NEW ZEALAND DATA SHEET

MONTELUKAST VIATRIS

Warning:

Serious Neuropsychiatric events

Neuropsychiatric events such as behavioural changes, depression and suicidality have been reported in all age groups taking montelukast (see sections 4.4 and 4.8). Events are generally mild and may be coincidental. However, the symptoms may be serious and continue if the treatment is not withdrawn.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.

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.

Excipients with known effect (Chewable Tablet): Aspartame and Cherry Flavour

Allergen Declaration (Chewable Tablet): Aspartame and sulfites.

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

Excipients with known effect (Film Coated Tablet): Mannitol

Allergen Declaration (Film Coated Tablet): Gluten from wheat

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 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: 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 relied upon 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.

Eosinophilic conditions

In rare cases patients receiving anti-asthma agents including leukotriene receptor antagonists, have experienced one or more of the following: eosinophilia, vasculitic rash, worsening pulmonary symptoms, cardiac complications, and/or neuropathy sometimes diagnosed as Churg-Strauss syndrome, a systemic eosinophilic vasculitis. 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, caution and appropriate clinical monitoring are recommended in patients receiving montelukast.

Montelukast Viatris 4 mg and 5 mg chewable tablets contain aspartame which is a source of phenylalanine.

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

Neuropsychiatric events

Neuropsychiatric events have been reported in adults, adolescents and children taking montelukast (see section 4.8).

Post-market reports with use of montelukast include agitation, aggressive behaviour or hostility, anxiousness, depression, dream abnormalities, hallucinations, insomnia, irritability, restlessness, somnambulism, suicidal thinking and behaviour and tremor. Events have been reported mostly during montelukast treatment, but some were reported after montelukast discontinuation. In many cases symptoms resolved after stopping montelukast, however, in some cases, symptoms persisted.

Neuropsychiatric events have been reported in patients with and without a history of psychiatric disorder.

Discuss risks of neuropsychiatric events with montelukast with patients and/or caregivers before starting treatment.

Patients, and/or caregivers and physicians should be alert for neuropsychiatric events when taking montelukast including changes in behaviour and new neuropsychiatric symptoms. Patients and/or caregivers should be instructed to notify their physician if these changes occur and to discontinue treatment. Prescribers should carefully evaluate the risks and benefits of continuing treatment with montelukast if such events occur.

Use in hepatic impairment

No dosage adjustment is necessary for the elderly or for 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

Because montelukast and its metabolites are eliminated by the biliary route, no dose adjustment is anticipated to be necessary in patients with renal impairment. Studies in patients with renal impairment have not been undertaken.

Use in elderly

In clinical studies, there were no age-related differences in the efficacy or safety profiles of montelukast.

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

Relatively high concentrations of montelukast competitively inhibit the activity of cytochromes P450 3A4 and 2C9. However, these concentrations are at least 15-fold higher than the peak plasma concentrations attained following a 10 mg oral dose of montelukast. Based on these and other *in vitro* results in human liver microsomes, therapeutic plasma concentrations of montelukast should not be expected to inhibit cytochromes P450 3A4, 2C9, 1A2, 2A6, 2C19 or 2D6. Theophylline plasma concentration was not affected by the recommended dose of montelukast (10 mg once daily). At 20 and 60-fold above the recommended dose, plasma concentration of concomitant theophylline was decreased. Theophylline dose adjustment or a change in the frequency of plasma theophylline monitoring is not necessary at the recommended dose of montelukast.

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. The effects of concomitant administration of montelukast and macrolide antimicrobials have not been studied.

The area under the plasma concentration-time curve (AUC) for montelukast was decreased approximately 40% in subjects with co-administration of phenobarbital. No dosage adjustment for montelukast is recommended.

In vitro studies have shown that montelukast is an inhibitor of CYP2C8. However, data from a clinical medicine-medicine interaction study involving montelukast and rosiglitazone (a probe substrate representative of medicines primarily metabolised by CYP2C8) demonstrated that montelukast does not inhibit CYP2C8 *in vivo*. Therefore, montelukast is not anticipated to alter the metabolism of medicines metabolised by this enzyme (e.g., paclitaxel, rosiglitazone, repaglinide).

In vitro studies have shown that montelukast is a substrate of CYP 2C8, 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. Based on available clinical experience no dosage adjustment of montelukast is required upon co-administration with gemfibrozil or other potent inhibitors of CYP 2C8. Specific *in vivo* data are not available for other known inhibitors of CYP 2C8 (e.g. trimethoprim). Although clinically important medicine interactions are not anticipated based on these findings, systemic exposure to montelukast is potentially increased and the physician should be aware of a possible increase in adverse reactions (see Section 4.9). Co-administration of montelukast with itraconazole alone resulted in no significant increase in the systemic exposure of montelukast.

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.

4.6 Fertility, pregnancy and lactation

Pregnancy

In animal studies, montelukast sodium had no adverse effects on embryofoetal development at oral doses up to 400 mg/kg/day in rats or up to 100 mg/kg/day in rabbits. Retardation of foetal growth and development was observed in rabbits dosed at 200 mg/kg/day, a dose level associated with severe maternal toxicity. Foetal exposure of montelukast was demonstrated in both species.

Available data from published prospective and retrospective cohort studies with montelukast use in pregnant women evaluating major birth defects have not established a medicine-associated risk. Available studies have methodologic limitations, including small sample size, in some cases retrospective data collection, and inconsistent comparator groups. Montelukast should be used during pregnancy only if clearly needed.

Breastfeeding

Studies in lactating rats have shown that montelukast is excreted into milk following oral doses of 100 and 200 mg/kg/day, and growth of the pups was slightly inhibited at the higher dose level.

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.

Fertility

Fertility and reproductive performance were not affected in studies with male rats given oral doses of up to 800 mg/kg/day, but fecundity was slightly reduced in female rats dosed orally at 200 mg/kg/day. The no-effect dose for the latter effect was 100 mg/kg/day, corresponding to systemic exposure, in terms of plasma AUC for parent drug, at least 20 times higher than that in women at recommended dose levels.

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

Montelukast has been generally well tolerated. Side effects, which usually were mild, generally did not require discontinuation of therapy. The overall incidence of side effects reported with Montelukast was comparable to placebo.

Adults 15 years of Age and Older with Asthma

Montelukast has been evaluated for safety in approximately 2600 adult patients 15 years of age and older in clinical studies. In two similarly designed, 12 week placebo-controlled clinical studies, the only adverse experiences reported as medicine-related in ≥ 1% of patients treated with montelukast and at a greater incidence than in patients treated with placebo were abdominal pain and headache. The incidences of these events were not significantly different in the two treatment groups.

In placebo-controlled clinical studies, the following adverse experiences reported with montelukast occurred in ≥ 1% of patients and at an incidence greater than or equal to that in patients treated with placebo, regardless of medicine relationship:

Table 1

Adverse experiences occurring in ≥ 1% of patients with an incidence greater than or equal to that in patients treated with placebo, regardless of medicine relationship

	Montelukast 10 mg/day (%) (n = 1955)	Placebo (%) (n = 1180)
Body as a Whole		
Asthenia/fatigue	1.8	1.2
Fever	1.5	0.9
Pain, abdominal	2.9	2.5
Trauma	1.0	0.8
Digestive System Disorders		
Diarrhoea	3.1	3.1
Dyspepsia	2.1	1.1
Gastroenteritis, infectious	1.5	0.5
Pain, dental	1.7	1.0
Nervous System/Psychiatric		
Dizziness	1.9	1.4
Headache	18.4	18.1
Insomnia	1.3	1.3
Respiratory System Disorders		
Congestion, nasal	1.6	1.3
Cough	2.7	2.4
Influenza	4.2	3.9
Skin/Skin Appendages Disorder		
Rash	1.6	1.2
Laboratory Adverse Experiences*		
ALT increased	2.1	2.0
AST increased	1.6	1.2
Pyuria	1.0	0.9

* Number of patients tested (montelukast and placebo, respectively): ALT and AST, 1935, 1170; pyuria, 1924, 1159.

Cumulatively, 544 patients were treated with montelukast for at least 6 months, 253 for one year and 21 for two years in clinical studies. With prolonged treatment, the adverse experience profile did not change.

Paediatric Patients 6 to 14 Years of Age with Asthma

Montelukast has been evaluated for safety in approximately 970 paediatric patients 6 to 14 years of age. The safety profile in paediatric patients is generally similar to the adult safety profile and to placebo. Cumulatively, 263 paediatric patients 6-14 years of age were treated with montelukast for at least 3 months, 164 for 6 months or longer in clinical studies. The safety profile in paediatric patients is generally similar to the adult safety profile and to placebo. With prolonged treatment, the adverse experience profile did not change.

In a 56-week active-controlled study comparing montelukast to inhaled fluticasone in paediatric patients 6-14 years of age with mild persistent asthma, the safety profile was consistent with the safety profile previously described for montelukast. In the study, the number of patients with asthma symptoms after treatment was 166 (33.5%) patients in the montelukast treatment group and 135 (27.1%) patients in the fluticasone treatment group.

In studies evaluating growth rate, the safety profile in these paediatric patients was consistent with the safety profile previously described for montelukast.

Paediatric Patients 2 to 5 Years of Age with Asthma

Montelukast has been evaluated in 573 paediatric patients 2 to 5 years of age. In a 12-week placebo-controlled clinical study, the only adverse experience reported as medicine related in > 1% of patients treated with montelukast and at a greater incidence than in patients treated with placebo was thirst. The incidence of thirst was not significantly different in the two treatment groups.

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 256 patients for 12 months or longer. With prolonged treatment, the adverse experience profile did not change.

Adults 15 Years of Age and Older with Seasonal Allergic Rhinitis

Montelukast has been evaluated in 2199 adult patients 15 years of age and older for the treatment of seasonal allergic rhinitis in clinical studies. Montelukast administered once daily in the morning or in the evening was generally well tolerated with a safety profile similar to that of placebo. In placebo-controlled clinical studies, no adverse experiences reported as medicine related in ≥1% of 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. The incidence of somnolence was similar to that of placebo in all studies.

Paediatric Patients 2 to 14 Years of Age with Seasonal Allergic Rhinitis

Montelukast has been evaluated in 280 paediatric patients 2 to 14 years of age for the treatment of seasonal allergic rhinitis in a 2-week, placebo-controlled, clinical study. Montelukast administered once daily in the evening was generally well tolerated with a safety profile similar to that of placebo. In this study, no adverse experiences reported as medicine related in ≥1% of patients with montelukast and at a greater incidence than in patients treated with placebo were observed.

Adults 15 Years of Age and Older with Asthma and Seasonal Allergic Rhinitis

Montelukast 10 mg film-coated tablets have been evaluated in approximately 400 asthmatic patients 15 years of age and older with seasonal allergic rhinitis. The safety profile in asthmatic patients with seasonal allergic rhinitis was consistent with that observed in patients with asthma.

Post-Marketing Experience

The following additional side effects have been reported in post-marketing use:

Infections and infestations: upper respiratory tract infection

Blood and lymphatic system disorders: increased bleeding tendency, thrombocytopenia

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

Psychiatric disorders: agitation including aggressive behaviour or hostility, anxiousness, depression, disorientation, disturbance in attention, dream abnormalities, dysphemia (stuttering), hallucinations, insomnia, memory impairment, obsessive-compulsive symptoms, psychomotor hyperactivity (including irritability, restlessness, and tremor), somnambulism (sleep walking), suicidal thinking and behaviour (suicidality), tic

Nervous system disorders: dizziness, drowsiness, paraesthesia/hypoesthesia, very rarely seizure

Cardiac disorders: palpitations

Respiratory, thoracic and mediastinal disorders: epistaxis, pulmonary eosinophilia

Gastrointestinal disorders: diarrhoea, dyspepsia, nausea, vomiting

Hepatobiliary disorders: increased ALT and AST, very rarely hepatitis (including cholestatic, hepatocellular, and mixed-pattern liver injury)

Skin and subcutaneous tissue disorders: angioedema, bruising, erythema multiforme†, erythema nodosum, pruritus, rash, urticaria

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

Renal and urinary disorders: enuresis in children

General disorders and administration site conditions: oedema, pyrexia

In rare cases, patients on therapy with montelukast may present with systemic eosinophilia, sometimes presenting with clinical features of vasculitis consistent with Churg-Strauss syndrome. These events usually, but not always, have been associated with the reduction of oral corticosteroid therapy. A causal association between montelukast and these underlying conditions has not been established (see Section 4.4).

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://pophealth.my.site.com/carmreportnz/s/.

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 risk assessment and advice on the 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, medicines 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 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). 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 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 nighttime 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 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 (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).

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:

FEV_1 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 FEV_1 was -0.02 L with a 95% CI of -0.06, 0.02. The mean increase from baseline in % predicted FEV_1 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 FEV_1 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 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).

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. 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 2 hours after administration in adults in the fasted state. 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/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

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 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

11 June 2025

Summary table of changes

Section	Summary of new information
Header	Added boxed warning on neuropsychiatric events.
All	Editorial updates.
4.4	Reworded information on eosinophilic conditions, use in hepatic impairment, use in renal impairment, use in elderly.
4.5, 4.6, 4.8	Whole sections updated.
4.9	Added risk assessment wording.