnancy</u>
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.

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

Breast-feeding
Studies in rats have shown that montelukast is excreted in milk (see section 5.3). It is unknown whether montelukast/metabolites are excreted in human milk.

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

4.7 Effects on ability to drive and use machines

Singulair Allergy has no or negligible influence on the ability to drive and use machines. However, individuals have reported drowsiness or dizziness.

4.8 Undesirable effects

Montelukast has been evaluated in patients with seasonal allergic rhinitis (2,199 adult patients 15 years of age and older). In the 2-week, placebo-controlled clinical studies, no drug-related adverse reactions reported as common (≥1/100 to <1/10) in patients treated with montelukast and at a greater incidence than in patients treated with placebo were observed. In a 4-week, placebo-controlled clinical study, the safety profile was consistent with that observed in 2-week studies.

In patients with asthma, montelukast has been evaluated in clinical studies as follows:

- 10 mg film-coated tablets in approximately 4,000 adult and adolescent patients with asthma 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 1,750 paediatric patients with asthma 6 to 14 years of age.

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

PATIENTS WITH ASTHMA		
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 with asthma 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	**AdverseReactions**	**Frequency Category***
Infections and infestations	upper respiratory infection[†]	Very Common
Blood and lymphatic system disorders	increased bleeding tendency	Rare
	thrombocytopenia	Very 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, 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
Skin and subcutaneous tissue disorders	rash[‡]	Common
	bruising, urticaria, pruritus	Uncommon
	angiooedema	Rare
	erythema nodosum, erythema multiforme	Very Rare
Musculoskeletal and connective tissue disorders	arthralgia, myalgia including muscle cramps	Uncommon
Renal and urinary disorders	enuresis in children	Uncommon
General disorders and administration site conditions	pyrexia[‡]	Common
	asthenia/fatigue, malaise, oedema	Uncommon

*Frequency Category: Defined for each Adverse Reaction by the incidence reported in the clinical trials data base: Very Common (≥1/10), Common (≥1/100 to <1/10), Uncommon (≥1/1,000 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 HPRA Pharmacovigilance. Website: www.hpra.ie.

4.9 Overdose

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 1,000 mg (approximately 61 mg/kg in a 42 month old child). The clinical and laboratory findings observed were consistent with the safety profile 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
No specific information is available on the treatment of overdose with montelukast. It is not known whether montelukast is dialyzable by peritoneal- or hemo-dialysis.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

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

Mechanism of action
The cysteinyl leukotrienes (LTC4, LTD4, LTE4), are potent inflammatory eicosanoids released from various cells including mast cells and eosinophils. These 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.

Pharmacodynamic effects
Montelukast is an orally active compound which binds with high affinity and selectivity to the $CysLT_1$ receptor. In clinical studies, montelukast inhibits bronchoconstriction due to inhaled LTD_4. 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.

Clinical efficacy and safety
Montelukast 10 mg tablets administered once daily in the evening to 1,189 adult and adolescent patients 15 years of age and older with seasonal allergic rhinitis resulted in a statistically significant improvement in the primary variable, daytime nasal symptoms score, and its individual components (nasal congestion, rhinorrhea, nasal itching, and sneezing); nighttime symptoms score, and its individual components (nasal congestion upon awakening, difficulty going to sleep, and nighttime awakenings); composite symptoms score (composed of the daytime nasal and nighttime symptoms scores); and global evaluations of allergic rhinitis by patients and by physicians, compared with placebo. In a separate 4-week study in which montelukast 10 mg tablets were administered to 445 patients 15 years of age and older with seasonal allergic rhinitis once daily in the morning, the efficacy over the initial 2 weeks was significantly different from placebo and consistent with the effect observed in studies using evening dosing. Additionally, the effect over the entire 4 weeks was consistent with the 2-week results.

In patients with seasonal allergic rhinitis aged 15 years and older who received montelukast, a median decrease of 13% in peripheral blood eosinophil counts was noted, compared with placebo, over the double-blind treatment periods.

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.

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, although itraconazole, an inhibitor of CYP 3A4, was shown not to change pharmacokinetic variables of montelukast in healthy subjects that received 10 mg montelukast daily. Based on *in vitro* results in human liver microsomes, therapeutic plasma concentrations of montelukast do not inhibit cytochromes P450 3A4, 2C9, 1A2, 2A6, 2C19, or 2D6. The contribution of 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

Microcrystalline cellulose
Lactose monohydrate
Croscarmellose sodium

Hyprolose (E463)
Magnesium stearate

Film coating:
Hypromellose
Hyprolose (E463)
Titanium dioxide (E 171)
Red and yellow ferric oxide (E 172)
Carnauba wax

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 years.

6.4 Special precautions for storage

Store in the original package in order to protect from light and moisture.

6.5 Nature and contents of container

Packaged in polyamide/PVC/aluminium blister package in:
Blisters in packages of: 7, 10, 14, 20, 28, 50, 56, 98, 100 and 200 tablets.
Not all pack sizes may be marketed.

6.6 Special precautions for disposal

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7 MARKETING AUTHORISATION HOLDER

Merck Sharp & Dohme Ireland (Human Health) Limited
Red Oak North
South County Business Park
Leopardstown
Dublin 18
Ireland

8 MARKETING AUTHORISATION NUMBER

PA1286/046/005

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

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Date of last renewal: 26 June 2008

10 DATE OF REVISION OF THE TEXT

April 2020