NEW ZEALAND DATA SHEET

MONTELUKAST VIATRIS

1. Product Name

Montelukast Viatris, 4 mg and 5 mg, chewable tablets and 10 mg film coated tablets.

2. Qualitative and Quantitative Composition

Each 4 mg chewable tablet contains 4.150 mg montelukast sodium, which is equivalent to 4.0 mg of montelukast.

Each 5 mg chewable tablet contains 5.190 mg montelukast sodium, which is equivalent to 5.0 mg of montelukast.

Each 10 mg film-coated tablet contains 10.4 mg montelukast sodium, which is equivalent to 10.0 mg of the free acid montelukast.

Excipient(s) with known effect: Montelukast Viatris 4mg and 5 mg chewable tablets contains aspartame and sulfites.

For the full list of excipients, see section 6.1.

3. Pharmaceutical Form

4 mg chewable tablet: A white to off-white coloured, oval, biconvex tablet debossed with “M” on one side and “MS1” on the other side.

5 mg chewable tablet: A white to off-white coloured, round, biconvex tablet debossed with “M” on one side and “MS2” on the other side.

10 mg film coated tablet: A blue film-coated, round bi-convex beveled edge shaped tablet debossed with “MO” over “10” on one side and “M” on the reverse.

4. Clinical Particulars

4.1 Therapeutic indications

Montelukast Viatris tablets are indicated in paediatric patients 2 years of age and older for the prophylaxis and chronic treatment of asthma, including the prevention of day-time and night-time symptoms and the prevention of exercise-induced bronchospasm.

Montelukast Viatris tablets are indicated in paediatric patients 2 years of age and older for the relief of day-time and night-time symptoms of seasonal allergic rhinitis and perennial allergic rhinitis.

4.2 Dose and method of administration

Montelukast Viatris tablets should be taken once daily. For asthma, the dose should be taken in the evening. For allergic rhinitis, the time of administration may be individualised to suit patient needs. Patients with both asthma and allergic rhinitis should take only one tablet daily in the evening.

Dose

Adults 15 years of age and older with asthma and/or allergic rhinitis

The dosage for adults 15 years of age and older is one 10 mg film coated tablet daily.

Paediatric patients 6 to 14 years of age with asthma and/or allergic rhinitis

The dosage for pediatric patients 6 to 14 years of age is one 5 mg chewable tablet daily.

Paediatric patients 2 to 5 years of age with asthma and/or allergic rhinitis

The dosage for pediatric patients 2 to 5 years of age is one 4 mg chewable tablet daily.

General recommendations

The therapeutic effect of montelukast on parameters of asthma control occurs within one day. Patients should be advised to continue taking Montelukast Viatris while their asthma is controlled, as well as during periods of worsening asthma. Montelukast Viatris should not be used concomitantly with other products containing the same active ingredient, montelukast.

No dosage adjustment is necessary for pediatric patients, for the elderly, for patients with renal insufficiency, or mild-to-moderate hepatic impairment, or for patients of either gender.

Therapy with Montelukast Viatris in relation to other treatments for asthma

Montelukast Viatris can be added to a patient's existing treatment regimen.

Reduction in concomitant therapy

Bronchodilator treatments

Montelukast Viatris can be added to the treatment regimen of patients who are not adequately controlled on bronchodilator alone. When a clinical response is evident (usually after the first dose), the patient's bronchodilator therapy can be reduced as tolerated.

Inhaled corticosteroids

Treatment with montelukast provides additional clinical benefit to patients treated with inhaled corticosteroids. A reduction in the corticosteroid dose can be made as tolerated. The dose should be reduced gradually with medical supervision. In some patients, the dose of inhaled corticosteroids can be tapered off completely. Montelukast Viatris should not be abruptly substituted for inhaled corticosteroids.

Oral corticosteroids

Limited data suggest that montelukast may provide additional clinical benefit in patients with oral corticosteroids.

Method of administration

4 mg and 5 mg chewable tablet: The tablets are to be chewed before swallowing. Montelukast Viatris chewable tablets should be taken 1 hour before or 2 hours after food.

10 mg film coated tablet: Oral use. Montelukast Viatris film coated tablets may be taken with or without food. Swallow whole – do not chew.

4.3 Contraindications

Hypersensitivity to the montelukast sodium or to any of the excipients listed in section 6.1.

4.4 Special warnings and precautions for use

The efficacy of oral montelukast for the treatment of acute asthma attacks has not been established. Therefore, oral montelukast should not be used to treat acute asthma attacks. Patients should be

advised to have appropriate rescue medication available. If an acute attack occurs, a short-acting inhaled β-agonist should be used. Patients should seek their doctors' advice as soon as possible if they need more inhalations of short-acting β-agonists than usual.

While the dose of concomitant inhaled corticosteroid may be reduced gradually under medical supervision, 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 have been reported in patients taking montelukast (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 montelukast if such events occur.

In rare cases patients receiving 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. Caution and appropriate clinical monitoring are recommended in patients receiving montelukast.

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.

Use in hepatic impairment

Patients with mild-to-moderate hepatic insufficiency and clinical evidence of cirrhosis had evidence of decreased metabolism of montelukast resulting in approximately 41% higher mean montelukast area under the plasma concentration curve (AUC) following a single 10 mg dose. The elimination of montelukast is slightly prolonged compared with that in healthy subjects (mean half-life, 7.4 hours). No dosage adjustment is required in patients with mild-to-moderate hepatic insufficiency. There are no clinical data in patients with severe hepatic insufficiency (Child-Pugh score > 9).

Use in renal impairment

Since montelukast and its metabolites are not excreted in the urine, the pharmacokinetics of montelukast were not evaluated in patients with renal insufficiency. No dosage adjustment is recommended in these patients.

Use in elderly

The pharmacokinetic profile and the oral bioavailability of a single 10 mg oral dose of montelukast are similar in elderly and younger adults. The plasma half-life of montelukast is slightly longer in the elderly. No dosage adjustment in the elderly is required

Use in paediatric

Montelukast has been studied in paediatric patients 2 to 14 years of age (see section 4.2). Safety and effectiveness in paediatric patients younger than 2 years of age have not been studied. Studies have shown that montelukast does not affect the growth rate of paediatric patients.

Effects on laboratory tests

No data available.

4.5 Interaction with other medicines and other forms of interaction

Montelukast may be administered with other therapies routinely used in the prophylaxis and chronic treatment of asthma, and in the treatment of allergic rhinitis. In medicine-interactions studies, the recommended clinical dose of montelukast did not have clinically important effects on the pharmacokinetics of the following medicines: theophylline, prednisone, prednisolone, oral contraceptives (ethinyl estradiol/norethindrone 35/1), terfenadine, digoxin and warfarin.

Although additional specific interaction studies were not performed, montelukast was used concomitantly with a wide range of commonly prescribed medicines in clinical studies without evidence of clinical adverse interactions. These medications included thyroid hormones, sedative hypnotics, nonsteroidal anti-inflammatory agents, benzodiazepines and decongestants.

The area under the plasma concentration-time 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 an inhibitor of CYP2C8. However, data from a clinical drug-drug interaction study involving montelukast and rosiglitazone (a probe substrate representative of drugs primarily metabolised by CYP2C8) demonstrated that montelukast does not inhibit CYP2C8 *in vivo*. Therefore, montelukast is not anticipated to alter the metabolism of drugs metabolised by this enzyme (e.g., paclitaxel, rosiglitazone, repaglinide).

In vitro studies have shown that montelukast is a substrate of CYP 2C8, and to a less significant extent, 2C9, and 3A4. Data from a clinical drug-drug interaction study involving montelukast and gemfibrozil (an inhibitor of both CYP 2C8 and 2C9) demonstrated that gemfibrozil increased the systemic exposure of montelukast by 4.4-fold. Co-administration of itraconazole, a strong CYP 3A4 inhibitor, with gemfibrozil and montelukast did not further increase the systemic exposure of montelukast. The effect of gemfibrozil on systemic exposure of montelukast is not considered to be clinically meaningful based on clinical safety data with doses greater than the 10 mg approved dose in adults (e.g., 200 mg/day to adult patients for 22 weeks, and up to 900 mg/day to patients for approximately one week) where clinically important adverse experiences were not observed. Therefore, no dosage adjustment of montelukast is required upon co-administration with gemfibrozil 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 other known inhibitors of CYP 2C8 (e.g., trimethoprim) are not anticipated. In addition, co-administration of montelukast with itraconazole, a strong inhibitor of CYP 3A4, alone resulted in no significant increase in the systemic exposure of montelukast.

There are no data available on the use of montelukast and alcohol.

4.6 Fertility, pregnancy and lactation

Pregnancy

Montelukast has not been studied in pregnant women. Montelukast should be used during pregnancy only if clearly needed. During worldwide marketing experience, congenital limb defects have been rarely reported in the offspring of women being treated with montelukast during pregnancy. Most of these women were also taking other asthma medications during their pregnancy. A causal relationship between these events and montelukast has not been established.

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.

Breastfeeding

It is not known if montelukast is excreted in human milk. Because many medicines are excreted in human milk, caution should be exercised when montelukast is given to a nursing mother.

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 mothers only if it is considered to be clearly essential.

Fertility

In pre-clinical studies, there were no significant results in reproduction studies conducted with montelukast sodium. In developmental toxicity studies, there were no treatment related adverse effects at doses up to 400 mg/kg/day in rats and up to 100 mg/kg/day in rabbits. Foetal exposure of montelukast sodium in rats and rabbits does occur and significant concentrations of medicine were observed in the milk of lactating rats. Animal studies do not indicate harmful effects with respect to effects on pregnancy or embryonal/foetal development.

4.7 Effects on ability to drive and use machines

There is no evidence that montelukast affects the ability to drive and use machines. However, individuals have reported drowsiness or dizziness. Patients should be warned about the potential for these undesirable effects and advised not to drive or operate machinery if these symptoms occur or until their individual susceptibility is known.

4.8 Undesirable effects

Pooled analyses of clinical trials experience

A pooled analysis of 41 placebo-controlled clinical studies (35 studies in patients 15 years of age and older; 6 studies in paediatric patients 6 to 14 years of age) was performed using a validated assessment method of suicidality. Among the 9929 patients who received montelukast and 7780 patients who received placebo in these studies, there was one patient with suicidal ideation in the group taking montelukast. There were no completed suicides, suicide attempts or preparatory acts toward suicidal behaviour in either treatment group.

A separate pooled analysis of 46 placebo-controlled clinical studies (35 studies in patients 15 years of age and older; 11 studies in paediatric patients 3 months to 14 years of age) assessing behaviour-related adverse experiences (BRAEs) was performed. Among the 11,673 patients who received montelukast and 8827 patients who received placebo in these studies, the frequency of patients with at least one BRAE was 2.73% in patients who received montelukast and 2.27% in patients who received placebo; the odds ratio was 1.12 (95% CI [0.93; 1.36]).

The clinical trials included in these pooled analyses were not designed specifically to examine suicidality or BRAEs 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.
- 4 mg chewable tablets in 851 paediatric patients 2 to 5 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)	Paediatric Patients 2 to 5 years old (one 12-week study; n=461) (one 48-week study; n=278)
Nervous system disorders	headache	headache	---
Gastro-intestinal disorders	abdominal pain	---	abdominal pain
General disorders and administration site conditions	---	---	thirst

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.

Cumulatively, 502 paediatric patients 2 to 5 years of age were treated with montelukast for at least 3 months, 338 for 6 months or longer, and 534 patients for 12 months or longer. With prolonged treatment, the safety profile did not change in these patients either.

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 disorders:	hypersensitivity reactions including anaphylaxis	Uncommon
	hepatic eosinophilic infiltration	Very Rare
Psychiatric disorders:	dream abnormalities including nightmares, insomnia, somnambulism, anxiousness, agitation including aggressive behaviour or hostility, depression, psychomotor hyperactivity (including irritability, restlessness, and tremor§)	Uncommon
	disturbance in attention, memory impairment, tic	Rare
	hallucinations, disorientation, suicidal thinking and behaviour (suicidality), obsessive-compulsive	Very Rare

	symptoms, dysphemia (stuttering)	
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	increased levels of serum transaminases (ALT and AST)	Common
	hepatitis (including cholestatic, hepatocellular, and mixed-pattern liver injury)	Very Rare
Skin and subcutaneous tissue disorders	rash‡	Common
	bruising, urticaria, pruritus	Uncommon
	angioedema	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 medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Healthcare professionals are asked to report any suspected adverse reactions https://nzphvc.otago.ac.nz/reporting/.

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 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.

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 overdosage with montelukast. It is not known whether montelukast is dialysable by peritoneal- or haemodialysis.

For further advice on management of overdose please contact the National Poisons Information Centre (0800 POISON or 0800 764 766).

5. Pharmacological Properties

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Leukotriene receptor antagonist, drugs for obstructive airway diseases, ATC code: R03DC03

Mechanism of action

Montelukast Viatris (montelukast sodium) is a selective and orally active leukotriene receptor antagonist that specifically inhibits cysteinyl leukotriene $CysLT_1$ receptor.

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 a number of airway actions, including 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 a potent, orally active compound that significantly improves parameters of asthmatic inflammation. In clinical studies, montelukast inhibits bronchoconstriction due to inhaled LTD4 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). In adult and paediatric patients 2 to 14 years of age, montelukast, compared with placebo, decreased peripheral blood eosinophils while improving clinical asthma control.

Based on biochemical and pharmacological bioassays, it binds with high affinity and selectivity to the $CysLT_1$ receptor (in preference to other pharmacologically important airway receptors such as the prostanoid, cholinergic, or β-adrenergic receptor). Montelukast potently inhibits physiologic actions of LTC_4, LTD_4, and LTE_4 at the $CysLT_1$ receptor without any agonist activity.

Clinical trials

In studies in adults, montelukast, 10 mg once daily, compared with placebo, demonstrated significant improvements in morning FEV1 (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.

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 a 12-week, placebo-controlled study in paediatric patients 2 to 5 years of age, montelukast 4 mg once daily improved parameters of asthma control compared with placebo irrespective of concomitant controller therapy (inhaled/nebulized corticosteroids or inhaled/nebulized sodium cromoglycate). Sixty percent of patients were not on any other controller therapy. Montelukast improved daytime symptoms (including coughing, wheezing, trouble breathing and activity limitation) and night-time symptoms compared with placebo. Montelukast also decreased "as-needed" β-agonist use and corticosteroid rescue for worsening asthma compared with placebo. Patients receiving montelukast had more days without asthma than those receiving placebo. A treatment effect was achieved after the first dose.

In a 12-month, placebo-controlled study in paediatric patients 2 to 5 years of age with mild asthma and episodic exacerbations, montelukast 4 mg once daily significantly ($p \leq 0.001$) reduced the yearly rate of asthma exacerbation episodes (EE) compared with placebo (1.60 EE vs. 2.34 EE, respectively), [EE defined as ≥3 consecutive days with daytime symptoms requiring β-agonist use, or corticosteroids (oral or inhaled), or hospitalization for asthma]. The percentage reduction in yearly EE rate was 31.9%, with a 95% CI of 16.9, 44.1.

In a placebo-controlled study in paediatric patients 6 months to 5 years of age who had intermittent asthma but did not have persistent asthma, treatment with montelukast was administered over a 12-month period, either as a once-daily 4 mg regimen or as a series of 12-day courses that each were started when an episode of intermittent symptoms began. No significant difference was observed between patients treated with montelukast 4 mg or placebo in the number of asthma episodes

culminating in an asthma attack, defined as an asthma episode requiring utilization of health-care resources such as an unscheduled visit to a doctor's office, emergency room, or hospital; or treatment with oral, intravenous, or intramuscular corticosteroid.

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 (FEV1 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).

In a 12-month study comparing the efficacy of montelukast to inhaled fluticasone on asthma control in paediatric patients 6 to 14 years of age with mild persistent asthma, montelukast was non-inferior to fluticasone in increasing the percentage of asthma rescue-free days (RFDs), the primary endpoint. Averaged over the 12-month treatment period, the percentage of asthma RFDs increased from 61.6 to 84.0 in the montelukast group and from 60.9 to 86.7 in the fluticasone group. The between group difference in LS mean increase in the percentage of asthma RFDs was statistically significant (-2.8 with a 95% CI of -4.7, -0.9), but within the limit pre-defined to be clinically not inferior. Both montelukast and fluticasone also improved asthma control on secondary variables assessed over the 12-month treatment period: FEV1 increased from 1.83 L to 2.09 L in the montelukast group and from 1.85 L to 2.14 L in the fluticasone group. The between-group difference in LS mean increase in FEV1 was -0.02 L with a 95% CI of -0.06, 0.02. The mean increase from baseline in % predicted FEV1 was 0.6% in the montelukast treatment group, and 2.7% in the fluticasone treatment group. The difference in LS means for the change from baseline in the % predicted FEV1 was significant: -2.2% with a 95% CI of -3.6, -0.7. The percentage of days with β-agonist use decreased from 38.0 to 15.4 in the montelukast group, and from 38.5 to 12.8 in the fluticasone group. The between group difference in LS means for the percentage of days with β-agonist use was significant: 2.7 with a 95% CI of 0.9, 4.5. The percentage of patients with an asthma attack (an asthma attack being defined as a period of worsening asthma that required treatment with oral steroids, an unscheduled visit to the doctor’s office, an emergency room visit, or hospitalization) was 32.2 in the montelukast group and 25.6 in the fluticasone group; the odds ratio (95% CI) being significant: equal to 1.38 (1.04, 1.84). The percentage of patients with systemic (mainly oral) corticosteroid use during the study period was 17.8% in the montelukast group and 10.5% in the fluticasone group. The between group difference in LS means was significant: 7.3% with a 95%CI of 2.9; 11.7.

Significant reduction of exercise-induced bronchoconstriction (EIB) was demonstrated in a 12-week study in adults (maximal fall in FEV1 22.33% for montelukast vs 32.40% for placebo; time to recovery to within 5% of baseline FEV1 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 FEV1 18.27% vs 26.11%; time to recovery to within 5% of baseline FEV1 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 (FEV1 8.55% vs -1.74% change from baseline and decrease in total β-agonist use -27.78% vs 2.09% change from baseline).

Gender

The pharmacokinetics of montelukast are similar in males and females.

Elderly

The pharmacokinetic profile and the oral bioavailability of a single 10 mg oral dose of montelukast are similar in elderly and younger adults. 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. In clinical studies, there do not appear to be any differences in clinically important effects.

Adolescents and paediatric patients

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

Pharmacokinetic studies using either the chewable tablet or film-coated tablet show that the plasma profile of the 5 mg chewable tablet in paediatric patients 6 to 14 years of age is similar to that of a 10 mg film-coated tablet in adults. In a pharmacokinetic study in paediatric patients 2 to 5 years of age, the plasma profile of the 4 mg chewable tablet was also similar to that of a 10 mg film-coated tablet in adults. The 5 mg chewable tablet should be used in paediatric patients 6 to 14 years of age and the 4 mg chewable tablet in paediatric patients 2 to 5 years of age.

5.2 Pharmacokinetic properties

Absorption

Montelukast is rapidly absorbed following oral administration. For a 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.

For the 5 mg chewable tablet, the C_{max} is achieved 2 hours after administration in adults in the fasted state. The mean oral bioavailability is 73%. The mean oral bioavailability is 73% and is decreased to 63% by a standard meal.

For the 4 mg chewable tablet, C_{max} is achieved 2 hours after administration in paediatric patients 2 to 5 years of age in the fasted state. The mean C_{max} is 66% higher while mean C_{min} is lower than in adults receiving a 10 mg tablet.

Safety and efficacy were demonstrated in clinical studies where the 4 mg chewable tablet, 5 mg chewable tablet, and a 10 mg film-coated tablet were 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 to 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 paediatric patients.

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. *In vitro* studies using human liver microsomes indicate that cytochrome P450 3A4 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 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 montelukast and its metabolites are excreted almost exclusively via the bile.

In several studies, the mean plasma half-life of montelukast ranged 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. No difference in pharmacokinetics was noted between dosing in the morning or in the evening. During once-daily dosing with 10 mg montelukast, there is little accumulation of the parent medicine in plasma (~14%).

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), 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 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

Montelukast Viatris 4 mg and 5 mg chewable tablet contains:

- mannitol
- microcrystalline cellulose
- croscarmellose sodium
- aspartame (E951)
- colloidal anhydrous silica
- magnesium stearate
- sodium lauryl sulfate

- The cherry flavour (501027 AP 0551) contains:
    - maize maltodextrin
    - benzyl alcohol (E1519)
    - triethyl citrate (E1505)

Montelukast Viatris 4 mg and 5 mg chewable tablet contains aspartame and sulfites.

Montelukast Viatris 10 mg film coated tablet contains:

- microcrystalline cellulose
- mannitol
- croscarmellose sodium
- magnesium stearate
- sodium laurylsulfate
- silica colloidal anhydrous.
- The film coating consists of:
    - polydextrose
    - titanium dioxide
    - hypromellose
    - triacetin
    - indigo carmine aluminium lake (E132)
    - macrogol 400
    - sunset yellow aluminium lake (E110)
    - macrogol 8000

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 years.

6.4 Special precautions for storage

4 mg and 5 mg chewable tablet: Store at or below 25°C. Protect from light and moisture.

10 mg film coated tablet: Store at or below 25°C.

6.5 Nature and contents of container

Montelukast Viatris 4mg and 5mg chewable tablets are available in blister packs comprised of laminate with desiccant layer on one side and hard tempered Al foil on the other side, of 28 tablets and HDPE bottle with PP cap and a silica gel desiccant, of 100 tablets.

Montelukast Viatris 10 mg tablets are available in OPA/AL/PVC/AL blister packs of 28 tablets and PP bottle with PE cap and silica gel desiccant, of 500 tablets.

Not all pack types and sizes may be marketed.

6.6 Special precautions for disposal

Not applicable.

7. Medicines Schedule

Prescription Medicine

8. Sponsor Details

Viatris Ltd
PO Box 11-183
Ellerslie
AUCKLAND
www.viatris.co.nz
Telephone 0800 168 169

9. Date of First Approval

4 mg and 5 mg chewable tablet: 13 November 2014

10 mg film coated tablet: 10 December 2014

10. Date of Revision of the Text

16 August 2022

Summary table of changes

Section	Summary of new information
Header	Updated sponsor logo.
All	Name change from Montelukast Mylan to Montelukast Viatris.
2	Update to declaration of excipients with known effect for Montelukast chewable 4mg and 5mg tablet contains aspartame and sulfite.
6.1	Removed gluten free and lactose free statement. Added allergen statement for Montelukast Viatris 4mg and 5mg chewable tablets contains aspartame and sulfite.
8	Updated sponsor details.
10	Updated date of text revision.