

PRODUCT MONOGRAPH

^{Pr} APO-MONTELUKAST

montelukast (as montelukast sodium)

10 mg tablets

Apotex Standard

Leukotriene Receptor Antagonist

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PART I: HEALTH PROFESSIONAL INFORMATION

SUMMARY PRODUCT INFORMATION

Route of Administration	Dosage Form / Strength	All Non-Medicinal Ingredients
Oral	tablets / 10 mg	Core tablet contains: Lactose Monohydrate (Pharmatose 200 M), Cellulose, Microcrystalline (Avicel PH 101), Croscarmellose Sodium (AC-Di-Sol®-Type SD-711), Hydroxy Propyl Cellulose (Klucel- LF), Magnesium Stearate (Ligamed MF-2-V) Coating contains: Hydroxy Propyl Cellulose, HPMC 2910/ Hypromellose 6cP, Titanium Dioxide, Iron Oxide Yellow, Carnauba Wax & Iron Oxide Red.

INDICATIONS AND CLINICAL USE

APO-MONTELUKAST (montelukast sodium) is indicated in adult and adolescents 15 years and older for the prophylaxis and chronic treatment of asthma, including prevention of day- and night-time symptoms, the treatment of acetylsalicylic acid (ASA)-sensitive asthmatic patients, and the prevention of exercise-induced bronchoconstriction.

APO-MONTELUKAST is effective alone or in combination with other agents used in the maintenance treatment of chronic asthma. APO-MONTELUKAST and inhaled corticosteroids may be used concomitantly with additive effects to control asthma or to reduce the inhaled corticosteroid dose while maintaining clinical stability.

In patients who continue to experience asthma symptoms, APO-MONTELUKAST can be an additional treatment option following initial management with an “as needed” short-acting beta-agonist (SABA), an inhaled corticosteroid, or inhaled corticosteroid together with a long-acting beta agonist.

In adults, APO-MONTELUKAST can be a treatment option after “as needed” SABAs if patients remain symptomatic and cannot or will not use an inhaler device or would prefer not to be treated with an inhaled corticosteroid.

APO-MONTELUKAST can be a treatment option in patients who experience exercise-induced bronchoconstriction.

APO-MONTELUKAST is indicated for the relief of symptoms of seasonal allergic rhinitis in patients 15 years old or older. APO-MONTELUKAST should be considered when other treatments are not effective or not tolerated.

CONTRAINDICATIONS

- Patients who are hypersensitive to this drug or to any ingredient in the formulation. For a complete listing, see the DOSAGE FORMS, COMPOSITION AND PACKAGING section of the product monograph.

WARNINGS AND PRECAUTIONS

Information to be Provided to the Patient

Patients should be advised to take APO-MONTELUKAST daily as prescribed, even when they are asymptomatic as well as during periods of asthma worsening, and to contact their physicians if their asthma is not well-controlled. Patients should be advised that APO-MONTELUKAST is not for the treatment of acute asthma attacks. They should have appropriate rescue medication available.

General

The efficacy of oral montelukast sodium for the treatment of acute asthma attacks has not been established. Therefore, APO-MONTELUKAST should not be used to treat acute asthma attacks. Patients should be advised to have appropriate rescue medication available.

While the dose of concomitant inhaled corticosteroid may be reduced gradually under medical supervision, APO-MONTELUKAST should not be abruptly substituted for inhaled or oral corticosteroids.

When APO-MONTELUKAST is prescribed for the prevention of exercise-induced bronchoconstriction, patients should be advised to always have readily available appropriate rescue medication.

Patients with known acetylsalicylic acid (ASA) sensitivity should continue avoidance of ASA or non-steroidal anti-inflammatory agents while taking APO-MONTELUKAST. Although APO-MONTELUKAST is effective in improving airway function in asthmatic patients with documented ASA sensitivity, it has not been shown to truncate

bronchoconstrictor response to ASA and other non-steroidal anti-inflammatory drugs in ASA-sensitive asthmatic patients.

Neuropsychiatric post-marketing events

Neuropsychiatric events have been reported in adult, adolescent, and paediatric patients taking montelukast sodium. Post-market reports with montelukast sodium use include agitation, aggressive behaviour or hostility, anxiousness, depression, disorientation, disturbance in attention, dream abnormalities, hallucinations, insomnia, irritability, memory impairment, obsessive-compulsive symptoms, restlessness, somnambulism, suicidal thinking and behaviour (including suicide), tic and tremor. The clinical details of some post-marketing reports involving montelukast sodium appear consistent with a drug-induced effect.

Physicians should discuss these adverse experiences with their patients and /or caregivers. Patients and/or caregivers should be instructed to notify their physician if these changes occur. Physicians should carefully evaluate the risks and benefits of continuing treatment with montelukast sodium if such events occur.

Eosinophilic Conditions

In rare cases, patients with asthma on therapy with montelukast sodium 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 events have been reported as occurring both with and without steroid withdrawal or reduction. Physicians should be alert to eosinophilia, vasculitic rash, arthralgia, worsening pulmonary symptoms, cardiac complications, and/or neuropathy presenting in their patients (see ADVERSE REACTIONS). A causal association between montelukast sodium and these underlying conditions has not been established.

Hepatic/Biliary

Hepatic Insufficiency: 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).

Post-Marketing Surveillance: In post-marketing surveillance, elevations in serum transaminases have been reported in patients who were treated with montelukast sodium. These events were usually asymptomatic and transient. Serious hepatic adverse events such as jaundice have been reported although no deaths or liver transplantations have been attributed to the use of montelukast sodium (see ADVERSE REACTIONS).

Special Populations

Pregnant Women: Montelukast sodium has not been studied in pregnant women. APO-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 sodium during pregnancy. Most of these women were also taking other asthma medications during their pregnancy. A causal relationship between these events and montelukast sodium has not been established.

Nursing Women: It is not known if montelukast sodium is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when APO-MONTELUKAST is given to a nursing mother.

Geriatrics (>65 years of age): In clinical studies, there were no age-related differences in the efficacy or safety profiles of montelukast sodium.

Effects on Ability to Drive and Use Machines

There is no evidence that montelukast sodium affects the ability to drive and use machines.

ADVERSE REACTIONS

Adverse Drug Reaction Overview

Montelukast sodium 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 sodium was comparable to placebo.

Clinical Trial Adverse Drug Reactions

Adults 15 Years of Age and Older with Asthma

Montelukast sodium 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 drug-related in $\geq 1\%$ of patients treated with montelukast sodium 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 trials, the following adverse experiences reported with montelukast sodium occurred in $\geq 1\%$ of patients and at an incidence greater than or equal to that in patients treated with placebo, regardless of drug relationship:

Adverse Experiences Occurring in $\geq 1\%$ of Patients with an Incidence \geq to that in Patients Treated with Placebo, Regardless of Drug Relationship

	Montelukast sodium 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		
Diarrhea	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 sodium and placebo, respectively):
ALT and AST, 1935, 1170; pyuria, 1924, 1159.

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

Adults 15 Years of Age and Older with Seasonal Allergic Rhinitis

Montelukast sodium has been evaluated in 1751 adult patients 15 years of age and older for the treatment of seasonal allergic rhinitis in clinical studies. Montelukast sodium administered once daily at bedtime was generally well tolerated with a safety profile similar to that of placebo. In similar designed, 2-week, placebo-controlled, clinical studies, no adverse experience reported as drug related in $\geq 1\%$ of patients treated with montelukast sodium and at a greater incidence than in patients treated with placebo were observed. The incidence of somnolence was similar to that of placebo.

Post-Market Adverse Drug Reactions

The following adverse drug reactions have been reported very rarely (<1/10,000) in post marketing use of montelukast sodium. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

Infections and Infestations: upper respiratory infection

Blood and lymphatic system disorders: increased bleeding tendency, thrombocytopenia.

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

Psychiatric disorders: agitation including aggressive behavior or hostility (including temper tantrums in pediatric patients), very rarely reported as serious; anxiousness, depression, disorientation, disturbance in attention, irritability, memory impairment, obsessive-compulsive symptoms, restlessness, somnambulism, sleep disorders including dream abnormalities and insomnia, suicidal thinking and behavior (suicidality), tic, tremor, and visual hallucinations.

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

Cardiac disorders: palpitations

Respiratory, thoracic and mediastinal disorders: epistaxis, pulmonary eosinophilia

Gastrointestinal disorders: diarrhea, dyspepsia, nausea, vomiting

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

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

Hepato-biliary disorders: increased ALT, AST, and isolated cases of hepatitis, (including cholestatic, hepatocellular, and mixed-pattern liver injury). In post-marketing surveillance, elevations in serum transaminases have been reported in patients who were treated with montelukast sodium. These events were usually asymptomatic and transient. Serious hepatic adverse events such as jaundice have been reported although no deaths or liver transplantations have been attributed to the use of montelukast sodium (see WARNINGS AND PRECAUTIONS).

Renal and urinary disorders: enuresis in children

General disorders: asthenia/fatigue, edema, pyrexia

Eosinophilic Conditions

In rare cases, patients with asthma on therapy with montelukast sodium 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 events have been reported as occurring both with and without steroid withdrawal or reduction. Physicians should be alert to eosinophilia, vasculitic rash, arthralgia, worsening pulmonary symptoms, cardiac complications, and/or neuropathy presenting in their patients. A causal association between montelukast sodium and these underlying conditions has not been established (see WARNINGS AND PRECAUTIONS, Eosinophilic Conditions).

DRUG INTERACTIONS

Overview

APO-MONTELUKAST may be administered with other therapies routinely used in the prophylaxis and chronic treatment of asthma, and in the treatment of allergic rhinitis (see Drug-Drug Interactions).

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

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 drugs primarily metabolized by CYP 2C8) in 12 healthy individuals demonstrated that the pharmacokinetics of rosiglitazone are not altered when the drugs are coadministered, indicating that montelukast does not inhibit CYP 2C8 *in vivo*. Therefore, montelukast is not anticipated to alter the metabolism of drugs metabolized by this enzyme (e.g., paclitaxel, rosiglitazone, repaglinide). Based on further *in vitro* results in human liver microsomes, therapeutic plasma concentrations of montelukast do not inhibit CYP 3A4, 2C9, 1A2, 2A6, 2C19, or 2D6.

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. Based on clinical experience, no dosage adjustment of montelukast is required upon co-administration with gemfibrozil (see OVERDOSAGE). Based on *in vitro* data, clinically important drug interactions with other known inhibitors of CYP 2C8 (e.g., trimethoprim) are not anticipated. Co-administration of montelukast with itraconazole, a strong CYP 3A4 inhibitor, resulted in no significant increase in the systemic exposure of montelukast. In addition, co-

administration of itraconazole, gemfibrozil and montelukast did not further increase the systematic exposure of montelukast.

Drug-Drug Interactions

Montelukast 10 mg once daily to pharmacokinetic steady state:

- did not cause clinically significant changes in the kinetics of an intravenous dose of theophylline.
- did not change the pharmacokinetic profile of warfarin or influence the effect of a single 30 mg oral dose of warfarin on prothrombin time or INR (International Normalized Ratio).
- did not change the pharmacokinetic profile or urinary excretion of immunoreactive digoxin.
- did not change the plasma concentration profile of terfenadine or its carboxylated metabolite and does not prolong the QTc interval following co-administration with terfenadine 60 mg twice daily.

Montelukast at doses of ≥ 100 mg daily to pharmacokinetic steady state:

- did not significantly alter the plasma concentrations of either component of an oral contraceptive containing norethindrone 1 mg /ethinyl estradiol 35 mcg.
- did not cause any clinically significant change in plasma profiles of either prednisone and prednisolone following administration of either oral prednisone or IV prednisolone.

Phenobarbital, which induces hepatic metabolism, decreased the AUC of montelukast approximately 40% following a single 10 mg dose of montelukast; no dosage adjustment for APO-MONTELUKAST is recommended.

DOSAGE AND ADMINISTRATION

Dosing Considerations

The safety and efficacy of montelukast sodium was demonstrated in clinical trials where it was administered in the evening without regard to the time of food ingestion. There have been no clinical trials evaluating the relative efficacy of morning versus evening dosing. However, no difference in pharmacokinetics was noted between morning and evening dosing.

General Recommendations

The therapeutic effect of APO-MONTELUKAST on parameters of asthma occurs within one day. APO-MONTELUKAST tablets can be taken with or without food. Patients should be advised to continue taking APO-MONTELUKAST while their asthma is controlled, as well as during periods of worsening asthma.

Therapy with APO-MONTELUKAST in Relation to Other Treatments for Asthma

APO-MONTELUKAST can also be added to a patient's existing treatment regimen.

Bronchodilator Treatments: APO-MONTELUKAST 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 APO-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. It remains to be determined whether the withdrawal from inhaled corticosteroids can be maintained for extended periods, or possibly indefinitely. APO-MONTELUKAST should not be abruptly substituted for inhaled corticosteroids.

Oral Corticosteroids: Limited data suggest that montelukast sodium may provide additional clinical benefit in patients currently treated with oral corticosteroids.

Recommended Dose and Dosage Adjustment

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

The dosage for adults 15 years of age and older is one 10 mg tablet daily to be taken in the evening.

Special Population

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.

Missed Dose

APO-MONTELUKAST should be taken as prescribed. However, if a dose is missed, the usual schedule should be resumed as prescribed.

OVERDOSAGE

For management of a suspected drug overdose, contact your regional Poison Control Centre .

No specific information is available on the treatment of overdose with montelukast sodium. In chronic asthma studies, montelukast sodium 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 sodium. These include reports in adults and children with a dose as high as 1000 mg. The clinical and laboratory findings observed were consistent with the safety profile in adults and pediatric patients. There were no adverse experiences in the majority of overdose reports.

The adverse experiences were consistent with the safety profile of montelukast sodium and most frequently included abdominal pain, somnolence, thirst, headache, vomiting, psychomotor hyperactivity, and less frequently convulsion.

It is not known whether montelukast is dialyzable by peritoneal dialysis or hemodialysis.

ACTION AND CLINICAL PHARMACOLOGY

Mechanism of Action

The cysteinyl leukotrienes (LTC₄, LTD₄, LTE₄), are potent inflammatory eicosanoids released from various cells including mast cells and eosinophils. These important pro-asthmatic mediators bind to cysteinyl leukotriene (CysLT) receptors. The CysLT type-1 (CysLT₁) receptor is found in the human airway (including airway smooth muscle cells and airway macrophages) and on other pro-inflammatory cells (including eosinophils and certain myeloid stem cells). CysLTs have been correlated with the pathophysiology of asthma and allergic rhinitis. In asthma, leukotriene-mediated effects include 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.

Montelukast sodium has not been assessed in intranasal challenge studies. The clinical relevance of intranasal challenge studies is unknown.

Montelukast is an orally active compound that improves parameters of asthmatic inflammation. Based on biochemical and pharmacological bioassays, it binds with high affinity and selectivity to the CysLT₁ receptor (in preference to other pharmacologically important airway receptors such as the prostanoid, cholinergic, or β -adrenergic receptor). Montelukast potentially inhibits physiologic actions of LTC₄, LTD₄, and LTE₄ at the CysLT₁ receptor without any agonist activity.

Pharmacodynamics

Montelukast causes inhibition of airway cysteinyl leukotriene receptors as demonstrated by the ability to inhibit bronchoconstriction due to inhaled LTD₄ in asthmatic patients. Doses as low as 5 mg cause substantial blockage of LTD₄-induced bronchoconstriction. In a placebo-controlled, crossover study (n = 12), montelukast sodium inhibited early- and late-phase bronchoconstriction due to antigen challenge by 75% and 57% respectively.

Montelukast causes bronchodilation within 2 hours of oral administration; these effects were additive to the bronchodilation caused by a β -agonist.

Clinical studies in adults 15 years of age and older demonstrated there is no additional clinical benefit to montelukast doses above 10 mg once daily. This was shown in two

chronic asthma studies using doses up to 200 mg once daily and in one exercise challenge study using doses up to 50 mg, evaluated at the end of the once daily dosing interval.

The effect of montelukast sodium on eosinophils in the peripheral blood was examined in clinical trials in adults and pediatric (6 to 14 years of age) asthmatic patients. Montelukast sodium decreased mean peripheral blood eosinophils approximately 13% to 15% from baseline compared with placebo over the double-blind treatment periods. In patients with seasonal allergic rhinitis aged 15 years and older who received montelukast sodium, a median decrease of 13% in peripheral blood eosinophil counts was noted, compared with placebo, over the double-blind treatment periods.

There have been no clinical trials evaluating the relative efficacy of morning versus evening dosing. Although the pharmacokinetics of montelukast are similar whether dosed in the morning or the evening, efficacy was demonstrated in clinical trials in adults and pediatric patients in which montelukast was administered in the evening without regard to the time of food ingestion.

Pharmacokinetics

Absorption: Montelukast is rapidly absorbed following oral administration. For the 10 mg film-coated tablet, the mean peak plasma concentration (C_{max}) is achieved in 3 to 4 hours (T_{max}) after administration in adults in the fasted state. The mean oral bioavailability is 64%. The oral bioavailability and C_{max} are neither influenced by a standard meal in the morning nor by a high fat snack in the evening. Safety and efficacy were demonstrated in clinical trials where the 10 mg film-coated tablet were administered in the evening 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 liters. Studies in rats with radiolabeled montelukast indicate minimal distribution across the blood-brain barrier. In addition, concentrations of radiolabeled material at 24 hours postdose were minimal in all other tissues.

Metabolism: Montelukast is extensively metabolized. In studies with therapeutic doses, plasma concentrations of metabolites of montelukast are undetectable at steady state in adults and pediatric patients.

In vitro studies using human liver microsomes indicate that cytochrome P450 3A4, 2C8 and 2C9 are involved in the metabolism of montelukast. CYP 2C8 appears to play a major role in the metabolism of montelukast at clinically relevant concentrations.

Excretion: The plasma clearance of montelukast averages 45 mL/min in healthy adults. Following an oral dose of radiolabeled montelukast, 86% of the radioactivity was recovered in 5-day fecal collections and <0.2% was recovered in urine. Coupled with estimates of montelukast oral bioavailability, this indicates 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 drug in plasma (~14%).

Special Populations and Conditions

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

Geriatrics: 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.

Gender: The pharmacokinetics of montelukast are similar in males and females.

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.

Hepatic Insufficiency: 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 hepatitis or severe hepatic insufficiency (Child-Pugh score >9).

Renal Insufficiency: 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.

STORAGE AND STABILITY

Store at room temperature (15°C to 30°C).

DOSAGE FORMS, COMPOSITION AND PACKAGING

Dosage Forms	Tablets
Strength	10 mg
Description	Beige coloured, rounded square shaped, film-coated tablets debossed with 'X' on one side and '54' on other side.
Composition	Non-medicinal ingredients Lactose Monohydrate (Pharmatose 200 M), Cellulose, Microcrystalline (Avicel PH 101), Croscarmellose Sodium (AC-Di-Sol [®] -Type SD-711), Hydroxy Propyl Cellulose (Klucel- LF), Magnesium Stearate (Ligamed MF-2-V), Hydroxy Propyl Cellulose, HPMC 2910/ Hypromellose 6cP, Titanium Dioxide, Iron Oxide Yellow, Carnauba Wax & Iron Oxide Red (NF).
Packing	Blister Pack: 3 x 10's HDPE container: 90's count

PART II: SCIENTIFIC INFORMATION

PHARMACEUTICAL INFORMATION

Drug Substance

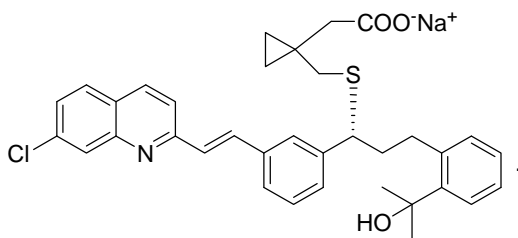
Proper name: montelukast sodium

Chemical name: 2-[1-[1(R)-[3-[2(E)-(7-Chloroquinolin-2-yl) vinyl] phenyl]-3-[2-hydroxy-1-methylethyl)phenyl]propylsulfanylmethyl] cyclopropyl] acetic acid sodium salt

Molecular formula: $C_{35}H_{35}ClNaO_3S$

Molecular mass: 608.17 g/mol

Structural formula:



Physicochemical properties:

Montelukast sodium is White or almost white, hygroscopic powder. Montelukast sodium is freely soluble in water and methylene chloride and freely soluble to very soluble in ethanol (96%).

CLINICAL TRIALS

Comparative Bio-availability data for Montelukast Tablets 10 mg

A double blind, randomized, two treatment, two sequence, two period, cross-over, single-dose, comparative oral bioavailability study of APO-MONTELUKAST (montelukast sodium) tablets 10 mg (Test) Apotex Inc. and Singulair® (montelukast sodium) tablets 10 mg (Reference) of Merck Frosst Canada Ltd., Canada was conducted in 27 healthy, adult, male subjects under fasting conditions.

Summary Table of the Comparative Bio-availability Data

Montelukast (1 x 10 mg) From measured data Geometric Mean Arithmetic Mean (CV %)				
Parameter	Test*	Reference†	% Ratio of Geometric Means	90% Confidence Interval
AUC _{0→t} (hr.ng/mL)	2731.53 2833.71 (28.5)	2622.45 2720.61 (26.7)	104.16	98.51-110.14
AUC _{0→∞} (hr. ng/mL)	2786.83 2892.57 (28.6)	2675.24 2778.06 (27.0)	104.17	98.46-110.21
C _{max} (ng/mL)	419.14 433.96 (28.3)	392.21 406.34 (27.4)	106.87	99.14-115.20
T _{max} § (h)	3.00 (1.50-5.00)	3.50 (1.50-5.00)		
T _½ § (h)	5.53 (22.0)	5.58 (15.0)		

*APO-MONTELUKAST (Montelukast sodium) Tablets 10 mg, Apotex Inc.

† SINGULAIR® (Montelukast sodium) Tablets 10 mg, Merck Frosst Canada Ltd., Canada were purchased from Canada.

§ Expressed as the Median (Range) only.

§ Expressed as arithmetic mean (%CV) only.

Study Results – Asthma

Adults 15 Years of Age and Older

The efficacy of montelukast sodium for the chronic treatment of asthma in adults 15 years of age and older was demonstrated in two (US and Multinational) similarly-designed 12-week, double-blind, placebo-controlled studies in 1325 patients (795 treated with montelukast sodium and 530 treated with placebo). Patients were symptomatic and using approximately 5 puffs of β -agonist per day on an “as-needed” basis. The mean baseline percent of predicted forced expiratory volume in 1 second (FEV₁) was 66% (approximate range, 40 to 90%). In these studies, asthma symptoms, asthma-related outcomes, respiratory function, and as-needed β -agonist use were measured. Endpoints were analyzed in each study and in a combined analysis according to a prespecified data analysis plan. The following clinical results were observed:

Asthma Symptoms and Asthma-related Outcomes

Montelukast sodium, 10 mg once daily at bedtime, significantly improved measurements of patient-reported daytime symptoms and nighttime awakenings in each study and in the combined analysis, compared with placebo. In patients with nocturnal awakenings of at least 2 nights per week, montelukast sodium reduced the nocturnal awakenings by 34% from baseline, significantly better than the reduction of 14% for the placebo group (combined analysis).

Montelukast sodium, compared with placebo, significantly improved asthma-related outcome measurements. In the combined analysis, montelukast sodium, compared with placebo, decreased asthma attacks by 37%, corticosteroids rescue by 39%, discontinuations due to worsening asthma by 65%, asthma exacerbations by 38% and increased asthma-free days by 42%.

Physicians' and patients' global asthma evaluations and asthma-specific quality-of-life evaluations (in all domains, including normal daily activity and asthma symptoms) were significantly better with montelukast sodium in each study and in the combined analysis compared with placebo.

Respiratory Function

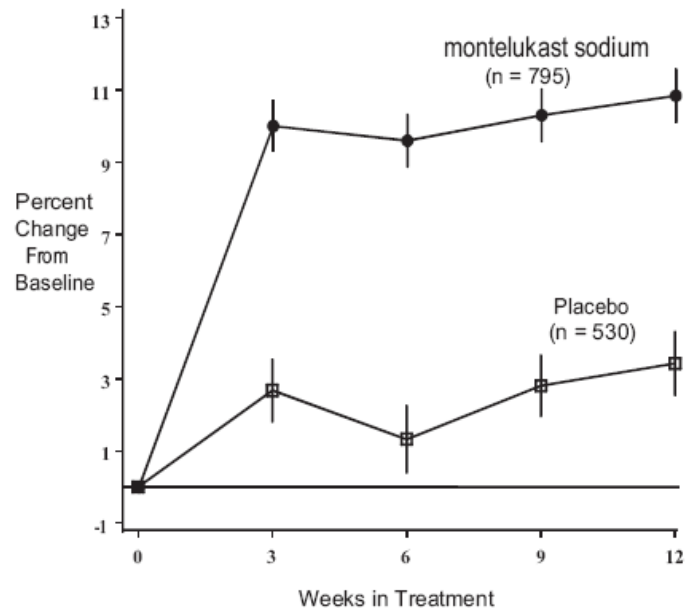
Compared with placebo, montelukast sodium caused significant improvements in parameters of respiratory function (FEV₁, and peak expiratory flow rate, PEFr) in each study and in the combined analysis:

Effect of Montelukast Sodium, 10 mg Daily, on Parameters of Respiratory Function in Adults 15 Years and Older (Combined Analysis)

	Montelukast Sodium (n=795)	Placebo (n=530)
Morning FEV1 (% change from baseline)	10.4*	2.7
AM PEFr (L/min change from baseline)	24.5*	3.3
PM PEFr (L/min change from baseline)	17.9*	2.0

* Significantly better than placebo (p≤0.001)

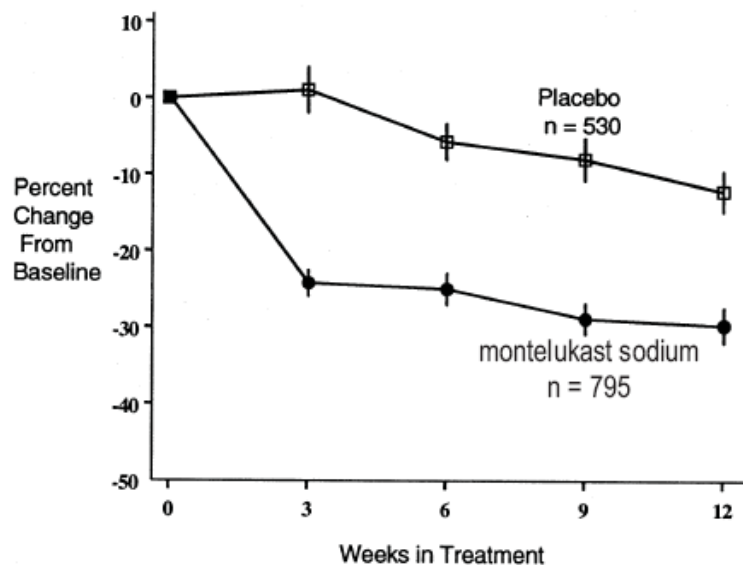
Figure 1
Morning FEV₁ (Percent Change from Baseline)



β-agonist Use

Compared with placebo, montelukast sodium significantly decreased the use of “as-needed” β-agonist by 26.1% from baseline compared with 4.6% in the placebo group in the combined analysis. The decreases were also significant in each of the studies ($p \leq 0.001$).

Figure 2
“As-Needed” β-agonist Use (Percent Change from Baseline)



Onset of Action and Maintenance of Benefits

In each study and in the combined analysis the treatment effect of montelukast sodium, measured by daily diary card parameters, including symptom scores, “as-needed” β -agonist use and PEF measurements, was achieved after the first dose and was maintained throughout the dosing interval (24 hours). Treatment effect also remained constant during continuous once-daily administration in extension trials for up to one year. Withdrawal of montelukast sodium in asthmatic patients after 12 weeks of continuous use, as with all asthma therapies, resulted in a gradual decline toward baseline. Additionally, withdrawal of montelukast sodium did not cause rebound worsening of asthma (see also Effects on Exercise-induced Bronchoconstriction).

Effects Relative to Inhaled Corticosteroids

In one of the two 12-week, double-blind studies in adults (Multinational), montelukast sodium was compared with inhaled beclomethasone (200 mcg twice daily with a spacer device). Montelukast sodium demonstrated a more rapid initial response although over the full duration of the study, beclomethasone provided a greater average treatment effect. However, a high percent of patients treated with montelukast sodium achieved similar clinical responses compared with inhaled beclomethasone (50% of patients on beclomethasone achieved an improvement in FEV₁ of approximately 11% or more over baseline while 42% of patients treated with montelukast sodium achieved the same response).

Effects in Patients on Concomitant Inhaled Corticosteroids

Separate studies in adults demonstrated the ability of montelukast sodium to add to the clinical effect of inhaled corticosteroids, and to allow steroid tapering when used concomitantly.

Three large studies demonstrated montelukast sodium has additional benefits in patients taking corticosteroids. In a randomized, placebo-controlled, parallel-group study (n=226), stable asthmatic patients on initial inhaled corticosteroid doses of approximately 1600 mcg per day reduced their steroid use by approximately 37% during a placebo run-in period. Montelukast sodium allowed a further 47% reduction in inhaled corticosteroid dose compared with 30% for placebo over the 12-week active treatment period ($p \leq 0.050$). Approximately 40 % of the montelukast-treated patients and 29% of the placebo-treated patients could be tapered off inhaled corticosteroids and remained off inhaled corticosteroids at the conclusion of the study ($p=NS$). It is not known whether the results of this study are generalizable to asthmatics who require higher doses of inhaled corticosteroids or systemic corticosteroids.

In another randomized, placebo-controlled, parallel-group trial (n=642) in a similar population of adult patients previously maintained, but not adequately controlled, on inhaled corticosteroids (beclomethasone 400 mcg/day), the addition of montelukast sodium to beclomethasone resulted in statistically significant improvements in FEV₁ compared with those patients who were continued on beclomethasone alone or those patients who were withdrawn from beclomethasone and treated with montelukast or placebo alone over the last 10 weeks of the 16-week, blinded treatment period. Patients

who were randomized to treatment arms containing beclomethasone had statistically significantly better asthma control than those patients randomized to montelukast sodium alone or placebo alone as indicated by FEV₁, daytime asthma symptoms, PEF, nocturnal awakenings due to asthma, and “as-needed” β -agonist requirements. While the dose of inhaled corticosteroid may be reduced gradually under medical supervision, montelukast sodium should not be abruptly substituted for inhaled or oral corticosteroids.

In adult asthmatic patients with documented ASA sensitivity, nearly all of whom were receiving concomitant inhaled and/or oral corticosteroids, a 4-week, randomized, parallel-group trial (n=80) demonstrated that montelukast sodium, compared with placebo, resulted in significant improvement in parameters of asthma control. The magnitude of effect of montelukast sodium in ASA-sensitive patients was similar to the effect observed in the general population of asthmatic patients studied. The effect of montelukast sodium on the bronchoconstrictor response to ASA or other non-steroidal anti-inflammatory drugs in ASA-sensitive asthmatic patients has not been evaluated (see WARNINGS AND PRECAUTIONS).

Effects on Exercise-induced Bronchoconstriction

In a 12-week, parallel group study of 110 adult patients 15 years of age and older, montelukast sodium, 10 mg, prevented exercise-induced bronchoconstriction (EIB) as demonstrated by significant inhibition of the following, compared with placebo:

- the extent and duration of fall in FEV₁ over 60 minutes after exercise (as measured by the area under the % fall in FEV₁ versus time curve after exercise, AUC);
- the maximal percent fall in FEV₁ after exercise;
- the time to recovery to within 5% of the pre-exercise FEV₁.

Protection was consistent throughout the 12-week treatment period, indicating that tolerance did not occur. In a separate crossover study, protection was observed after two once-daily doses.

Effects on Asthmatic Inflammation

Several studies have shown montelukast sodium inhibits parameters of asthmatic inflammation. In a placebo-controlled, crossover study (n=12), montelukast sodium inhibited early- and late-phase bronchoconstriction due to antigen challenge by 75% and 57%, respectively.

Because inflammatory cell (eosinophil) infiltration is an important feature of asthma, the effects of montelukast sodium on eosinophils in the peripheral blood and airway were examined. In Phase IIb/III clinical trials in adults, montelukast sodium significantly decreased peripheral blood eosinophils approximately 15% from baseline, compared with placebo.

In a 4-week, randomized, parallel group study (n=40) in adults, montelukast sodium significantly decreased airway eosinophils (as assessed in sputum) by 48% from baseline compared with an increase of 23% from baseline with placebo. In this study, peripheral

blood eosinophils significantly decreased, and clinical asthma endpoints improved with treatment with montelukast sodium.

Study Results – Seasonal Allergic Rhinitis

The efficacy of montelukast sodium for the treatment of seasonal allergic rhinitis was investigated in similarly designed randomized, 2-week, double-blind, placebo-controlled trials. Patients were 15 years of age and older with a history of seasonal allergic rhinitis, a positive skin test to at least one relevant seasonal allergen, and active symptoms of seasonal allergic rhinitis at study initiation.

In a combined analysis of three pivotal studies, montelukast sodium 10-mg tablets administered to 1189 patients once daily in the evening resulted in a statistically significant improvement in the primary endpoint, daytime nasal symptoms score, and its individual components (nasal congestion, rhinorrhea, nasal itching, and sneezing); nighttime symptoms score, and its individual components (nasal congestion upon awakening, difficulty going to sleep, and nighttime awakenings); daytime eye symptoms score, and its individual components (tearing, itchy, red, and puffy eyes); global evaluations of allergic rhinitis by patients and by physicians; and composite symptoms score (composed of the daytime nasal and nighttime symptoms scores), compared with placebo.

TOXICOLOGY

Animal Toxicology

No mortality occurred following a single oral administration of montelukast sodium at doses up to 5000 mg/kg, in mice and rats, (15,000 mg/m² and 29,500 mg/m² in mice and rats, respectively) the maximum dose tested (oral aLD₅₀ >5000 mg/kg). This dose is equivalent to 25,000 times the recommended daily adult human dose (determined using mg/kg/day values).*

Chronic Toxicity

The toxic potential of montelukast sodium was evaluated in a series of repeated dose toxicity studies of up to 53 weeks in monkeys and rats and up to 14 weeks in infant monkeys and in mice. Montelukast sodium was well tolerated at doses which provide a wide margin of safety based on total dose administered. The no effect level was evaluated to be 150 mg/kg/day in female monkeys, 300 mg/kg/day in male monkeys, 50 mg/kg/day in rats, >150 mg/kg/day in infant monkeys and 50 mg/kg/day in mice. For all toxicological parameters, the no effect level was at least 125 times the recommended human dose (determined using mg/kg/day values).* There were no findings that would preclude administration at the therapeutic dosage level for both adults and pediatric patients.

* Based on an adult patient weight of 50 kg.

Carcinogenicity

No evidence of tumorigenicity was seen in a 2-year carcinogenicity study in Sprague-Dawley rats, at oral (gavage) doses up to 200 mg/kg/day (approximately 160 times the maximum recommended daily oral doses in adults and 190 times the maximum recommended daily oral dose in children, on a mg/m² basis) or in a 92-week carcinogenicity study in mice at oral doses up to 100 mg/kg/day (approximately 40 times the maximum recommended daily oral dose in adults and 50 times the maximum recommended daily oral dose in children, on a mg/m² basis).

Mutagenesis

Montelukast demonstrated no evidence of mutagenic or clastogenic activity in the following assays: the microbial mutagenesis assay, the V-79 mammalian cell mutagenesis assay, the alkaline elution assay in rat hepatocytes, the chromosomal aberration assay in Chinese hamster ovary cells, and in the *in vitro* mouse bone marrow chromosomal aberration assay.

Reproduction and Teratology

In fertility studies in female rats, montelukast produced reductions in fertility and fecundity indices at an oral dose of 200 mg/kg (approximately 160 times the maximum recommended daily oral dose in adults on a mg/m² basis). No effects on female fertility or fecundity were observed at an oral dose of 100 mg/kg (approximately 80 times the maximum recommended daily oral dose in adults, on a mg/m² basis). Montelukast had no effects on fertility in male rats at oral doses up to 800 mg/kg (approximately 650 times the maximum recommended daily oral dose in adults, on a mg/m² basis).

No teratogenicity was observed in rats at oral doses up to 400 mg/kg/day (approximately 320 times the maximum recommended daily oral dose in adults, on a mg/m² basis) and in rabbits at oral doses up to 300 mg/kg/day (approximately 490 times the maximum recommended daily oral doses in adults, on a mg/m² basis).

Montelukast crosses the placenta following oral dosing in rats and rabbits. There are, however, no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, montelukast sodium should be used during pregnancy only if clearly needed.