

PRODUCT NAME	Montelukast Sodium Tablets and Montelukast Sodium Chewable Tablets USP Montelukast Sodium Oral Granules	COUNTRY : US	LOCATION : Indrad/Dahej	Supersedes A/W No.:	
ITEM / PACK	Outset	NO. OF COLORS: 1	SUBSTRATE : 40 g/m ² Bible Paper		V. No.: 01
DESIGN STYLE	Front Side	PANTONE SHADE NOS.:			
CODE	8097170	Activities	Department	Name	Signature
DIMENSIONS (MM)	525 x 370	Prepared By	Pkg.Dev	Reviewed By	Pkg.Dev
ART WORK SIZE	S/S	DATE	22-10-2024	Approved By	Quality
		Font Size 6 pt_Med. 10 pt			



Note: Pharma code/ Bar code and adjacent text must be visible on folded leaflet.
These details can be moved by printed to arrange pharma code/ Bar code and adjacent text visible on folded leaflet.

HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use MONTELUKAST SODIUM safely and effectively. See full prescribing information for MONTELUKAST SODIUM.

MONTELUKAST SODIUM tablets, for oral use
MONTELUKAST SODIUM chewable tablets, for oral use
MONTELUKAST SODIUM oral granules
Initial U.S. Approval: 1998

WARNING: SERIOUS NEUROPSYCHIATRIC EVENTS
See full prescribing information for complete boxed warning.

• **Serious neuropsychiatric events have been reported in patients taking montelukast sodium (5.1).**

• **Discuss benefits and risks of montelukast sodium with patients and caregivers (5.1).**

• **Monitor for neuropsychiatric symptoms in patients taking montelukast sodium (5.1).**

• **Discontinue montelukast sodium immediately if neuropsychiatric symptoms occur (5.1).**

Because the benefits of montelukast sodium may not outweigh the potential risk of neuropsychiatric symptoms in patients with allergic rhinitis, reserve use for patients who have an inadequate response or intolerance to alternative therapies (2, 3, 5.1).

RECENT MAJOR CHANGES

Boxed Warnings and Usage (1.3, 1.4) 04/2020
Warnings and Precautions (2.1, 2.2, 2.3, 2.4) 02/2021
Warnings and Precautions (2.1, 2.2, 2.3, 2.4) 02/2021

INDICATIONS AND USAGE

Montelukast sodium is a leukotriene receptor antagonist indicated for:

- Prophylaxis and chronic treatment of asthma in patients 12 months of age and older (1.1).
- Acute prevention of exercise-induced bronchoconstriction (EIB) in patients 6 years of age and older (1.2).
- Relief of symptoms of allergic rhinitis (AR); seasonal allergic rhinitis (SAR) in patients 2 years of age and older; and perennial allergic rhinitis (PAR) in patients 6 months of age and older. Reserve use for patients who have an inadequate response or intolerance to alternative therapies (1.3).

Limitations of Use

- Not indicated to treat an acute asthma attack (5.2).

DOSE AND ADMINISTRATION

Administration (by indications):

- Asthma: Once daily in the evening for patients 12 months of age and older (2.1).
- Acute prevention of EIB: One tablet at least 2 hours before exercise for patients 6 years of age and older (2.2).

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FULL PRESCRIBING INFORMATION

WARNING: SERIOUS NEUROPSYCHIATRIC EVENTS

Serious neuropsychiatric (NP) events have been reported with the use of montelukast sodium. The types of events reported were highly variable, and included, but were not limited to, agitation, aggression, depression, sleep disturbances, suicidal thoughts and behavior (including suicide). The mechanisms underlying NP events associated with montelukast sodium use are currently not well understood (see *Warnings and Precautions (5.1)*).

Because of the risk of NP events, the benefits of montelukast sodium may not outweigh the risks in some patients, particularly when the symptoms of disease may be mild and adequately treated with alternative therapies. Reserve use of montelukast sodium for patients with allergic rhinitis who have an inadequate response or intolerance to alternative therapies (see *Indications and Usage (1.3)*). In patients with asthma or exercise-induced bronchoconstriction, consider the benefits and risks before prescribing montelukast sodium.

Discuss the benefits and risks of montelukast sodium with patients and caregivers when prescribing montelukast sodium. Advise patients and/or caregivers to be alert for changes in behavior or new NP symptoms when taking montelukast sodium. If changes in behavior are observed, or if new NP symptoms or suicidal thoughts and/or behavior occur, advise patients to discontinue montelukast sodium and contact a healthcare provider immediately (see *Warnings and Precautions (5.1)*).

INDICATIONS AND USAGE

1.1 Asthma
Montelukast sodium is indicated for the prophylaxis and chronic treatment of asthma in adults and pediatric patients 12 months of age and older.

1.2 Exercise-Induced Bronchoconstriction (EIB)
Montelukast sodium is indicated for prevention of exercise-induced bronchoconstriction (EIB) in patients 6 years of age and older.

1.3 Allergic Rhinitis
Montelukast sodium is indicated for the relief of symptoms of seasonal allergic rhinitis in patients 2 years of age and older and perennial allergic rhinitis in patients 6 months of age and older. Because the benefits of montelukast sodium may not outweigh the risk of neuropsychiatric symptoms in patients with allergic rhinitis (see *Warnings and Precautions (5.1)*), reserve use for patients who have an inadequate response or intolerance to alternative therapies.

1.4 Limitations of Use
Montelukast sodium is not indicated for the treatment of an acute asthma attack.

2 DOSE AND ADMINISTRATION

2.1 Asthma
For asthma, administer montelukast sodium orally once daily in the evening, with or without food. There have been no clinical trials in patients with asthma to evaluate the relative efficacy of morning versus evening dosing. The following doses are recommended:

Table 1: Recommended Dosage in Asthma	
Age	Dose
Adult and adolescent patients 15 years of age and older	one 10 mg tablet
Pediatric patients 6 to 14 years of age	one 5 mg chewable tablet
Pediatric patients 2 to 5 years of age*	one 4 mg chewable tablet or one packet of 4 mg oral granules
Pediatric patients 12 to 23 months of age*	one packet of 4 mg oral granules

*Safety and effectiveness in pediatric patients less than 12 months of age with asthma have not been established.

Patients who miss a dose should take the next dose at their regular time and should not take 2 doses at the same time.

2.2 Exercise-Induced Bronchoconstriction (EIB)
For prevention of EIB, administer a single dose of montelukast sodium orally at least 2 hours, before exercise. The following doses are recommended:

Table 2: Recommended Dosage in Exercise-Induced Bronchoconstriction (EIB)	
Age	Dose
Adult and adolescent patients 15 years of age and older	one 10 mg tablet
Pediatric patients 6 to 14 years of age*	one 5 mg chewable tablet

*Safety and effectiveness in patients younger than 6 years of age have not been established.

An additional dose of montelukast sodium should not be taken within 24 hours of a previous dose. Patients already taking montelukast sodium daily for another indication (including chronic asthma) should not take an additional dose to prevent EIB. All patients should have available for rescue a short-acting β₂-agonist.

Daily administration of montelukast sodium for the chronic treatment of asthma has not been established to prevent acute episodes of EIB.

2.3 Allergic Rhinitis
For allergic rhinitis, administer montelukast sodium orally once daily without regard to time of food ingestion. Time of administration in patients with allergic rhinitis can be individualized to suit patient needs. The following doses for the treatment of symptoms of seasonal allergic rhinitis are recommended:

Table 3: Recommended Dosage in Seasonal Allergic Rhinitis	
Age	Dose
Adult and adolescent patients 15 years of age and older	one 10 mg tablet
Pediatric patients 6 to 14 years of age	one 5 mg chewable tablet
Pediatric patients 2 to 5 years of age*	one 4 mg chewable tablet or one packet of 4 mg oral granules

*Safety and effectiveness in pediatric patients younger than 2 years of age with seasonal allergic rhinitis have not been established.

The following doses for the treatment of symptoms of perennial allergic rhinitis are recommended:

Table 4: Recommended Dosage in Perennial Allergic Rhinitis	
Age	Dose
Adult and adolescent patients 15 years of age and older	one 10 mg tablet
Pediatric patients 6 to 14 years of age	one 5 mg chewable tablet
Pediatric patients 2 to 5 years of age*	one 4 mg chewable tablet or one packet of 4 mg oral granules

*Safety and effectiveness in pediatric patients younger than 6 months of age with perennial allergic rhinitis have not been established.

Patients who miss a dose should take the next dose at their regular time and should not take 2 doses at the same time.

2.4 Asthma and Allergic Rhinitis
In patients with both asthma and allergic rhinitis, administer only one montelukast sodium dose orally once daily in the evening.

Patients who miss a dose should take the next dose at their regular time and should not take 2 doses at the same time.

2.5 Instructions for Administration of Oral Granules
Montelukast sodium 4-mg oral granules can be administered either directly in the mouth, dissolved in 1 teaspoonful (5 mL) of cold or room temperature baby formula or breast milk, or mixed with a spoonful of cold or room temperature soft foods; based on stability studies, only applesauce, carrots, rice, or ice cream should be used. The packet should not be opened until ready to use. After opening the packet, the full dose (with or without mixing with baby formula, breast milk, or food) must be administered within 15 minutes. If mixed with baby formula, breast milk, or food, montelukast sodium oral granules must not be stored for future use. Discard any unused portion of montelukast sodium oral granules as not intended to be dissolved in any liquid other than baby formula or breast milk for administration. However, liquids may be taken subsequent to administration. Montelukast sodium oral granules can be administered without regard to the time of meals.

3 DOSE FORMS AND STRENGTHS

- Montelukast sodium tablets USP, 10 mg are light brown colored, round, biconvex film coated tablets debossed with "1081" on one side and "10 MG" on other side.
- Montelukast sodium chewable tablets USP, 4mg are pink colored, oval biconvex shaped, uncoated tablets, debossed with "079" on one side and "4 MG" on other side.
- Montelukast sodium chewable tablets USP, 5mg are pink colored, round shaped, uncoated tablets, debossed with "1080" on one side and "5 MG" on other side.
- Montelukast sodium oral granules USP, 4 mg are white to off white granules with 500 mg net weight, packed in a child-resistant foil packet.

4 CONTRAINDICATIONS
Montelukast sodium is contraindicated in patients with hypersensitivity to any of its components.

5 WARNINGS AND PRECAUTIONS

5.1 Neuropsychiatric Events
Serious neuropsychiatric (NP) events have been reported with use of montelukast sodium. These postmarketing reports have been highly variable and included, but were not limited to, agitation, aggressive behavior or hostility, anxiety, depression, disorientation, disturbance in attention, dream abnormalities, dysphemia (stuttering), hallucinations, insomnia, irritability, memory impairment, obsessive-compulsive symptoms, restlessness, somnambulism, suicidal thoughts and behavior (including suicide), tic, and tremor. NP events have been reported in adult, adolescent, and pediatric patients with and without a previous history of psychiatric disorder. NP events have been reported mostly during montelukast sodium treatment, but some were reported after montelukast sodium discontinuation. Animal studies showed that montelukast distributes into the brain in rats (see *Clinical Pharmacology (12.3)*). To be alert for changes in behavior or for new NP symptoms when taking montelukast sodium. If changes in behavior are observed, or if new NP symptoms or suicidal thoughts and/or behavior occur, advise patients to discontinue montelukast sodium and contact a healthcare provider immediately. In many cases, symptoms resolved after stopping montelukast sodium therapy; however, in some cases symptoms persisted after discontinuation of montelukast sodium. Therefore, continue to monitor and provide supportive care until symptoms resolve. Re-evaluate the benefits and risks of restarting treatment with montelukast sodium if such events occur.

5.2 Acute Asthma
Montelukast sodium is not indicated for use in the reversal of bronchospasm in acute asthma attacks, including status asthmaticus. Patients should be advised to have appropriate rescue medication available. Therapy with montelukast sodium can be continued during acute exacerbations of asthma. Patients who have exacerbations of asthma should have available for rescue a short-acting inhaled β₂-agonist.

5.3 Concomitant Corticosteroid Use
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.

5.4 Aspirin Sensitivity
Patients with known aspirin sensitivity should continue avoidance of aspirin or non-steroidal anti-inflammatory drugs (NSAIDs) when taking montelukast sodium. Although aspirin sensitivity may be improved with increasing airway function in asthmatics with documented aspirin sensitivity, it has not been shown to truncate bronchoconstrictor response to aspirin and other non-steroidal anti-inflammatory drugs in aspirin-sensitive asthmatic patients (see *Clinical Studies (14.1)*).

5.5 Eosinophilic Conditions
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 sometimes associated with the non-steroidal anti-inflammatory drug therapy. Physicians should be alert for changes in behavior, 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 *Adverse Reactions (5.6)*).

5.6 Risk in Patients with Phenylephrine
Montelukast sodium contains aspartame, a source of phenylephrine. Phenylephrine can be harmful to patients with phenylephrine (PKU). Each 4 mg and 5 mg chewable tablet contains 0.674 mg and 0.842 mg of phenylephrine, respectively. Before prescribing montelukast sodium to a patient with PKU, consider the combined daily amount of phenylephrine from all sources, including montelukast sodium.

6 ADVERSE REACTIONS

The following clinically significant adverse reactions are described elsewhere in the labeling:

- Neuropsychiatric Events (see *Warnings and Precautions (5.1)*).

6.1 Clinical Trials Experience
Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in clinical practice. In the following description of clinical trials experience, adverse reactions are listed regardless of causality assessment.

The most common adverse reactions (incidence ≥5% and greater than placebo, listed in descending order of frequency) in controlled clinical trials were upper respiratory infection, fever, headache, pharyngitis, cough, abdominal pain, diarrhea, otitis media, influenza, rhinorrhea, sinusitis, otitis.

Adults and Adolescents 15 Years of Age and Older with Asthma
Montelukast sodium has been evaluated for safety in approximately 2,950 adult and adolescent patients 15 years of age and older in clinical trials. In placebo-controlled clinical trials, the following adverse reactions reported with montelukast sodium occurred in greater than or equal to 1% of patients and at an incidence greater than that in patients treated with placebo:

Table 5: Adverse Reactions Occurring in ≥1% of Patients with an Incidence Greater than that in Patients Treated with Placebo		
Montelukast Sodium (%) (n=1,955)	Placebo (%) (n=1,180)	
Body As A Whole		
Pain, abdominal	2.9	2.5
Fever	1.5	0.9
Trauma	1.0	0.8
Digestive System Disorders		
Dyspepsia	2.1	1.1
Gas	1.8	1.2
Gastroenteritis, infectious	1.5	0.5
Nervous System/Psychiatric		
Headache	18.4	18.1
Dizziness	1.9	1.4

Respiratory System Disorders

Influenza 4.2 3.9
Cough 2.7 2.4
Congestion, nasal 1.6 1.3

Skin/Skin Appendages Disorder

Rash 1.6 1.2

Laboratory Adverse Reactions*

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, 1,935, 1,170; pyuria, 1,824, 1,159.

The frequency of less common adverse reactions was comparable between montelukast sodium and placebo. The safety profile of montelukast sodium, when administered as a single dose for prevention of EIB in adult and adolescent patients 15 years of age and older, was consistent with the safety profile previously described for montelukast sodium.

Cumulatively, 569 patients were treated with montelukast sodium for at least 6 months, 480 for one year, and 49 for two years in clinical trials. With prolonged treatment, the adverse reaction profile did not significantly change.

Pediatric Patients 6 to 14 Years of Age with Asthma
Montelukast sodium has been evaluated for safety in 476 pediatric patients 6 to 14 years of age. Cumulatively, 289 pediatric patients were treated with montelukast sodium for at least 6 months, and 241 for one year or longer in clinical trials. The safety profile of montelukast sodium in the 6-week, double-blind, pediatric efficacy trial was generally similar to the adult safety profile. In pediatric patients 6 to 14 years of age receiving montelukast sodium, the following reactions occurred with a frequency ≥2% and more frequently than in patients receiving placebo: pharyngitis, influenza, fever, sinusitis, nausea, diarrhea, dyspepsia, otitis, viral infection, and taryngitis. The frequency of less common adverse reactions was comparable between montelukast sodium and placebo. With prolonged treatment, the adverse reaction profile did not significantly change.

The safety profile of montelukast sodium, when administered as a single dose for prevention of EIB in pediatric patients 6 years of age and older, was consistent with the safety profile previously described for montelukast sodium.

In studies evaluating growth rate, the safety profile in these pediatric patients was consistent with the safety profile previously described for montelukast sodium. In a 56-week, double-blind study evaluating growth rate in pediatric patients 6 to 9 years of age receiving montelukast sodium, the following reactions occurred with the use of montelukast sodium in this age group occurred with a frequency ≥2% and more frequently than in pediatric patients who received placebo: headache, rhinitis (infective), varicella, gastroenteritis, atopic dermatitis, acute bronchitis, tooth infection, sinus infection, and myopia.

Pediatric Patients 2 to 5 Years of Age with Asthma
Montelukast sodium has been evaluated for safety in 573 pediatric patients 2 to 5 years of age in single- and multiple-dose studies. Cumulatively, 426 pediatric patients 2 to 5 years of age were treated with montelukast sodium for at least 3 months, 230 for 6 months or longer, and 63 patients for one year or longer in clinical trials. In pediatric patients 2 to 5 years of age receiving montelukast sodium, the following reactions occurred with a frequency ≥2% and more frequently than in pediatric patients who received placebo: fever, cough, abdominal pain, diarrhea, headache, rhinorrhea, sinusitis, otitis, influenza, rash, ear pain, gastroenteritis, eczema, urticaria, varicella, pneumonia, dermatitis, and conjunctivitis.

Pediatric Patients 6 to 23 Months of Age with Asthma
Safety and effectiveness in pediatric patients younger than 12 months of age with asthma have not been established.

Montelukast sodium has been evaluated for safety in 175 pediatric patients 6 to 23 months of age. The safety profile of montelukast sodium in this age group was consistent with that observed in 2-week studies. The incidence of somnolence was similar to that of placebo in all studies.

Adults and Adolescents 15 Years of Age and Older with Seasonal Allergic Rhinitis
Montelukast sodium has been evaluated for safety in 2,199 adult and adolescent patients 15 years of age and older in clinical trials. Montelukast sodium administered once daily in the morning or in the evening had a safety profile similar to that of placebo. In a placebo-controlled clinical trials, the following reaction was reported with montelukast sodium with a frequency ≥1% and at an incidence greater than placebo: upper respiratory infection. 1.9% of patients receiving montelukast sodium vs. 1.5% of patients receiving placebo. In a 4-week, placebo-controlled clinical trial, 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.

Pediatric Patients 2 to 14 Years of Age with Seasonal Allergic Rhinitis
Montelukast sodium has been evaluated in 280 pediatric patients 2 to 14 years of age in a 2-week, multicenter, double-blind, placebo-controlled safety study. Montelukast sodium administered once daily in the evening had a safety profile similar to that of placebo. In this study, the following reactions occurred with a frequency ≥2% and at an incidence greater than placebo: headache, otitis media, pharyngitis, and upper respiratory infection.

Adults and Adolescents 15 Years of Age and Older with Perennial Allergic Rhinitis
Montelukast sodium has been evaluated for safety in 3,357 adult and adolescent patients 15 years of age and older with perennial allergic rhinitis of whom 1,632 received montelukast sodium in two, 6-week, clinical studies. Montelukast sodium administered once daily had a safety profile consistent with that observed in patients with seasonal allergic rhinitis and similar to that of placebo. In these two studies, the following reactions were reported with montelukast sodium with a frequency ≥1% and at an incidence greater than placebo: sinusitis, upper respiratory infection, sinus headache, cough, epistaxis, and increased ALT. The incidence of somnolence was similar to that of placebo in all studies.

Pediatric Patients 6 Months to 14 Years of Age with Perennial Allergic Rhinitis
The safety in patients 2 to 14 years of age with perennial allergic rhinitis is supported by the safety in patients 2 to 14 years of age with seasonal allergic rhinitis. The safety in patients 6 to 23 months of age is supported by data from pharmacokinetic and safety and efficacy studies in asthma in this pediatric population and from adult pharmacokinetic studies.

6.2 Postmarketing Experience
The following adverse reactions have been identified during post-approval 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.

Blood and Lymphatic system disorders
increased bleeding tendency, thrombocytopenia

Immune system disorders
hypersensitivity reactions including anaphylaxis, hepatic eosinophilic infiltration

Psychiatric disorders
including, but not limited to, agitation, aggressive behavior or hostility, anxiety, depression, disorientation, disturbance in attention, dream abnormalities, dysphemia (stuttering), hallucinations, insomnia, irritability, memory impairment, obsessive-compulsive symptoms, restlessness, somnambulism, suicidal thoughts and behavior (including suicide), tic, and tremor (see *Boxed Warning, Warnings and Precautions (5.1)*).

Nervous system disorders
drowsiness, paraesthesia/hypoesthesia, seizures

Cardiac disorders
palpitations

Respiratory, thoracic and mediastinal disorders
epistaxis, pulmonary eosinophilia

Gastrointestinal disorders
diarrhea, dyspepsia, nausea, pancreatitis, vomiting

Hepatoabular disorders
Cases of cholestatic hepatitis, hepatocellular liver injury, and mixed-pattern liver injury have been reported in patients treated with montelukast sodium. Most of these occurred in combination with other confounding factors, such as use of other medications, or when montelukast sodium was administered to patients who had underlying potential for liver disease such as alcohol use or other forms of hepatitis.

Skin and subcutaneous tissue disorders
angioedema, bruising, erythema multiforme, erythema nodosum, pruritus, Stevens-Johnson syndrome/toxic epidermal necrolysis, urticaria

Musculoskeletal and connective tissue disorders
arthralgia, myalgia including muscle cramps

Renal and urinary disorders
enuresis in children

General disorders and administration site conditions
edema

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 reactions have been sometimes associated with the reduction of oral corticosteroid therapy. Physicians should be alert for changes in behavior, worsening pulmonary symptoms, cardiac complications, and/or neuropathy presenting in their patients (see *Warnings and Precautions (5.5)*).

7 DRUG INTERACTIONS

No dose adjustment is needed when montelukast sodium is co-administered with theophylline, prednisone, prednisolone, oral contraceptives, levothyroxine, gentamicin, flucanazole, warfarin, fentanyl, tramadol, thyroid hormones, sedative hypnotics, non-steroidal anti-inflammatory agents, benzodiazepines, decongestants, and Cytochrome P450 (CYP) enzyme inducers (see *Clinical Pharmacology (12.3)*).

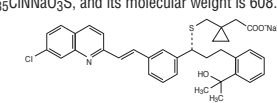
8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy
Risk Summary
Montelukast sodium was published prospective and retrospective cohort studies over decades with montelukast use in pregnant women have not established a drug-associated risk of major birth defects (see *Data*). In animal reproduction studies, no adverse developmental effects were observed with oral administration of montelukast to pregnant rats and rabbits during organogenesis at doses approximately 100 and 120 times, respectively, the maximum recommended human daily oral dose (MRHDOD) based on AUCs (see *Data*).

The estimated background risk of major birth defects and miscarriage for the indicated population is unknown. All pregnancies have a background risk of birth defect, loss, or other adverse outcomes. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2 to 4% and 15 to 20%, respectively.

8.2 Lactation
Montelukast sodium is described chemically as [R-(E)]-1-[1]-[3]-[12]-[7]-chloro-2-quinolinyl[thienyl]phenyl]-3-[2-(1-hydroxy-1-methyl[thienyl]propyl)thio]methyl cyclopropaneacetic acid.

The empirical formula is C₂₅H₂₆ClN₂O₂S₂ and its molecular weight is 608.18. The structural formula is:



Montelukast sodium is a hygroscopic, optically active, white to off-white powder. Montelukast sodium is freely soluble in ethanol, methanol, and water and practically insoluble in acetonitrile.

Each 10-mg film-coated montelukast sodium tablet USP contains 10.4 mg montelukast sodium, which is equivalent to 4 mg of montelukast, and the following inactive ingredients: croscarmellose sodium, ferric oxide red, ferric oxide yellow, hydroxypropyl cellulose, hypromellose, lactose monohydrate, magnesium stearate, microcrystalline cellulose, and titanium dioxide.

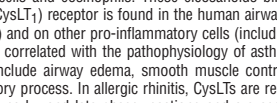
Each 4-mg and 5-mg chewable montelukast sodium tablet USP contains 4.2 and 5.2 mg montelukast sodium, respectively, which are equivalent to 4 and 5 mg of montelukast, respectively. Both chewable tablets contain the following inactive ingredients: aspartame, cellulose microcrystalline, cherry flavor, croscarmellose sodium, ferric oxide red, hypromellose, lactose monohydrate, magnesium stearate, microcrystalline cellulose, and titanium dioxide.

Each packet of montelukast sodium oral granules USP 4 mg contains 4.16 mg Montelukast sodium USP, which is equivalent to 4 mg of montelukast. The oral granule formulation contains the following inactive ingredients: mannitol, hydroxypropyl cellulose, tribasic sodium phosphate and magnesium stearate.

11 DESCRIPTION
Montelukast sodium, the active ingredient in montelukast sodium tablets USP and montelukast sodium oral granules USP, is a selective and orally active leukotriene receptor antagonist that inhibits the cysteinyl leukotriene CysLT₂ receptor.

Montelukast sodium is described chemically as [R-(E)]-1-[1]-[3]-[12]-[7]-chloro-2-quinolinyl[thienyl]phenyl]-3-[2-(1-hydroxy-1-methyl[thienyl]propyl)thio]methyl cyclopropaneacetic acid.

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Each 4-mg and 5-mg chewable montelukast sodium tablet USP contains 4.2 and 5.2 mg montelukast sodium, respectively, which are equivalent to 4 and 5 mg of montelukast, respectively. Both chewable tablets contain the following inactive ingredients: aspartame, cellulose microcrystalline, cherry flavor, croscarmellose sodium, ferric oxide red, hypromellose, lactose monohydrate, magnesium stearate, microcrystalline cellulose, and titanium dioxide.

Each packet of montelukast sodium oral granules USP 4 mg contains 4.16 mg Montelukast sodium USP, which is equivalent to 4 mg of montelukast. The oral granule formulation contains the following inactive ingredients: mannitol, hydroxypropyl cellulose, tribasic sodium phosphate and magnesium stearate.

Clinical Considerations

Disease-associated maternal and/or embryofetal risk
Poorly or moderately controlled asthma in pregnancy increases the maternal risk of perinatal adverse outcomes such as pre-eclampsia and infant prematurity, low birth weight, and small for gestational age. Data:

Human Data
Published data from prospective and retrospective cohort studies have not identified an association with montelukast sodium use during pregnancy and major birth defects. Available studies have methodologic limitations, including small sample size, in some cases retrospective data collection, and inconsistent comparator groups.

Animal Data
In embryo-fetal development studies, montelukast administered to pregnant rats and rabbits during organogenesis (gestation days 6 to 17 in rats and 6 to 18 in rabbits) did not cause any adverse developmental effects at maternal oral doses up to 400 and 300 mg/kg/day in rats and rabbits, respectively (approximately 100 and 110 times the AUC in humans at the MRHDOD, respectively).

6.2 Lactation
Risk Summary
A published clinical lactation study reports the presence of montelukast in human milk. Data available on the 49 for two years in clinical trials. With prolonged treatment, the adverse reaction profile did not significantly change.

Pediatric Patients 6 to 14 Years of Age with Asthma
Montelukast sodium has been evaluated for safety in 476 pediatric patients 6 to 14 years of age. Cumulatively, 289 pediatric patients were treated with montelukast sodium for at least 6 months, and 241 for one year or longer in clinical trials. The safety profile of montelukast sodium in the 6-week, double-blind, pediatric efficacy trial was generally similar to the adult safety profile. In pediatric patients 6 to 14 years of age receiving montelukast sodium, the following reactions occurred with a frequency ≥2% and more frequently than in patients receiving placebo: pharyngitis, influenza, fever, sinusitis, nausea, diarrhea, dyspepsia, otitis, viral infection, and taryngitis. The frequency of less common adverse reactions was comparable between montelukast sodium and placebo. With prolonged treatment, the adverse reaction profile did not significantly change.

The safety profile of montelukast sodium, when administered as a single dose for prevention of EIB in pediatric patients 6 years of age and older, was consistent with the safety profile previously described for montelukast sodium.

In studies evaluating growth rate, the safety profile in these pediatric patients was consistent with the safety profile previously described for montelukast sodium. In a 56-week, double-blind study evaluating growth rate in pediatric patients 6 to 9 years of age receiving montelukast sodium, the following reactions occurred with the use of montelukast sodium in this age group occurred with a frequency ≥2% and more frequently than in pediatric patients who received placebo: headache, rhinitis (infective), varicella, gastroenteritis, atopic dermatitis, acute bronchitis, tooth infection, sinus infection, and myopia.

Pediatric Patients 2 to 5 Years of Age with Asthma
Montelukast sodium has been evaluated for safety in 573 pediatric patients 2 to 5 years of age in single- and multiple-dose studies. Cumulatively, 426 pediatric patients 2 to 5 years of age were treated with montelukast sodium for at least 3 months, 230 for 6 months or longer, and 63 patients for one year or longer in clinical trials. In pediatric patients 2 to 5 years of age receiving montelukast sodium, the following reactions occurred with a frequency ≥2% and more frequently than in pediatric patients who received placebo: fever, cough, abdominal pain, diarrhea, headache, rhinorrhea, sinusitis, otitis, influenza, rash, ear pain, gastroenteritis, eczema, urticaria, varicella, pneumonia, dermatitis, and conjunctivitis.

Pediatric Patients 6 to 23 Months of Age with Asthma
Safety and effectiveness in pediatric patients younger than 12 months of age with asthma have not been established.

Montelukast sodium has been evaluated for safety in 175 pediatric patients 6 to 23 months of age. The safety profile of montelukast sodium in this age group was consistent with that observed in 2-week studies. The incidence of somnolence was similar to that of placebo in all studies.

Adults and Adolescents 15 Years of Age and Older with Seasonal Allergic Rhinitis
Montelukast sodium has been evaluated for safety in 2,199 adult and adolescent patients 15 years of age and older in clinical trials. Montelukast sodium administered once daily in the morning or in the evening had a safety profile similar to that of placebo. In a placebo-controlled clinical trials, the following reaction was reported with montelukast sodium with a frequency ≥1% and at an incidence greater than placebo: upper respiratory infection. 1.9% of patients receiving montelukast sodium vs. 1.5% of patients receiving placebo. In a 4-week, placebo-controlled clinical trial, 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.

Pediatric Patients 2 to 14 Years of Age with Seasonal Allergic Rhinitis
Montelukast sodium has been evaluated in 280 pediatric patients 2 to 14 years of age in a 2-week, multicenter, double-blind, placebo-controlled safety study. Montelukast sodium administered once daily in the evening had a safety profile similar to that of placebo. In this study, the following reactions occurred with a frequency ≥2% and at an incidence greater than placebo:

PRODUCT NAME	Montelukast Sodium Tablets and Montelukast Sodium Chewable Tablets USP	COUNTRY : US	LOCATION : Indrad/Dahej	Supersedes A/W No.:	
ITEM / PACK	Outsert	NO. OF COLORS: 1	SUBSTRATE : 40 g/m ² Bible Paper		V. No. : 01
DESIGN STYLE	Back Side	PANTONE SHADE NOS.:			
CODE	8097170		Activities	Department	Name
DIMENSIONS (MM)	525 x 370		Prepared By	Pkg.Dev	Signature
ART WORK SIZE	S/S	Black	Reviewed By	Pkg.Dev	
DATE	22-10-2024	Font Size 6 pt_Med. 10 pt	Approved By	Quality	Date

Note: Pharma code/ Bar code and adjacent text must be visible on folded leaflet. These details can be moved by printed to arrange pharma code/ Bar code and adjacent text visible on folded leaflet.



experience, no dosage adjustment of montelukast is required upon co-administration with gemfibrozil *[see Overdosage (10)]*.

13. NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

No evidence of tumorigenicity was seen in carcinogenicity studies of either 2 years in Sprague-Dawley rats or 92 weeks in mice at oral gavage doses up to 200 mg/kg/day or 100 mg/kg/day, respectively. The estimated exposure in rats was approximately 120 and 75 times the AUC for adults and children, respectively, at the maximum recommended daily oral dose. The estimated exposure in mice was approximately 45 and 25 times the AUC for adults and children, respectively, at the maximum recommended daily oral dose.

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 vivo* mouse bone marrow chromosomal aberration assay.

In fertility studies in female rats, montelukast produced reductions in fertility and fecundity indices at an oral dose of 200 mg/kg (estimated exposure was approximately 70 times the AUC for adults at the maximum recommended daily oral dose). No effects on fertility or fecundity were observed at an oral dose of 100 mg/kg (estimated exposure was approximately 20 times the AUC for adults at the maximum recommended daily oral dose). Montelukast had no effects on fertility in male rats at oral doses up to 800 mg/kg (estimated exposure was approximately 160 times the AUC for adults at the maximum recommended daily oral dose).

14. CLINICAL STUDIES

14.1 Asthma

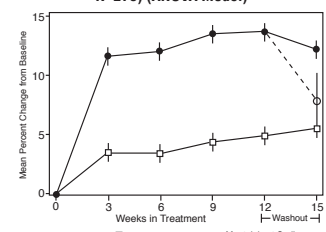
Adults and Adolescents 15 Years of Age and Older with Asthma

Clinical trials in adults and adolescents 15 years of age and older demonstrated there is no additional clinical benefit to montelukast doses above 10 mg once daily.

The efficacy of montelukast sodium for the chronic treatment of asthma in adults and adolescents 15 years of age and older was demonstrated in two (U.S. and Multinational) similarly designed, randomized, 12-week, double-blind, placebo-controlled trials in 1,576 patients (795 treated with montelukast sodium, 530 treated with placebo, and 251 treated with active control). The median age was 33 years (range 15 to 85); 56.8% were females and 43.2% were males. The ethnic/racial distribution in these studies was 71.6% Caucasian, 17.7% Hispanic, 7.2% other origins and 3.5% Black. Patients had mild or moderate asthma and were non-smokers who required approximately 5 puffs of inhaled β₂-agonist per day on an "as-needed" basis. The patients had a mean baseline percent of predicted forced expiratory volume in 1 second (FEV₁) of 66% (approximate range, 40 to 90%). The co-primary endpoints in these trials were FEV₁ and daytime asthma symptoms. In both studies after 12 weeks, there was a statistically significant improvement in FEV₁ and a statistically significant decrease in the number of rescue inhaler puffs used in patients receiving montelukast sodium vs. 4.2%-change in the placebo group, p<0.001; the change from baseline in FEV₁ for montelukast sodium was 0.32 liters compared with 0.10 liters for placebo, corresponding to a between-group difference of 0.22 liters (p<0.001, 95% CI 0.17 liters, 0.27 liters). The results of the Multinational trial on FEV₁ were similar.

The results of the U.S. trial on the primary endpoint, morning FEV₁, expressed as mean percent change from baseline averaged over the 12-week treatment period, are shown in FIGURE 2. Compared with placebo, treatment with one montelukast sodium 10-mg tablet daily in the evening resulted in a statistically significant increase in FEV₁ percent change from baseline (13.0%-change in the group treated with montelukast sodium vs. 4.2%-change in the placebo group, p<0.001); the change from baseline in FEV₁ for montelukast sodium was 0.32 liters compared with 0.10 liters for placebo, corresponding to a between-group difference of 0.22 liters (p<0.001, 95% CI 0.17 liters, 0.27 liters). The results of the Multinational trial on FEV₁ were similar.

Figure 2: FEV₁ Mean Percent Change from Baseline (U.S. Trial: Montelukast Sodium N=406; Placebo N=70) (ANOVA Model)



The effect of montelukast sodium on other primary and secondary endpoints, represented by the Multinational study is shown in TABLE 6. Results on these endpoints were similar in the US study.

Table 6: Effect of Montelukast Sodium on Primary and Secondary Endpoints in a Multinational Placebo-controlled Trial (ANOVA Model)

Endpoint	Montelukast Sodium		Placebo			
	N	Mean Change from Baseline	N	Mean Change from Baseline		
Daytime Asthma Symptoms (0 to 6 scale)	372	2.35	-0.49*	245	2.40	-0.26
β ₂ -agonist (puffs per day)	371	5.35	-1.65*	241	5.78	-0.42
AM PEFR (L/min)	372	339.57	25.03*	244	335.24	1.83
PM PEFR (L/min)	372	355.23	20.13*	244	354.02	-0.49
Nocturnal Awakenings (f/week)	285	5.46	-2.03*	195	5.57	-0.78

*p<0.001, compared with placebo

Both studies evaluated the effect of montelukast sodium on secondary outcomes, including asthma attack (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), and use of oral corticosteroids for asthma rescue. In the Multinational study, significantly fewer patients (15.6% of patients) on montelukast sodium experienced asthma attacks compared with patients on placebo (27.3%, p<0.001). In the US study, 7.8% of patients on montelukast sodium and 10.3% of patients on placebo experienced asthma attacks, but the difference between the two treatment groups was not significant (p=0.334). In the Multinational study, significantly fewer patients (14.8% of patients) on montelukast sodium were prescribed oral corticosteroids for asthma rescue compared with patients on placebo (25.7%, p<0.001). In the US study, 6.9% of patients on montelukast sodium and 9.9% of patients on placebo were prescribed oral corticosteroids for asthma rescue, but the difference between the two treatment groups was not significant (p=0.196).

Onset of Action and Maintenance of Effects

In each placebo-controlled trial in adults, the treatment effect of montelukast sodium, measured by daily diary card parameters, including symptom scores, "as-needed" β₂-agonist use, and PEFR measurements, was achieved after the first dose and was maintained throughout the dosing interval (24 hours). No significant change in treatment effect was observed during continuous once-daily evening administration in non-placebo-controlled extension trials for up to one year. Withdrawal of montelukast sodium in asthmatic patients after 12 weeks of continuous use did not cause rebound worsening of asthma.

Pediatric Patients 6 to 14 Years of Age with Asthma

The efficacy of montelukast sodium in pediatric patients 6 to 14 years of age was demonstrated in one 8-week, double-blind, placebo-controlled trial in 536 patients (201 treated with montelukast sodium and 135 treated with placebo) using inhaled β₂-agonist on an "as-needed" basis. The patients had a mean baseline percent predicted FEV₁ of 72% (approximate range, 45 to 90%) and a mean daily inhaled β₂-agonist requirement of 3.4 puffs of albuterol. Approximately 36% of the patients were on inhaled corticosteroids. The median age was 11 years (range 6 to 15); 55.4% were females and 44.6% were males. The ethnic/racial distribution in this study was 80.1% Caucasian, 12.8% Black, 4.5% Hispanic, and 2.7% other origins.

Compared with placebo, treatment with one 5-mg montelukast sodium chewable tablet daily resulted in a significant improvement in mean morning FEV₁ percent change from baseline (8.7% in the group treated with montelukast sodium vs. 4.2% change from baseline in the placebo group, p<0.001). There was a significant decrease in the mean percent change in daily "as-needed" inhaled β₂-agonist use (11.7% decrease from baseline in the group treated with montelukast sodium vs. 8.2% increase from baseline in the placebo group, p<0.05). This effect represents a mean decrease from baseline of 0.56 and 0.23 puffs per day for the montelukast and placebo groups, respectively. Subgroup analyses indicated that younger pediatric patients aged 6 to 11 had efficacy results comparable to those of the older pediatric patients aged 12 to 14.

Similar to the adult studies, no significant change in the treatment effect was observed during continuous once-daily administration in one open-label extension trial without a concurrent placebo group for up to 6 months.

Pediatric Patients 2 to 5 Years of Age with Asthma

The efficacy of montelukast sodium for the chronic treatment of asthma in pediatric patients 2 to 5 years of age was explored in a 12-week, placebo-controlled safety and tolerability study in 689 patients, 461 of whom were treated with montelukast sodium. The median age was 4 years (range 2 to 6); 41.5% were females and 58.5% were males. The ethnic/racial distribution in this study was 56.5% Caucasian, 20.9% Hispanic, 14.4% other origins, and 8.3% Black.

While the primary objective was to determine the safety and tolerability of montelukast sodium in this age group, the study included exploratory efficacy evaluations, including daytime and overnight asthma symptom scores, β₂-agonist use, oral corticosteroid rescue, and the physician's global evaluation. The findings of these exploratory efficacy evaluations, along with pharmacokinetics and extrapolation of efficacy data from older patients, support the overall conclusion that montelukast sodium is efficacious in the maintenance treatment of asthma in patients 2 to 5 years of age.

Effects in Patients on Concomitant Corticosteroids

Separate trials in adults evaluated the ability of montelukast sodium to add to the clinical effect of inhaled corticosteroids and to allow inhaled corticosteroid tapering when used concomitantly.

One randomized, placebo-controlled, parallel-group trial (n=226) enrolled adults with stable asthma with a mean FEV₁ of approximately 84% of predicted who were previously maintained on various inhaled corticosteroids (delivered by metered-dose aerosol or dry powder inhalers). The median age was 41.5 years (range 16 to 70); 52.2% were females and 47.8% were males. The ethnic/racial distribution in this study was 82.0% Caucasian, 3.5% Black, 2.2% Hispanic, and 2.2% Asian. The types of inhaled corticosteroids and their mean baseline requirements included beclomethasone dipropionate (mean dose, 1.203 mcg/day), triamcinolone acetonide (mean dose, 2.004 mcg/day), flunisolide (mean dose, 1.971 mcg/day), fluticasone propionate (mean dose, 1.083 mcg/day), or budesonide (mean dose, 1.192 mcg/day). Some of these inhaled corticosteroids were non-U.S.-approved formulations, and doses expressed may not be exact. The pre-study inhaled corticosteroid requirements were reduced by approximately 37% during a 5- to 7-week placebo run-in period designed to titrate patients toward their lowest effective inhaled corticosteroid dose. Treatment with montelukast sodium resulted in a further 47% reduction in mean inhaled corticosteroid dose compared with a mean reduction of 30% in the placebo group over the 12-week active treatment period (p=0.05). It is not known whether the results of this study can be generalized to patients with asthma 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 who were not adequately controlled on inhaled corticosteroids (beclomethasone 336 mcg/day), the addition of montelukast sodium to beclomethasone resulted in statistically significant improvements in FEV₁ compared with those who were continued on beclomethasone alone or those 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, PEFR, nocturnal awakenings due to asthma, and "as-needed" β₂-agonist requirements. In adult patients with asthma with documented aspirin 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 aspirin-sensitive patients was similar to the effect observed in the general population of asthma patients studied. The effect of montelukast sodium on the bronchostimulant response to aspirin or other non-steroidal anti-inflammatory drugs in aspirin-sensitive asthmatic patients has not been evaluated. *[see Warnings and Precautions (5.4)]*.

14.2 Exercise-Induced Bronchoconstriction (EIB)

Exercise-Induced Bronchoconstriction (Adults, Adolescents, and Pediatric Patients 6 years of age and older)
The efficacy of montelukast sodium, 10 mg, when given as a single dose 2 hours before exercise for the prevention of EIB was investigated in three (U.S. and Multinational), randomized, double-blind, placebo-controlled crossover studies that included a total of 160 adult and adolescent patients 15 years of age and older with EIB. Exercise challenge testing was conducted at 2 hours, 8.5 or 12 hours, and 24 hours following administration of a single dose of study drug (montelukast sodium 10 mg or placebo). The primary endpoint was the mean maximum percent fall in FEV₁ following the 2 hours post-dose exercise challenge in all three studies (Study A, Study B, and Study C). In Study A, a single dose of montelukast sodium 10 mg demonstrated a statistically significant protective benefit against EIB when taken 2 hours prior to exercise. Some patients were protected from EIB at 8.5 and 24 hours after administration; however, some patients were not. The results for the mean maximum percent fall at each timepoint in Study A are shown in TABLE 7 and are represented by the results from the other two studies.

Table 7: Mean Maximum Percent Fall in FEV₁ Following Exercise Challenge in Study A (N=47) ANOVA Model

Time of exercise challenge following medication administration	Montelukast Sodium	Placebo	Treatment difference % for Montelukast Sodium versus Placebo (95% CI)*
2 hours <td>13</td> <td>22</td> <td>-9 (-12, -5)</td>	13	22	-9 (-12, -5)
8.5 hours <td>12</td> <td>17</td> <td>-5 (-9, -2)</td>	12	17	-5 (-9, -2)
24 hours <td>10</td> <td>14</td> <td>-4 (-7, -1)</td>	10	14	-4 (-7, -1)

*Least squares-mean

The efficacy of montelukast sodium 5-mg chewable tablets, when given as a single dose 2 hours before exercise for the prevention of EIB, was investigated in one multinational, randomized, double-blind, placebo-controlled crossover study that included a total of 64 pediatric patients 6 to 14 years of age with EIB. Exercise challenge testing was conducted at 2 hours and 24 hours following administration of a single dose of study drug (montelukast sodium 5 mg or placebo). The primary endpoint was the mean maximum percent fall in FEV₁ following the 2 hours post-dose exercise challenge. A single dose of montelukast sodium 5 mg demonstrated a statistically significant protective benefit against EIB when taken 2 hours prior to exercise (TABLE 8). Similar results were shown at 24 hours post-dose (a secondary endpoint). Some patients were protected from EIB at 24 hours after administration; however, some patients were not. No timepoints were assessed between 2 and 24 hours post-dose.

Table 8: Mean Maximum Percent Fall in FEV₁ Following Exercise Challenge in Pediatric Patients (N=64) ANOVA Model

Time of exercise challenge following medication administration	Montelukast Sodium	Placebo	Treatment difference % for Montelukast Sodium versus Placebo (95% CI)*
2 hours <td>15 <td>20 <td>-5 (-9, -1)</td> </td></td>	15 <td>20 <td>-5 (-9, -1)</td> </td>	20 <td>-5 (-9, -1)</td>	-5 (-9, -1)
24 hours <td>13 <td>17 <td>-4 (-7, -1)</td> </td></td>	13 <td>17 <td>-4 (-7, -1)</td> </td>	17 <td>-4 (-7, -1)</td>	-4 (-7, -1)

*Least squares-mean

The efficacy of montelukast sodium for prevention of EIB in patients below 6 years of age has not been established.

Daily administration of montelukast sodium for the chronic treatment of asthma has not been established to prevent acute episodes of EIB. In a 12-week, randomized, double-blind, parallel group study of 110 adult and adolescent asthmatics 15 years of age and older, with a mean baseline FEV₁ percent of predicted of 83% and with documented exercise-induced exacerbation of asthma, treatment with montelukast sodium, 10 mg, once daily in the evening, resulted in a statistically significant reduction in mean maximal percent fall in FEV₁ and mean time to recovery to within 5% of the pre-exercise FEV₁. Exercise challenge was conducted at the end of the dosing interval (i.e., 20 to 24 hours after the preceding dose). This effect was maintained throughout the 12-week treatment period. Montelukast sodium did not occur. Montelukast sodium did not prevent clinically significant deterioration in maximal percent fall in FEV₁ after exercise (i.e., ≥20% decrease from pre-exercise baseline) in 52% of patients studied. In a separate crossover study in adults, a similar effect was observed after two once-daily 10-mg doses of montelukast sodium.

In pediatric patients 6 to 14 years of age, using the 5-mg chewable tablet, a 2-day crossover study demonstrated that tolerance did not occur. Montelukast sodium did not prevent clinically significant deterioration in maximal percent fall in FEV₁ after exercise in adults, a similar effect was observed after two once-daily 10-mg doses of montelukast sodium.

14.3 Allergic Rhinitis (Seasonal and Perennial)
Seasonal Allergic Rhinitis

The efficacy of montelukast sodium tablets for the treatment of seasonal allergic rhinitis was investigated in 5 similarly designed, randomized, double-blind, parallel-group, placebo- and active-controlled (loratadine) trials conducted in North America. The 5 trials enrolled a total of 5,029 patients, of whom 1,799 were treated with montelukast sodium tablets. Patients were 15 to 82 years of age 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 entry.

The period of randomized treatment was 2 weeks in 4 trials and 4 weeks in one trial. The primary outcome variable was mean change from baseline in daytime nasal symptoms score (the average of individual scores of nasal congestion, rhinorrhea, nasal itching, sneezing) as assessed by patients on a 0 to 3 categorical scale. Four of the five trials showed a significant reduction in daytime nasal symptoms scores with montelukast sodium 10-mg tablets compared with placebo. The results of one trial are shown below. The median age in this trial was 35.0 years (range 15 to 81); 65.4% were females and 34.6% were males. The ethnic/racial distribution in this study was 83.1% Caucasian, 6.4% other origins, 5.8% Black, and 4.8% Hispanic. The mean changes from baseline in daytime nasal symptoms score in the treatment groups that received montelukast sodium tablets, loratadine, and placebo are shown in TABLE 8. The remaining three trials that demonstrated efficacy showed similar results. Efficacy was demonstrated for seasonal allergic rhinitis when montelukast was administered in the morning or the evening.

Treatment Group (N)	Baseline Mean Score	Mean Change from Baseline	Difference Between Treatment and Placebo (95% CI) Least-Squares Mean
Montelukast 10 mg (344)	2.09	-0.39	-0.13† (-0.21, -0.06)
Placebo (351)	2.10	-0.26	N.A.
Active Control† (Loratadine 10 mg) (599)	2.06	-0.46	-0.24† (-0.31, -0.17)

* Average of individual scores of nasal congestion, rhinorrhea, nasal itching, sneezing as assessed by patients on a 0 to 3 categorical scale.

† Statistically different from placebo (p<0.001).

‡ The study was not designed for statistical comparison between Montelukast Sodium and the active control (loratadine).

Perennial Allergic Rhinitis

The efficacy of montelukast sodium tablets for the treatment of perennial allergic rhinitis was investigated in 2 randomized, double-blind, placebo-controlled studies conducted in North America and Europe. The two studies enrolled a total of 3,357 patients, of whom 1,632 received montelukast sodium 10-mg tablets. Patients 15 to 82 years of age with perennial allergic rhinitis as confirmed by history and a positive skin test to at least one relevant perennial allergen (dust mites, animal dander, and/or mold spores), who had active symptoms at the time of study entry, were enrolled. In the study in which efficacy was demonstrated, the median age was 35 years (range 15 to 81); 64.1% were females and 35.9% were males. The ethnic/racial distribution in this study was 83.2% Caucasian, 8.1% Black, 5.4% Hispanic, 2.3% Asian, and 1.0% other origins. Montelukast sodium 10-mg tablets once daily was shown to significantly reduce symptoms of perennial allergic rhinitis over a 6-week treatment period (TABLE 10); in this study the primary outcome variable was mean change from baseline in daytime nasal symptoms score (the average of individual scores of nasal congestion, rhinorrhea, and sneezing).

Table 10: Effects of Montelukast Sodium on Daytime Nasal Symptoms Score* in a Placebo-controlled Trial in Patients with Perennial Allergic Rhinitis (ANOVA Model)

Treatment Group (N)	Baseline Mean Score	Mean Change from Baseline	Difference Between Treatment and Placebo (95% CI) Least-Squares Mean
Montelukast 10 mg (1,000)	2.09	-0.42	-0.06† (-0.12, -0.04)
Placebo (980)	2.10	-0.35	N.A.

* Average of individual scores of nasal congestion, rhinorrhea, sneezing as assessed by patients on a 0 to 3 categorical scale.

† Statistically different from placebo (p<0.001).

The other 6-week study evaluated montelukast 10 mg (n=626), placebo (n=609), and an active-control (cetirizine 10 mg, n=120). The primary analysis compared the mean change from baseline in daytime nasal symptoms score for montelukast sodium vs. placebo over the first 4 weeks of treatment; the study was not designed for statistical comparison between montelukast sodium and the active-control. The primary outcome variable included nasal itching in addition to nasal congestion, rhinorrhea, and sneezing. The estimated difference between montelukast sodium and placebo was -0.04 with a 95% CI of (-0.09, 0.01). The estimated difference between the active-control and placebo was -0.10 with a 95% CI of (-0.19, -0.01).

16. HOW SUPPLIED/STORAGE AND HANDLING

Montelukast sodium oral granules USP, 4 mg, are white to off white granules with 500 mg net weight, packed in a child-resistant foil packet. They are supplied as follows:
NDC 13668-531-11 unit packet
NDC 13668-531-34 carton with 30 packets.

For Montelukast sodium film-coated tablets 10 mg

The tablets are available as follows:

Bottles of 30	NDC 13668-081-30
Bottles of 90	NDC 13668-081-90
Bottles of 500	NDC 13668-081-05
Bottles of 3,200	NDC 13668-081-32

For Montelukast sodium chewable tablets USP 4 mg and 5 mg The tablets are available as follows:
Montelukast sodium chewable tablets USP 4 mg, are pink colored, oval biconvex shaped, uncoated tablets, debossed with "1079" on one side and "4 MG" on other side. They are supplied as follows:

Bottles of 30	NDC 13668-079-30
Bottles of 90	NDC 13668-079-90
Bottles of 500	NDC 13668-079-05

Montelukast sodium chewable tablets USP 5 mg, are pink colored, round shaped, uncoated tablets, debossed with "1080" on one side and "5 MG" on other side. They are supplied as follows:

Bottles of 30	NDC 13668-080-30
Bottles of 90	NDC 13668-080-90
Bottles of 500	NDC 13668-080-05

Storage
Store montelukast sodium 4-mg oral granules, montelukast sodium 4-mg chewable tablets, 5-mg chewable tablets and 10-mg film-coated tablets at 20° to 25° (68° to 77°F); excursions permitted to 15° to 30°C (59° to 86°F) [see USP Controlled Room Temperature]. Protect from moisture and light. Store in original package.

17. PATIENT COUNSELING INFORMATION

For the tablets and chewable tablets, advise the patient and/or caregiver to read the FDA-approved patient labeling (Medication Guide). For the oral granules, advise the patient and/or caregiver to read the FDA-approved patient labeling (Medication Guide and Instructions for Use).

- Advise patients about the potential risk for serious neuropsychiatric symptoms and behavioral changes with montelukast sodium use *[see Warnings and Precautions (5.1)]*.
- Discuss the benefits and risks of montelukast sodium with patients when prescribing or continuing treatment with montelukast sodium. *[see Warnings and Precautions (5.1)]*.
- Advise patients to monitor for changes in behavior or neuropsychiatric symptoms in patients taking montelukast sodium *[see Warnings and Precautions (5.1)]*.
- Instruct patients to discontinue montelukast sodium and contact a healthcare provider immediately if changes in behavior or thinking that are not typical for the patient occur, or if the patient develops suicidal ideation or suicidal behavior *[see Warnings and Precautions (5.1)]*.
- Advise patients to take montelukast sodium daily as prescribed, even when they are asymptomatic, as well as during periods of worsening asthma, and to contact their physicians if their asthma is not well controlled.
- Advise patients that oral montelukast sodium is not for the treatment of acute asthma attacks. They should have appropriate short-acting inhaled β₂-agonist medication available to treat asthma exacerbations. Patients who have exacerbations of asthma after exercise should be instructed to have available for rescue a short-acting inhaled β₂-agonist. Daily administration of montelukast sodium for the chronic treatment of asthma has not been established to prevent acute episodes of EIB *[see Warnings and Precautions (5.2)]*.
- Advise patients to seek medical attention if short-acting inhaled bronchodilators are needed more often than usual, or if more than the maximum number of inhalations of short-acting bronchodilator treatment prescribed for a 24-hour period are needed.
- Instruct patients to continue other anti-asthma medications as prescribed unless instructed by a physician.
- Instruct patients with known aspirin sensitivity to continue avoidance of aspirin or non-steroidal anti-inflammatory agents while taking montelukast sodium *[see Warnings and Precautions (5.4)]*.
- Inform phenylketonuric patients that the 4-mg and 5-mg chewable tablets contain phenylalanine (a source of aspartame) *[see Warnings and Precautions (5.6)]*.

MEDICATION GUIDE

Montelukast Sodium (mon te loo' kast soe' dee um) Tablets USP and Montelukast Sodium (mon te loo' kast soe' dee um) Chewable Tablets USP
Montelukast Sodium (mon te loo' kast soe' dee um) Oral Granules USP

What is the most important information I should know about montelukast sodium?
Serious mental health problems have happened in people taking montelukast sodium or even after treatment has stopped. This can happen in people with or without a history of mental health problems. Stop taking montelukast sodium and tell your healthcare provider right away if you or your child have any unusual changes in behavior or thinking, including any of these symptoms:

- agitation, including aggressive behavior or hostility
- attention problems
- bad or vivid dreams
- depression
- disorientation (confusion)
- feeling anxious
- irritability
- hallucinations (seeing or hearing things that are not really there)
- memory problems
- obsessive-compulsive symptoms
- restlessness
- suicidal thoughts and actions (including suicide)
- tremor
- trouble sleeping
- uncontrolled muscle movements

What is Montelukast Sodium?

Montelukast