SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Monkasta 10 mg film-coated tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each film-coated tablet contains 10 mg montelukast (as montelukast sodium).

Excipient(s) with known effect
Each film-coated tablet contains 81.94 mg lactose.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Film-coated tablet.
The film-coated tablets are apricot-coloured, round, slightly biconvex, with bevelled edges.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Monkasta is indicated in the treatment of asthma as add-on therapy in those patients with mild to moderate persistent asthma who are inadequately controlled on inhaled corticosteroids and in whom "as-needed" short-acting β-agonists provide inadequate clinical control of asthma. In those asthmatic patients in whom Monkasta is indicated in asthma, Monkasta can also provide symptomatic relief of seasonal allergic rhinitis.

Monkasta is also indicated in the prophylaxis of asthma in which the predominant component is exercise-induced bronchoconstriction.

4.2 Posology and method of administration

Posology
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.

General recommendations
The therapeutic effect of Monkasta on parameters of asthma control occurs within one day. Monkasta may be taken with or without food. Patients should be advised to continue taking Monkasta even if their asthma is under control, as well as during periods of worsening asthma. Monkasta should not be used concomitantly with other products containing the same active ingredient, montelukast.

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.

Therapy with Monkasta in relation to other treatments for asthma
Monkasta can be added to a patient's existing treatment regimen.

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

Paediatric population
Do not give Monkasta 10 mg film-coated tablets to children less than 15 years of age. The safety and efficacy of montelukast 10 mg film-coated tablets in children less than 15 years has 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

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 doctor's advice as soon as possible if they need more inhalations of short-acting β-agonists than usual.

Montelukast should not be substituted abruptly 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 have been sometimes associated with the reduction or withdrawal of oral corticosteroid therapy. 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. 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.

Neuropsychiatric events such as behavioural changes, depression and suicidality have been reported in all age groups taking montelukast (see section 4.8). The symptoms may be serious and continue if the treatment is not withdrawn. Therefore the treatment with montelukast should be discontinued if neuropsychiatric symptoms occur during treatment.
Advise patients and/or caregivers to be alert for neuropsychiatric events and instruct them to notify their physician if these changes in behaviour occur.

Special information about some of the ingredients
Monkasta contains lactose. Patients with rare hereditary problems of galactose intolerance, total lactase deficiency or glucose-galactose malabsorption should not take this medicine.

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

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 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 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 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.

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

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.
Monkasta 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.

Monkasta 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

Monkasta 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 clinical studies as follows:

- 10 mg film coated tablets in approximately 4,000 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 1,750 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:

System Organ 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	**Frequency Category***	**Adverse Reactions**
Infections and infestations	Very Common	upper respiratory infection†
Blood and lymphatic system disorders	Rare	increased bleeding tendency
	Very Rare	thrombocytopenia
Immune system disorders	Uncommon	hypersensitivity reactions including anaphylaxis
	Very Rare	hepatic eosinophilic infiltration
Psychiatric disorders	Uncommon	dream abnormalities including nightmares, insomnia, somnambulism, anxiety, agitation including aggressive behaviour or hostility, depression, psychomotor hyperactivity (including irritability, restlessness, tremor§)
	Rare	disturbance in attention, memory impairment, tic
	Very Rare	hallucinations, disorientation, suicidal thinking and behaviour (suicidality), obsessive-compulsive symptoms, dysphemia
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)
	Very Rare	pulmonary eosinophilia
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	erythema nodosum, erythema multiforme
Musculoskeletal and connective tissue disorders	Uncommon	arthralgia, myalgia, including muscular cramps
Renal and urinary disorders	Uncommon	enuresis in children
General disorders and administration site conditions	Common	pyrexia‡
	Uncommon	asthenia/fatigue, malaise, oedema

* 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 via the ADR Reporting Website: www.medicinesauthority.gov.mt/adrportal.

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 dialysable by peritoneal- or haemo-dialysis.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Other systemic drugs for obstructive airway diseases, Leukotriene receptor antagonists, ATC code: R03DC03.

Mechanism of action

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 (CysLT) receptors. The CysLT type-1 ($CysLT_1$) 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 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) and in peripheral blood while improving clinical asthma control.

Clinical efficacy and safety

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 night-time 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).

A clinical study was conducted to evaluate montelukast for the symptomatic treatment of seasonal allergic rhinitis in adult and adolescent asthmatic patients 15 years of age and older with concomitant seasonal allergic rhinitis. In this study montelukast 10 mg tablets administered once daily demonstrated a statistically significant improvement in the Daily Rhinitis Symptoms score, compared with placebo. The Daily Rhinitis Symptoms score is the average of the Daytime Nasal Symptoms score (mean of nasal congestion, rhinorrhoea, sneezing, nasal itching) and the Night-time Symptoms score (mean of nasal congestion upon awakening, difficulty going to sleep, and night-time awakenings scores). 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.

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).

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 (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).

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 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 radiolabelled montelukast indicate minimal distribution across the blood-brain barrier. In addition, concentrations of radiolabelled 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.

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 radiolabelled 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.

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, 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 5,000 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

Tablet core:
Lactose monohydrate
Cellulose, powdered
Cellulose, microcrystalline
Croscarmellose sodium
Magnesium stearate

Film coating:
Hypromellose (E464)
Titanium dioxide (E171)
Talc
Propylene glycol
Iron oxide, red (E172)
Iron oxide, yellow (E172)

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.

6.5 Nature and contents of container

Blister (OPA/Alu/PVC//Alu), pack sizes: 7, 10, 14, 20, 28, 30, 49, 50, 56, 84, 90, 98, 100, 140 or 200 film-coated tablets, in a box.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

No special requirements.

7. MARKETING AUTHORISATION HOLDER

TAD Pharma GmbH
Heinz-Lohmann-Straße 5
27472 Cuxhaven
Germany

8. MARKETING AUTHORISATION NUMBER(S)

MA982/01002

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 17th February 2022

10. DATE OF REVISION OF THE TEXT

07-02-2024

Detailed information on this medicinal product is available on the website of Malta Medicines Authority: https://medicinesauthority.gov.mt/medicinesdatabase