CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

020829Orig1s055

Trade Name:	**SINGULAIR**
Generic or Proper Name:	(montelukast sodium)
Sponsor:	MERCK & CO, INC.
Approval Date:	August 10, 2010

Indication: **SINGULAIR** is a leukotriene receptor antagonist indicated for:

- The prophylaxis and chronic treatment of asthma in adults and pediatric patients 12 months of age and older.
- Acute prevention of exercise-induced bronchoconstriction (EIB) in patients 15 years of age and older.
- 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.

CENTER FOR DRUG EVALUATION AND RESEARCH

020829Orig1s055

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CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

020829Orig1s055

APPROVAL LETTER

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 20-829/S-055
20-830/S-056
21-409/S-031

Merck and Co., Inc.
P.O. Box 2000, RY32-605
Rahway, NJ 07065-0900

Attention: Margaret E. McCann, D.V.M, Ph.D.
Director, Worldwide Regulatory Affairs

Dear Dr. McCann:

Please refer to your supplemental new drug applications dated April 14, 2010, and received April 14, 2010, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Singulair (montelukast sodium) tablets, chewable tablets and oral granules.

We also acknowledge receipt of your submissions dated May 05, and July 01 and 12, 2010.

These Changes Being Effected supplemental new drug applications provide for the addition of the term disorientation to the WARNINGS and PRECAUTIONS and ADVERSE REACTIONS sections of the package insert and to the possible side effects section of the patient package insert.

We have completed our review of these applications, as amended. These applications are approved, effective on the date of this letter, for use as recommended in the enclosed agreed upon labeling text.

As soon as possible, but no later than 14 days from the date of this letter, submit, using the FDA automated drug registration and listing system (eLIST), the content of labeling [21 CFR 314.50(l)] in structured product labeling (SPL) format, as described at http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm, that is identical to the enclosed labeling (text for the package insert) and include the labeling changes proposed in any pending "Changes Being Effected" (CBE) supplements. Information on submitting SPL files using eLIST may be found in the guidance for industry titled "SPL Standard for Content of Labeling Technical Qs and As" at http://www.fda.gov/downloads/DrugsGuidanceComplianceRegulatoryInformation/Guidances/UCM072392.pdf.

The SPL will be accessible from publicly available labeling repositories.

Also within 14 days, amend all pending supplemental applications for this NDA, including pending "Changes Being Effected" (CBE) supplements, for which FDA has not yet issued an action letter, with the content of labeling [21 CFR 314.50(l)(1)(i)] in MS Word format that includes the changes approved in this supplemental application.

NDA 20-829/S-055
20-830/S-056
21-409/S-031

If you issue a letter communicating important information about this drug product (i.e., a "Dear Health Care Professional" letter), we request that you submit a copy of the letter to this NDA and a copy to the following address:

MEDWATCH
Food and Drug Administration
5515 Security Lane
HFD-001, Suite 5100
Rockville, MD 20852

We remind you that you must comply with reporting requirements for an approved NDA (21 CFR 314.80 and 314.81).

If you have any questions, call Sadaf Nabavian, Regulatory Project Manager, at (301) 796-2777.

Sincerely,

{See appended electronic signature page}

Badrul A. Chowdhury, M.D., Ph.D.
Director
Division of Pulmonary, Allergy, and
Rheumatology Drug Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

Enclosure: Approved Labeling

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-21409	SUPPL-31	MERCK RESEARCH LABORATORIES DIV MERCK CO INC	SINGULAIR(MONTELUKAST SODIUM)4MG GRANULE
NDA-20830	SUPPL-56	MERCK AND CO INC	SINGULAIR(MONTELUKAST SODIUM)CHEWABLE TA
NDA-20829	SUPPL-55	MERCK RESEARCH LABORATORIES DIV MERCK CO INC	SINGULAIR (MONTELUKAST SODIUM) TABS

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

BADRUL A CHOWDHURY
08/10/2010

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

020829Orig1s055

LABELING

Merck Sharp & Dohme Corp., a subsidiary of
MERCK & CO., INC.
Whitehouse Station, NJ 08889, USA

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

SINGULAIR®
(montelukast sodium) tablets, chewable tablets, and oral granules
Initial U.S. Approval: 1998

---------- RECENT MAJOR CHANGES ----------
Warnings and Precautions, Neuropsychiatric Events (5.4) 04/2010

---------- INDICATIONS AND USAGE ----------
SINGULAIR® 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 15 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 (1.3).

----------DOSAGE AND ADMINISTRATION ----------
Administration (by indications):
- Asthma (2.1): Once daily in the evening for patients 12 months and older.
- Acute prevention of EIB (2.2): 10 mg tablet at least 2 hours before exercise for patients 15 years of age and older.
- Seasonal allergic rhinitis (2.3): Once daily for patients 2 years and older.
- Perennial allergic rhinitis (2.3): Once daily for patients 6 months and older.

Dosage (by age):
- 15 years and older: one 10-mg tablet.
- 6 to 14 years: one 5-mg chewable tablet.
- 2 to 5 years: one 4-mg chewable tablet or one packet of 4-mg oral granules.
- 6 to 23 months: one packet of 4-mg oral granules.

Patients with both asthma and allergic rhinitis should take only one dose daily in the evening (2.4). For oral granules: Must administer within 15 minutes after opening the packet (with or without mixing with food) (2.5).

----------DOSAGE FORMS AND STRENGTHS----------
- SINGULAIR 10-mg Film-Coated Tablets
- SINGULAIR 5-mg and 4-mg Chewable Tablets
- SINGULAIR 4-mg Oral Granules

---------- CONTRAINDICATIONS ----------
- Hypersensitivity to any component of this product (4).

----------WARNINGS AND PRECAUTIONS ----------
- Do not prescribe SINGULAIR to treat an acute asthma attack.
- Advise patients to have appropriate rescue medication available (5.1).
- Inhaled corticosteroid may be reduced gradually. Do not abruptly substitute SINGULAIR for inhaled or oral corticosteroids (5.2).
- Patients with known aspirin sensitivity should continue to avoid aspirin or non-steroidal anti-inflammatory agents while taking SINGULAIR (5.3).
- Neuropsychiatric events have been reported with SINGULAIR. Instruct patients to be alert for neuropsychiatric events. Evaluate the risks and benefits of continuing treatment with SINGULAIR if such events occur (5.4 and 6.2).
- Systemic eosinophilia, sometimes presenting with clinical features of vasculitis consistent with Churg-Strauss syndrome, has been reported. These events usually, but not always, have been associated with the reduction of oral corticosteroid therapy (5.5 and 6.2).
- Inform patients with phenylketonuria that the 4-mg and 5-mg chewable tablets contain phenylalanine (5.6).

----------ADVERSE REACTIONS ----------
Most common adverse reactions (incidence ≥5% and greater than placebo listed in descending order of frequency): upper respiratory infection, fever, headache, pharyngitis, cough, abdominal pain, diarrhea, otitis media, influenza, rhinorrhea, sinusitis, otitis (6.1).

To report SUSPECTED ADVERSE REACTIONS, contact Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc., at 1-877-888-4231 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling.

Revised: 05/2010

FULL PRESCRIBING INFORMATION: CONTENTS*

*Sections or subsections omitted from the full prescribing information are not listed.

FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

1.1 Asthma

SINGULAIR[1] 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

SINGULAIR is indicated for prevention of exercise-induced bronchoconstriction (EIB) in patients 15 years of age and older.

1.3 Allergic Rhinitis

SINGULAIR 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.

2 DOSAGE AND ADMINISTRATION

2.1 Asthma

SINGULAIR should be taken once daily in the evening. The following doses are recommended:

For adults and adolescents 15 years of age and older: one 10-mg tablet.

For pediatric patients 6 to 14 years of age: one 5-mg chewable tablet.

For pediatric patients 2 to 5 years of age: one 4-mg chewable tablet or one packet of 4-mg oral granules.

For 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.

There have been no clinical trials in patients with asthma to evaluate the relative efficacy of morning versus evening dosing. The pharmacokinetics of montelukast are similar whether dosed in the morning or evening. Efficacy has been demonstrated for asthma when montelukast was administered in the evening without regard to time of food ingestion.

2.2 Exercise-Induced Bronchoconstriction (EIB) in Patients 15 Years of Age and Older

For prevention of EIB, a single 10 mg dose of SINGULAIR should be taken at least 2 hours before exercise. An additional dose of SINGULAIR should not be taken within 24 hours of a previous dose. Patients already taking SINGULAIR 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 β-agonist. Safety and effectiveness in patients younger than 15 years of age have not been established. Daily administration of SINGULAIR for the chronic treatment of asthma has not been established to prevent acute episodes of EIB.

2.3 Allergic Rhinitis

For allergic rhinitis, SINGULAIR should be taken once daily. Efficacy was demonstrated for seasonal allergic rhinitis when montelukast was administered in the morning or the evening without regard to time of food ingestion. The time of administration may be individualized to suit patient needs.

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

For adults and adolescents 15 years of age and older: one 10-mg tablet.

For pediatric patients 6 to 14 years of age: one 5-mg chewable tablet.

For 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.

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[1] Registered trademark of Merck Sharp & Dohme Corp., a subsidiary of **Merck & Co., Inc.**

The following doses for the treatment of symptoms of perennial allergic rhinitis are recommended:
For adults and adolescents 15 years of age and older: one 10-mg tablet.
For pediatric patients 6 to 14 years of age: one 5-mg chewable tablet.
For pediatric patients 2 to 5 years of age: one 4-mg chewable tablet or one packet of 4-mg oral granules.
For pediatric patients 6 to 23 months of age: 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.

2.4 Asthma and Allergic Rhinitis

Patients with both asthma and allergic rhinitis should take only one SINGULAIR dose daily in the evening.

2.5 Instructions for Administration of Oral Granules

SINGULAIR 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, SINGULAIR oral granules must not be stored for future use. Discard any unused portion. SINGULAIR oral granules are 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. SINGULAIR oral granules can be administered without regard to the time of meals.

3 DOSAGE FORMS AND STRENGTHS

- SINGULAIR 10-mg Film-Coated Tablets are beige, rounded square-shaped tablets, with code MRK 117 on one side and SINGULAIR on the other.
- SINGULAIR 5-mg Chewable Tablets are pink, round, bi-convex-shaped tablets, with code MRK 275 on one side and SINGULAIR on the other.
- SINGULAIR 4-mg Chewable Tablets are pink, oval, bi-convex-shaped tablets, with code MRK 711 on one side and SINGULAIR on the other.
- SINGULAIR 4-mg Oral Granules are white granules with 500 mg net weight, packed in a child-resistant foil packet.

4 CONTRAINDICATIONS

Hypersensitivity to any component of this product.

5 WARNINGS AND PRECAUTIONS

5.1 Acute Asthma

SINGULAIR 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 SINGULAIR can be continued during acute exacerbations of asthma. Patients who have exacerbations of asthma after exercise should have available for rescue a short-acting inhaled β-agonist.

5.2 Concomitant Corticosteroid Use

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

5.3 Aspirin Sensitivity

Patients with known aspirin sensitivity should continue avoidance of aspirin or non-steroidal anti-inflammatory agents while taking SINGULAIR. Although SINGULAIR is effective in improving 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)]*.

5.4 Neuropsychiatric Events

Neuropsychiatric events have been reported in adult, adolescent, and pediatric patients taking SINGULAIR. Post-marketing reports with SINGULAIR use include agitation, aggressive behavior or hostility, anxiousness, depression, disorientation, dream abnormalities, hallucinations, insomnia, irritability, restlessness, somnambulism, suicidal thinking and behavior (including suicide), and tremor. The clinical details of some post-marketing reports involving SINGULAIR appear consistent with a drug-induced effect.

Patients and prescribers should be alert for neuropsychiatric events. Patients should be instructed to notify their prescriber if these changes occur. Prescribers should carefully evaluate the risks and benefits of continuing treatment with SINGULAIR if such events occur *[see Adverse Reactions (6.2)]*.

5.5 Eosinophilic Conditions

Patients with asthma on therapy with SINGULAIR 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 usually, but not always, have been associated with the reduction of oral corticosteroid therapy. Physicians should be alert to eosinophilia, vasculitic rash, worsening pulmonary symptoms, cardiac complications, and/or neuropathy presenting in their patients. A causal association between SINGULAIR and these underlying conditions has not been established *[see Adverse Reactions (6.2)]*.

5.6 Phenylketonuria

Phenylketonuric patients should be informed that the 4-mg and 5-mg chewable tablets contain phenylalanine (a component of aspartame), 0.674 and 0.842 mg per 4-mg and 5-mg chewable tablet, respectively.

6 ADVERSE REACTIONS

6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a 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

SINGULAIR has been evaluated for safety in approximately 2950 adult and adolescent patients 15 years of age and older in clinical trials. In placebo-controlled clinical trials, the following adverse experiences reported with SINGULAIR occurred in greater than or equal to 1% of patients and at an incidence greater than that in patients treated with placebo:

TABLE 1
Adverse Experiences Occurring in ≥1% of Patients
with an Incidence Greater than that in Patients Treated with Placebo

	SINGULAIR 10 mg/day (%) (n=1955)	Placebo (%) (n=1180)
Body As A Whole		
Pain, abdominal	2.9	2.5
Asthenia/fatigue	1.8	1.2
Fever	1.5	0.9
Trauma	1.0	0.8
Digestive System Disorders		
Dyspepsia	2.1	1.1
Pain, dental	1.7	1.0
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 Experiences**		
ALT increased	2.1	2.0
AST increased	1.6	1.2
Pyuria	1.0	0.9

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

The frequency of less common adverse events was comparable between SINGULAIR and placebo.

The safety profile of SINGULAIR, 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 SINGULAIR.

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

Pediatric Patients 6 to 14 Years of Age with Asthma

SINGULAIR has been evaluated for safety in 476 pediatric patients 6 to 14 years of age. Cumulatively, 289 pediatric patients were treated with SINGULAIR for at least 6 months, and 241 for one year or longer in clinical trials. The safety profile of SINGULAIR in the 8-week, double-blind, pediatric efficacy trial was generally similar to the adult safety profile. In pediatric patients 6 to 14 years of age receiving SINGULAIR, the following events occurred with a frequency ≥2% and more frequently than in pediatric patients who received placebo: pharyngitis, influenza, fever, sinusitis, nausea, diarrhea, dyspepsia, otitis, viral infection, and laryngitis. The frequency of less common adverse events was comparable between SINGULAIR and placebo. With prolonged treatment, the adverse experience profile did not significantly change.

In studies evaluating growth rate, the safety profile in these pediatric patients was consistent with the safety profile previously described for SINGULAIR. In a 56-week, double-blind study evaluating growth rate in pediatric patients 6 to 8 years of age receiving SINGULAIR, the following events not previously observed with the use of SINGULAIR 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, skin infection, and myopia.

Pediatric Patients 2 to 5 Years of Age with Asthma

SINGULAIR 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

SINGULAIR 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 SINGULAIR, the following events 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.

SINGULAIR has been evaluated for safety in 175 pediatric patients 6 to 23 months of age. The safety profile of SINGULAIR in a 6-week, double-blind, placebo-controlled clinical study was generally similar to the safety profile in adults and pediatric patients 2 to 14 years of age. In pediatric patients 6 to 23 months of age receiving SINGULAIR, the following events occurred with a frequency ≥2% and more frequently than in pediatric patients who received placebo: upper respiratory infection, wheezing; otitis media; pharyngitis, tonsillitis, cough; and rhinitis. The frequency of less common adverse events was comparable between SINGULAIR and placebo.

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

SINGULAIR has been evaluated for safety in 2199 adult and adolescent patients 15 years of age and older in clinical trials. SINGULAIR administered once daily in the morning or in the evening had a safety profile similar to that of placebo. In placebo-controlled clinical trials, the following event was reported with SINGULAIR with a frequency ≥1% and at an incidence greater than placebo: upper respiratory infection, 1.9% of patients receiving SINGULAIR vs. 1.5% of patients receiving placebo. In a 4-week, placebo-controlled clinical study, the safety profile was consistent with that observed in 2-week studies. The incidence of somnolence was similar to that of placebo in all studies.

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

SINGULAIR has been evaluated in 280 pediatric patients 2 to 14 years of age in a 2-week, multicenter, double-blind, placebo-controlled, parallel-group safety study. SINGULAIR administered once daily in the evening had a safety profile similar to that of placebo. In this study, the following events 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

SINGULAIR has been evaluated for safety in 3357 adult and adolescent patients 15 years of age and older with perennial allergic rhinitis of whom 1632 received SINGULAIR in two, 6-week, clinical studies. SINGULAIR 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 events were reported with SINGULAIR 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.

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 Post-Marketing Experience

The following adverse reactions have been identified during post-approval use of SINGULAIR. 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.

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

Psychiatric disorders: agitation including aggressive behavior or hostility, anxiousness, depression, disorientation, dream abnormalities, hallucinations, insomnia, irritability, restlessness, somnambulism, suicidal thinking and behavior (including suicide), tremor *[see Warnings and Precautions (5.4)]*.

Nervous system disorders: drowsiness, paraesthesia/hypoesthesia, seizures.

Cardiac disorders: palpitations.

Respiratory, thoracic and mediastinal disorders: epistaxis.

Gastrointestinal disorders: diarrhea, dyspepsia, nausea, pancreatitis, vomiting.

Hepatobiliary disorders: Cases of cholestatic hepatitis, hepatocellular liver-injury, and mixed-pattern liver injury have been reported in patients treated with SINGULAIR. Most of these occurred in combination with other confounding factors, such as use of other medications, or when SINGULAIR 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 nodosum, pruritus, urticaria.

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

General disorders and administration site conditions: edema.

Patients with asthma on therapy with SINGULAIR 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 usually, but not always, have been associated with the reduction of oral corticosteroid therapy. Physicians should be alert to eosinophilia, vasculitic rash, 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 SINGULAIR is co-administered with theophylline, prednisone, prednisolone, oral contraceptives, terfenadine, digoxin, warfarin, 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

Pregnancy Category B: There are no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, SINGULAIR should be used during pregnancy only if clearly needed.

Teratogenic Effect: No teratogenicity was observed in rats and rabbits at doses approximately 100 and 110 times, respectively, the maximum recommended daily oral dose in adults based on AUCs *[see Nonclinical Toxicology (13.2)]*.

During worldwide marketing experience, congenital limb defects have been rarely reported in the offspring of women being treated with SINGULAIR during pregnancy. Most of these women were also taking other asthma medications during their pregnancy. A causal relationship between these events and SINGULAIR has not been established.

Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc., maintains a registry to monitor the pregnancy outcomes of women exposed to SINGULAIR while pregnant. Patients and healthcare providers are encouraged to report any prenatal exposure to SINGULAIR by calling the Pregnancy Registry at 1-800-986-8999.

8.3 Nursing Mothers

Studies in rats have shown that montelukast is excreted in milk. It is not known if montelukast is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when SINGULAIR is given to a nursing mother.

8.4 Pediatric Use

Safety and efficacy of SINGULAIR have been established in adequate and well-controlled studies in pediatric patients with asthma 6 to 14 years of age. Safety and efficacy profiles in this age group are similar to those seen in adults *[see Adverse Reactions (6.1), Clinical Pharmacology, Special Populations (12.3), and Clinical Studies (14.1)]*.

The efficacy of SINGULAIR for the treatment of seasonal allergic rhinitis in pediatric patients 2 to 14 years of age and for the treatment of perennial allergic rhinitis in pediatric patients 6 months to 14 years of age is supported by extrapolation from the demonstrated efficacy in patients 15 years of age

and older with allergic rhinitis as well as the assumption that the disease course, pathophysiology and the drug's effect are substantially similar among these populations.

The safety of SINGULAIR 4-mg chewable tablets in pediatric patients 2 to 5 years of age with asthma has been demonstrated by adequate and well-controlled data *[see Adverse Reactions (6.1)]*. Efficacy of SINGULAIR in this age group is extrapolated from the demonstrated efficacy in patients 6 years of age and older with asthma and is based on similar pharmacokinetic data, as well as the assumption that the disease course, pathophysiology and the drug's effect are substantially similar among these populations. Efficacy in this age group is supported by exploratory efficacy assessments from a large, well-controlled safety study conducted in patients 2 to 5 years of age.

The safety of SINGULAIR 4-mg oral granules in pediatric patients 12 to 23 months of age with asthma has been demonstrated in an analysis of 172 pediatric patients, 124 of whom were treated with SINGULAIR, in a 6-week, double-blind, placebo-controlled study *[see Adverse Reactions (6.1)]*. Efficacy of SINGULAIR in this age group is extrapolated from the demonstrated efficacy in patients 6 years of age and older with asthma based on similar mean systemic exposure (AUC), and that the disease course, pathophysiology and the drug's effect are substantially similar among these populations, supported by efficacy data from a safety trial in which efficacy was an exploratory assessment.

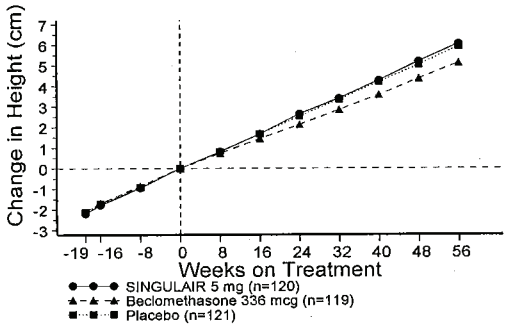
The safety of SINGULAIR 4-mg and 5-mg chewable tablets in pediatric patients aged 2 to 14 years with allergic rhinitis is supported by data from studies conducted in pediatric patients aged 2 to 14 years with asthma. A safety study in pediatric patients 2 to 14 years of age with seasonal allergic rhinitis demonstrated a similar safety profile *[see Adverse Reactions (6.1)]*. The safety of SINGULAIR 4-mg oral granules in pediatric patients as young as 6 months of age with perennial allergic rhinitis is supported by extrapolation from safety data obtained from studies conducted in pediatric patients 6 months to 23 months of age with asthma and from pharmacokinetic data comparing systemic exposures in patients 6 months to 23 months of age to systemic exposures in adults.

The safety and effectiveness in pediatric patients below the age of 12 months with asthma and 6 months with perennial allergic rhinitis have not been established. The safety and effectiveness in pediatric patients below the age of 15 years with exercise-induced bronchoconstriction have not been established.

Growth Rate in Pediatric Patients

A 56-week, multi-center, double-blind, randomized, active- and placebo-controlled parallel group study was conducted to assess the effect of SINGULAIR on growth rate in 360 patients with mild asthma, aged 6 to 8 years. Treatment groups included SINGULAIR 5 mg once daily, placebo, and beclomethasone dipropionate administered as 168 mcg twice daily with a spacer device. For each subject, a growth rate was defined as the slope of a linear regression line fit to the height measurements over 56 weeks. The primary comparison was the difference in growth rates between SINGULAIR and placebo groups. Growth rates, expressed as least-squares (LS) mean (95% CI) in cm/year, for the SINGULAIR, placebo, and beclomethasone treatment groups were 5.67 (5.46, 5.88), 5.64 (5.42, 5.86), and 4.86 (4.64, 5.08), respectively. The differences in growth rates, expressed as least-squares (LS) mean (95% CI) in cm/year, for SINGULAIR minus placebo, beclomethasone minus placebo, and SINGULAIR minus beclomethasone treatment groups were 0.03 (-0.26, 0.31), -0.78 (-1.06, -0.49); and 0.81 (0.53, 1.09), respectively. Growth rate (expressed as mean change in height over time) for each treatment group is shown in FIGURE 1.

FIGURE 1
Change in Height (cm) from Randomization Visit by Scheduled Week
(Treatment Group Mean ± Standard Error† of the Mean)



[†]The standard errors of the treatment group means in change in height are too small to be visible on the plot

8.5 Geriatric Use

Of the total number of subjects in clinical studies of montelukast, 3.5% were 65 years of age and over, and 0.4% were 75 years of age and over. No overall differences in safety or effectiveness were observed between these subjects and younger subjects, and other reported clinical experience has not identified differences in responses between the elderly and younger patients, but greater sensitivity of some older individuals cannot be ruled out. 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.

8.6 Hepatic Insufficiency

No dosage adjustment is required in patients with mild-to-moderate hepatic insufficiency *[see Clinical Pharmacology (12.3)]*.

8.7 Renal Insufficiency

No dosage adjustment is recommended in patients with renal insufficiency *[see Clinical Pharmacology (12.3)]*.

10 OVERDOSAGE

No mortality occurred following single oral doses of montelukast up to 5000 mg/kg in mice (estimated exposure was approximately 335 and 210 times the AUC for adults and children, respectively, at the maximum recommended daily oral dose) and rats (estimated exposure was approximately 230 and 145 times the AUC for adults and children, respectively, at the maximum recommended daily oral dose).

No specific information is available on the treatment of overdosage with SINGULAIR. In chronic asthma studies, montelukast has been administered at doses up to 200 mg/day to adult patients for 22 weeks and, in short-term studies, up to 900 mg/day to patients for approximately a week without clinically important adverse experiences. In the event of overdose, it is reasonable to employ the usual supportive measures; e.g., remove unabsorbed material from the gastrointestinal tract, employ clinical monitoring, and institute supportive therapy, if required.

There have been reports of acute overdosage in post-marketing experience and clinical studies with SINGULAIR. 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 overdosage reports. The most frequently occurring adverse experiences were consistent with the safety profile of SINGULAIR and included abdominal pain, somnolence, thirst, headache, vomiting and psychomotor hyperactivity.

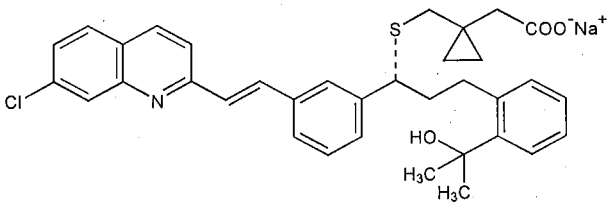
It is not known whether montelukast is removed by peritoneal dialysis or hemodialysis.

11 DESCRIPTION

Montelukast sodium, the active ingredient in SINGULAIR, is a selective and orally active leukotriene receptor antagonist that inhibits the cysteinyl leukotriene $CysLT_1$ receptor.

Montelukast sodium is described chemically as [*R*-(*E*)]-1-[[[1-[3-[2-(7-chloro-2-quinolinyl)ethenyl]phenyl]-3-[2-(1-hydroxy-1-methylethyl)phenyl]propyl]thio]methyl]cyclopropaneacetic acid, monosodium salt.

The empirical formula is $C_{35}H_{35}ClNNaO_3S$, 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 SINGULAIR tablet contains 10.4 mg montelukast sodium, which is equivalent to 10 mg of montelukast, and the following inactive ingredients: microcrystalline cellulose, lactose monohydrate, croscarmellose sodium, hydroxypropyl cellulose, and magnesium stearate. The film coating consists of: hydroxypropyl methylcellulose, hydroxypropyl cellulose, titanium dioxide, red ferric oxide, yellow ferric oxide, and carnauba wax.

Each 4-mg and 5-mg chewable SINGULAIR tablet 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: mannitol, microcrystalline cellulose, hydroxypropyl cellulose, red ferric oxide, croscarmellose sodium, cherry flavor, aspartame, and magnesium stearate.

Each packet of SINGULAIR 4-mg oral granules contains 4.2 mg montelukast sodium, which is equivalent to 4 mg of montelukast. The oral granule formulation contains the following inactive ingredients: mannitol, hydroxypropyl cellulose, and magnesium stearate.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

The cysteinyl leukotrienes (LTC_4, LTD_4, LTE_4) are products of arachidonic acid metabolism and are released from various cells, including mast cells and eosinophils. These eicosanoids bind to cysteinyl leukotriene (CysLT) receptors. The CysLT type-1 ($CysLT_1$) receptor is found in the human airway (including airway smooth muscle cells and airway macrophages) and on other pro-inflammatory cells (including eosinophils and certain myeloid stem cells). CysLTs have been correlated with the pathophysiology of asthma and allergic rhinitis. In asthma, leukotriene-mediated effects include airway edema, smooth muscle contraction, and altered cellular activity associated with the inflammatory process. 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.

Montelukast is an orally active compound that binds with high affinity and selectivity to the $CysLT_1$ receptor (in preference to other pharmacologically important airway receptors, such as the prostanoid, cholinergic, or β-adrenergic receptor). Montelukast inhibits physiologic actions of LTD_4 at the $CysLT_1$ receptor without any agonist activity.

12.2 Pharmacodynamics

Montelukast causes inhibition of airway cysteinyl leukotriene receptors as demonstrated by the ability to inhibit bronchoconstriction due to inhaled LTD_4 in asthmatics. Doses as low as 5 mg cause substantial blockage of LTD_4-induced bronchoconstriction. In a placebo-controlled, crossover study (n=12),

SINGULAIR inhibited early- and late-phase bronchoconstriction due to antigen challenge by 75% and 57%, respectively.

The effect of SINGULAIR on eosinophils in the peripheral blood was examined in clinical trials. In patients with asthma aged 2 years and older who received SINGULAIR, a decrease in mean peripheral blood eosinophil counts ranging from 9% to 15% was noted, compared with placebo, over the double-blind treatment periods. In patients with seasonal allergic rhinitis aged 15 years and older who received SINGULAIR, a mean increase of 0.2% in peripheral blood eosinophil counts was noted, compared with a mean increase of 12.5% in placebo-treated patients, over the double-blind treatment periods; this reflects a mean difference of 12.3% in favor of SINGULAIR. The relationship between these observations and the clinical benefits of montelukast noted in the clinical trials is not known *[see Clinical Studies (14)]*.

12.3 Pharmacokinetics

Absorption

Montelukast is rapidly absorbed following oral administration. After administration of the 10-mg film-coated tablet to fasted adults, the mean peak montelukast plasma concentration (C_{max}) is achieved in 3 to 4 hours (T_{max}). The mean oral bioavailability is 64%. The oral bioavailability and C_{max} are not influenced by a standard meal in the morning.

For the 5-mg chewable tablet, the mean C_{max} is achieved in 2 to 2.5 hours after administration to adults in the fasted state. The mean oral bioavailability is 73% in the fasted state versus 63% when administered with a standard meal in the morning.

For the 4-mg chewable tablet, the mean C_{max} is achieved 2 hours after administration in pediatric patients 2 to 5 years of age in the fasted state.

The 4-mg oral granule formulation is bioequivalent to the 4-mg chewable tablet when administered to adults in the fasted state. The co-administration of the oral granule formulation with applesauce did not have a clinically significant effect on the pharmacokinetics of montelukast. A high fat meal in the morning did not affect the AUC of montelukast oral granules; however, the meal decreased C_{max} by 35% and prolonged T_{max} from 2.3 ± 1.0 hours to 6.4 ± 2.9 hours.

The safety and efficacy of SINGULAIR in patients with asthma were demonstrated in clinical trials in which the 10-mg film-coated tablet and 5-mg chewable tablet formulations were administered in the evening without regard to the time of food ingestion. The safety of SINGULAIR in patients with asthma was also demonstrated in clinical trials in which the 4-mg chewable tablet and 4-mg oral granule formulations were administered in the evening without regard to the time of food ingestion. The safety and efficacy of SINGULAIR in patients with seasonal allergic rhinitis were demonstrated in clinical trials in which the 10-mg film-coated tablet was administered in the morning or evening without regard to the time of food ingestion.

The comparative pharmacokinetics of montelukast when administered as two 5-mg chewable tablets versus one 10-mg film-coated tablet have not been evaluated.

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 CYP3A4 and 2C9 are involved in the metabolism of montelukast. Clinical studies investigating the effect of known inhibitors of CYP3A4 (e.g., ketoconazole, erythromycin) or 2C9 (e.g., fluconazole) on montelukast pharmacokinetics have not been conducted. Based on further *in vitro* results in human liver microsomes, therapeutic plasma concentrations of montelukast do not inhibit CYP3A4, 2C9, 1A2, 2A6, 2C19, or 2D6 *[see Drug Interactions (7) and Clinical Pharmacology, Drug-Drug Interactions (12.3)]*. *In vitro* studies have shown that montelukast is a potent inhibitor of CYP2C8; however, data from a clinical drug-drug interaction study involving montelukast and rosiglitazone (a probe substrate representative of drugs primarily metabolized by CYP2C8) demonstrated that montelukast does not inhibit CYP2C8 *in vivo,* and therefore is not

anticipated to alter the metabolism of drugs metabolized by this enzyme *[see Drug Interactions (7) and Clinical Pharmacology, Drug-Drug Interactions (12.3)]*.

Elimination

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 that 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. During once-daily dosing with 10-mg montelukast, there is little accumulation of the parent drug in plasma (14%).

Special Populations

Hepatic Insufficiency: Patients with mild-to-moderate hepatic insufficiency and clinical evidence of cirrhosis had evidence of decreased metabolism of montelukast resulting in 41% (90% CI=7%, 85%) higher mean montelukast AUC following a single 10-mg dose. The elimination of montelukast was 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. The pharmacokinetics of SINGULAIR in patients with more severe hepatic impairment or with hepatitis have not been evaluated.

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.

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

Race: Pharmacokinetic differences due to race have not been studied.

Adolescents and Pediatric Patients: Pharmacokinetic studies evaluated the systemic exposure of the 4-mg oral granule formulation in pediatric patients 6 to 23 months of age, the 4-mg chewable tablets in pediatric patients 2 to 5 years of age, the 5-mg chewable tablets in pediatric patients 6 to 14 years of age, and the 10-mg film-coated tablets in young adults and adolescents ≥15 years of age.

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

The mean systemic exposure of the 4-mg chewable tablet in pediatric patients 2 to 5 years of age and the 5-mg chewable tablets in pediatric patients 6 to 14 years of age is similar to the mean systemic exposure of the 10-mg film-coated tablet in adults. The 5-mg chewable tablet should be used in pediatric patients 6 to 14 years of age and the 4-mg chewable tablet should be used in pediatric patients 2 to 5 years of age.

In children 6 to 11 months of age, the systemic exposure to montelukast and the variability of plasma montelukast concentrations were higher than those observed in adults. Based on population analyses, the mean AUC (4296 ng•hr/mL [range 1200 to 7153]) was 60% higher and the mean C_{max} (667 ng/mL [range 201 to 1058]) was 89% higher than those observed in adults (mean AUC 2689 ng•hr/mL [range 1521 to 4595]) and mean C_{max} (353 ng/mL [range 180 to 548]). The systemic exposure in children 12 to 23 months of age was less variable, but was still higher than that observed in adults. The mean AUC (3574 ng•hr/mL [range 2229 to 5408]) was 33% higher and the mean C_{max} (562 ng/mL [range 296 to 814]) was 60% higher than those observed in adults. Safety and tolerability of montelukast in a single-dose pharmacokinetic study in 26 children 6 to 23 months of age were similar to that of patients two years and above *[see Adverse Reactions (6.1)]*. The 4-mg oral granule formulation should be used for pediatric patients 12 to 23 months of age for the treatment of asthma, or for pediatric patients 6 to 23 months of age for the treatment of perennial allergic rhinitis. Since the 4-mg oral granule formulation is bioequivalent to the 4-mg chewable tablet, it can also be used as an alternative formulation to the 4-mg chewable tablet in pediatric patients 2 to 5 years of age.

Drug-Drug Interactions

Theophylline, Prednisone, and Prednisolone: SINGULAIR has been administered with other therapies routinely used in the prophylaxis and chronic treatment of asthma with no apparent increase in adverse reactions. In drug-interaction studies, the recommended clinical dose of montelukast did not have clinically

important effects on the pharmacokinetics of the following drugs: theophylline, prednisone, and prednisolone.

Montelukast at a dose of 10 mg once daily dosed to pharmacokinetic steady state, did not cause clinically significant changes in the kinetics of a single intravenous dose of theophylline [predominantly a cytochrome P450 (CYP) 1A2 substrate]. Montelukast at doses of ≥100 mg daily dosed to pharmacokinetic steady state, did not cause any clinically significant change in plasma profiles of prednisone or prednisolone following administration of either oral prednisone or intravenous prednisolone.

Oral Contraceptives, Terfenadine, Digoxin, and Warfarin: In drug interaction studies, the recommended clinical dose of montelukast did not have clinically important effects on the pharmacokinetics of the following drugs: oral contraceptives (norethindrone 1 mg/ethinyl estradiol 35 mcg), terfenadine, digoxin, and warfarin. Montelukast at doses of ≥100 mg daily dosed 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. Montelukast at a dose of 10 mg once daily dosed to pharmacokinetic steady state did not change the plasma concentration profile of terfenadine (a substrate of CYP3A4) or fexofenadine, the carboxylated metabolite, and did not prolong the QTc interval following co-administration with terfenadine 60 mg twice daily; did not change the pharmacokinetic profile or urinary excretion of immunoreactive digoxin; did not change the pharmacokinetic profile of warfarin (primarily a substrate of CYP2C9, 3A4 and 1A2) or influence the effect of a single 30-mg oral dose of warfarin on prothrombin time or the International Normalized Ratio (INR).

Thyroid Hormones, Sedative Hypnotics, Non-Steroidal Anti-Inflammatory Agents, Benzodiazepines, and Decongestants: Although additional specific interaction studies were not performed, SINGULAIR 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, non-steroidal anti-inflammatory agents, benzodiazepines, and decongestants.

Cytochrome P450 (CYP) Enzyme Inducers: Phenobarbital, which induces hepatic metabolism, decreased the area under the plasma concentration curve (AUC) of montelukast approximately 40% following a single 10-mg dose of montelukast. No dosage adjustment for SINGULAIR is recommended. It is reasonable to employ appropriate clinical monitoring when potent CYP enzyme inducers, such as phenobarbital or rifampin, are co-administered with SINGULAIR.

Montelukast is a potent inhibitor of CYP2C8 *in vitro.* However, data from a clinical drug-drug interaction study involving montelukast and rosiglitazone (a probe substrate representative of drugs primarily metabolized by CYP2C8) in 12 healthy individuals demonstrated that the pharmacokinetics of rosiglitazone are not altered when the drugs are coadministered, indicating that montelukast does not inhibit CYP2C8 *in vivo.* Therefore, montelukast is not anticipated to alter the metabolism of drugs metabolized by this enzyme (e.g., paclitaxel, rosiglitazone, and repaglinide).

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 female 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).

13.2 Animal Toxicology and/or Pharmacology

Reproductive Toxicology Studies

No teratogenicity was observed at oral doses up to 400 mg/kg/day and 300 mg/kg/day in rats and rabbits, respectively. These doses were approximately 100 and 110 times the maximum recommended daily oral dose in adults, respectively, based on AUCs. Montelukast crosses the placenta following oral dosing in rats and rabbits *[see Pregnancy (8.1)]*.

14 CLINICAL STUDIES

14.1 Asthma

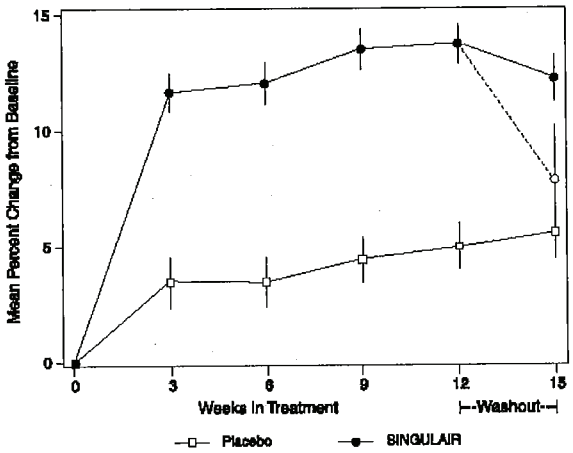
Adults and Adolescents 15 Years of Age and Older with Asthma

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 SINGULAIR 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 1576 patients (795 treated with SINGULAIR, 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 β-agonist per day on an "as-needed" basis. The patients had a mean baseline percent of predicted forced expiratory volume in 1 second (FEV_1) of 66% (approximate range, 40 to 90%). The co-primary endpoints in these trials were FEV_1 and daytime asthma symptoms. In both studies after 12 weeks, a random subset of patients receiving SINGULAIR was switched to placebo for an additional 3 weeks of double-blind treatment to evaluate for possible rebound effects.

The results of the U.S. trial on the primary endpoint, morning FEV_1, 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 SINGULAIR 10-mg tablet daily in the evening resulted in a statistically significant increase in FEV_1 percent change from baseline (13.0%-change in the group treated with SINGULAIR vs. 4.2%-change in the placebo group, $p<0.001$); the change from baseline in FEV_1 for SINGULAIR 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 FEV_1 were similar.

FIGURE 2
FEV_1 Mean Percent Change from Baseline
(U.S. Trial: SINGULAIR N=406; Placebo N=270)
(ANOVA Model)



The effect of SINGULAIR on other primary and secondary endpoints, represented by the Multinational study is shown in TABLE 2. Results on these endpoints were similar in the US study.

TABLE 2
Effect of SINGULAIR on Primary and Secondary Endpoints
in a Multinational Placebo-controlled Trial
(ANOVA Model)

	SINGULAIR			Placebo		
Endpoint	N	Baseline	Mean Change from Baseline	N	Baseline	Mean Change from Baseline
Daytime Asthma Symptoms (0 to 6 scale)	372	2.35	-0.49*	245	2.40	-0.26
β-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 (#/week)	285	5.46	-2.03*	195	5.57	-0.78

* p<0.001, compared with placebo

Both studies evaluated the effect of SINGULAIR 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 SINGULAIR experienced asthma attacks compared with patients on placebo (27.3%, $p < 0.001$). In the US study, 7.8% of patients on SINGULAIR 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 SINGULAIR 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 SINGULAIR 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 SINGULAIR, measured by daily diary card parameters, including symptom scores, "as-needed" β-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 SINGULAIR 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 SINGULAIR in pediatric patients 6 to 14 years of age was demonstrated in one 8-week, double-blind, placebo-controlled trial in 336 patients (201 treated with SINGULAIR and 135 treated with placebo) using an inhaled β-agonist on an "as-needed" basis. The patients had a mean baseline percent

predicted FEV_1 of 72% (approximate range, 45 to 90%) and a mean daily inhaled β-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); 35.4% were females and 64.6% 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 SINGULAIR chewable tablet daily resulted in a significant improvement in mean morning FEV_1 percent change from baseline (8.7% in the group treated with SINGULAIR vs. 4.2% change from baseline in the placebo group, $p<0.001$). There was a significant decrease in the mean percentage change in daily "as-needed" inhaled β-agonist use (11.7% decrease from baseline in the group treated with SINGULAIR 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 SINGULAIR 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 SINGULAIR. 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 SINGULAIR in this age group, the study included exploratory efficacy evaluations, including daytime and overnight asthma symptom scores, β-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 SINGULAIR is efficacious in the maintenance treatment of asthma in patients 2 to 5 years of age.

Effects in Patients on Concomitant Inhaled Corticosteroids

Separate trials in adults evaluated the ability of SINGULAIR 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 FEV_1 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 92.0% 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, 1203 mcg/day), triamcinolone acetonide (mean dose, 2004 mcg/day), flunisolide (mean dose, 1971 mcg/day), fluticasone propionate (mean dose, 1083 mcg/day), or budesonide (mean dose, 1192 mcg/day). Some of these inhaled corticosteroids were non-U.S.-approved formulations, and doses expressed may not be ex-actuator. 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 SINGULAIR 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 ($p\leq0.05$). 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 previously maintained, but not adequately controlled, on inhaled corticosteroids (beclomethasone 336 mcg/day), the addition of SINGULAIR to beclomethasone resulted in statistically significant improvements in FEV_1 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 SINGULAIR alone or placebo alone as indicated by FEV_1, daytime asthma symptoms, PEFR, nocturnal awakenings due to asthma, and "as-needed" β-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 SINGULAIR, compared with placebo, resulted in significant improvement in parameters of asthma control. The magnitude of effect of SINGULAIR in aspirin-sensitive patients was similar to the effect observed in the general population of asthma patients studied. The effect of SINGULAIR on the bronchoconstrictor response to aspirin or other non-steroidal anti-inflammatory drugs in aspirin-sensitive asthmatic patients has not been evaluated *[see Warnings and Precautions (5.3)]*.

14.2 Exercise-Induced Bronchoconstriction (EIB)

Exercise-Induced Bronchoconstriction - Single-Dose Administration (Adults and Adolescents 15 years of age and older)

The efficacy of SINGULAIR, 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 (SINGULAIR 10 mg or placebo). The primary endpoint was the mean maximum percent fall in FEV_1 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 SINGULAIR 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 3 and are representative of the results from the other two studies.

TABLE 3
Mean Maximum Percent Fall in FEV_1 Following Exercise Challenge in Study A (N=47)
ANOVA Model

Time of exercise challenge following medication administration	Mean Maximum percent fall in FEV_1*		Treatment difference % for SINGULAIR versus Placebo (95%CI)*
	SINGULAIR	Placebo	
2 hours	13	22	-9 (-12, -5)
8.5 hours	12	17	-5 (-9, -2)
24 hours	10	14	-4 (-7, -1)

*Least squares-mean

Daily administration of SINGULAIR for the chronic treatment of asthma has not been established to prevent acute episodes of EIB. The efficacy of SINGULAIR for prevention of EIB in patients below 15 years of age has not been established.

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 FEV_1 percent of predicted of 83% and with documented exercise-induced exacerbation of asthma, treatment with SINGULAIR, 10 mg, once daily in the evening, resulted in a statistically significant reduction in mean maximal percent fall in FEV_1 and mean time to recovery to within 5% of the pre-exercise FEV_1. 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 indicating that tolerance did not occur. SINGULAIR did not, however, prevent clinically significant deterioration in maximal percent fall in FEV_1 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 SINGULAIR.

In pediatric patients 6 to 14 years of age, using the 5-mg chewable tablet, a 2-day crossover study demonstrated effects similar to those observed in adults when exercise challenge was conducted at the end of the dosing interval (i.e., 20 to 24 hours after the preceding dose).

14.3 Allergic Rhinitis (Seasonal and Perennial)

Seasonal Allergic Rhinitis

The efficacy of SINGULAIR 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 5029 patients, of whom 1799 were treated with SINGULAIR 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 0-3 categorical scale.

Four of the five trials showed a significant reduction in daytime nasal symptoms scores with SINGULAIR 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 SINGULAIR tablets, loratadine, and placebo are shown in TABLE 4. The remaining three trials that demonstrated efficacy showed similar results.

TABLE 4
Effects of SINGULAIR on Daytime Nasal Symptoms Score* in a Placebo- and Active-controlled Trial in Patients with Seasonal Allergic Rhinitis (ANCOVA Model)

Treatment Group (N)	Baseline Mean Score	Mean Change from Baseline	Difference Between Treatment and Placebo (95% CI) Least-Squares Mean
SINGULAIR 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 0-3 categorical scale.
† The study was not designed for statistical comparison between SINGULAIR and the active control (loratadine).
‡ Statistically different from placebo ($p \leq 0.001$).

Perennial Allergic Rhinitis

The efficacy of SINGULAIR 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 3357 patients, of whom 1632 received SINGULAIR 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. SINGULAIR 10-mg tablets once daily was shown to significantly reduce symptoms of perennial allergic rhinitis over a 6-week treatment period

(TABLE 5); 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 5
Effects of SINGULAIR on Daytime Nasal Symptoms Score* in a Placebo-controlled Trial in Patients with Perennial Allergic Rhinitis (ANCOVA Model)

Treatment Group (N)	Baseline Mean Score	Mean Change from Baseline	Difference Between Treatment and Placebo (95% CI) Least-Squares Mean
SINGULAIR 10 mg (1000)	2.09	-0.42	-0.08† (-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 0-3 categorical scale.
† Statistically different from placebo ($p \leq 0.001$).

The other 6-week study evaluated SINGULAIR 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 SINGULAIR vs. placebo over the first 4 weeks of treatment; the study was not designed for statistical comparison between SINGULAIR and the active-control. The primary outcome variable included nasal itching in addition to nasal congestion, rhinorrhea, and sneezing. The estimated difference between SINGULAIR 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

No. 3841 — SINGULAIR Oral Granules, 4 mg, are white granules with 500 mg net weight, packed in a child-resistant foil packet. They are supplied as follows:

NDC 0006-3841-30 unit of use carton with 30 packets.

No. 3796 — SINGULAIR Tablets, 4 mg, are pink, oval, bi-convex-shaped chewable tablets, with code MRK 711 on one side and SINGULAIR on the other. They are supplied as follows:

NDC 0006-0711-31 unit of use high-density polyethylene (HDPE) bottles of 30 with a polypropylene child-resistant cap, an aluminum foil induction seal, and silica gel desiccant

NDC 0006-0711-54 unit of use high-density polyethylene (HDPE) bottles of 90 with a polypropylene child-resistant cap, an aluminum foil induction seal, and silica gel desiccant

NDC 0006-0711-28 unit dose paper and aluminum foil-backed aluminum foil peelable blister packs of 100.

No. 3760 — SINGULAIR Tablets, 5 mg, are pink, round, bi-convex-shaped chewable tablets, with code MRK 275 on one side and SINGULAIR on the other. They are supplied as follows:

NDC 0006-0275-31 unit of use high-density polyethylene (HDPE) bottles of 30 with a polypropylene child-resistant cap, an aluminum foil induction seal, and silica gel desiccant

NDC 0006-0275-54 unit of use high-density polyethylene (HDPE) bottles of 90 with a polypropylene child-resistant cap, an aluminum foil induction seal, and silica gel desiccant

NDC 0006-0275-28 unit dose paper and aluminum foil-backed aluminum foil peelable blister packs of 100

NDC 0006-0275-82 bulk packaging high-density polyethylene (HDPE) bottles of 1000 with a non-child-resistant white plastic closure with a wax paper/pulp liner, an aluminum foil induction seal, and silica gel desiccant.

No. 3761 — SINGULAIR Tablets, 10 mg, are beige, rounded square-shaped, film-coated tablets, with code MRK 117 on one side and SINGULAIR on the other. They are supplied as follows:

NDC 0006-0117-31 unit of use high-density polyethylene (HDPE) bottles of 30 with a polypropylene child-resistant cap, an aluminum foil induction seal, and silica gel desiccant

NDC 0006-0117-54 unit of use high-density polyethylene (HDPE) bottles of 90 with a polypropylene child-resistant cap, an aluminum foil induction seal, and silica gel desiccant

NDC 0006-0117-28 unit dose paper and aluminum foil-backed aluminum foil peelable blister pack of 100

NDC 0006-0117-80 bulk packaging high-density polyethylene (HDPE) bottles of 8000 with a non-child-resistant white plastic closure with a wax paper/pulp liner, an aluminum foil induction seal, and silica gel desiccant.

Storage

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

Storage for Bulk Bottles

Store bottles of 1000 SINGULAIR 5-mg chewable tablets and 8000 SINGULAIR 10-mg film-coated tablets at 25°C (77°F), excursions permitted to 15-30°C (59-86°F) [see USP Controlled Room Temperature]. Protect from moisture and light. Store in original container. When product container is subdivided, repackage into a well-closed, light-resistant container.

17 PATIENT COUNSELING INFORMATION

[See FDA-Approved Patient Labeling (17.2).]

17.1 Information for Patients

- Patients should be advised to take SINGULAIR 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.
- Patients should be advised that oral SINGULAIR is not for the treatment of acute asthma attacks. They should have appropriate short-acting inhaled β-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 β-agonist. Daily administration of SINGULAIR for the chronic treatment of asthma has not been established to prevent acute episodes of EIB.
- Patients should be advised that, while using SINGULAIR, medical attention should be sought 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.
- Patients receiving SINGULAIR should be instructed not to decrease the dose or stop taking any other anti-asthma medications unless instructed by a physician.
- Patients should be instructed to notify their physician if neuropsychiatric events occur while using SINGULAIR.
- Patients with known aspirin sensitivity should be advised to continue avoidance of aspirin or non-steroidal anti-inflammatory agents while taking SINGULAIR.

17.2 FDA-Approved Patient Labeling

See the full patient prescribing information for SINGULAIR.

US Patent No.: 5,565,473

Dist. by: Merck Sharp & Dohme Corp., a subsidiary of
MERCK & CO., INC., Whitehouse Station, NJ 08889, USA

Issued May 2010

9989618

Patient Information
SINGULAIR® (SING-u-lair)
(montelukast sodium)
Tablets

SINGULAIR®
(montelukast sodium)
Chewable Tablets

SINGULAIR®
(montelukast sodium)
Oral Granules

Read the Patient Information Leaflet that comes with SINGULAIR before you start taking it and each time you get a refill. There may be new information. This leaflet does not take the place of talking with your healthcare provider about your medical condition or your treatment.

What is SINGULAIR?

- SINGULAIR is a prescription medicine that blocks substances in the body called leukotrienes. This may help to improve symptoms of asthma and allergic rhinitis. SINGULAIR does not contain a steroid.

SINGULAIR is used to:

1. Prevent asthma attacks and for the long-term treatment of asthma in adults and children ages 12 months and older.
   Do not take SINGULAIR if you need relief right away for a sudden asthma attack. If you get an asthma attack, you should follow the instructions your healthcare provider gave you for treating asthma attacks.

2. Prevent exercise-induced asthma in people 15 years of age and older.

3. Help control the symptoms of allergic rhinitis (sneezing, stuffy nose, runny nose, itching of the nose). SINGULAIR is used to treat:
   - outdoor allergies that happen part of the year (seasonal allergic rhinitis) in adults and children ages 2 years and older, **and**
   - indoor allergies that happen all year (perennial allergic rhinitis) in adults and children ages 6 months and older.

Who should not take SINGULAIR?

Do not take SINGULAIR if you are allergic to any of its ingredients.

See the end of this leaflet for a complete list of the ingredients in SINGULAIR.

What should I tell my healthcare provider before taking SINGULAIR?

Before taking SINGULAIR, tell your healthcare provider if you:
- are allergic to aspirin
- have phenylketonuria. SINGULAIR chewable tablets contain aspartame, a source of phenylalanine

- have any other medical conditions
- are pregnant or plan to become pregnant. If you are pregnant or plan to become pregnant, SINGULAIR may not be right for you. If you become pregnant while taking SINGULAIR, talk to your healthcare provider about reporting your pregnancy to the Pregnancy Registry for SINGULAIR, or you can enroll in this registry by calling 1-800-986-8999.
- are breast-feeding or plan to breast-feed. It is not known if SINGULAIR passes into your breast milk. Talk to your healthcare provider about the best way to feed your baby while taking SINGULAIR.

Tell your healthcare provider about all the medicines you take, including prescription and non-prescription medicines, vitamins, and herbal supplements. Some medicines may affect how SINGULAIR works, or SINGULAIR may affect how your other medicines work.

How should I take SINGULAIR?

For anyone who takes SINGULAIR:

- Take SINGULAIR exactly as prescribed by your healthcare provider. Your healthcare provider will tell you how much SINGULAIR to take, and **when to take it.**
- Do not stop taking SINGULAIR or change when you take it without talking with your healthcare provider.
- You can take SINGULAIR with food or without food. See the information below in the section "How should I give SINGULAIR oral granules to my child?" for information about what foods and liquids can be taken with SINGULAIR oral granules.
- **If you or your child misses a dose of SINGULAIR, just take the next dose at your regular time.** Do not take 2 doses at the same time.
- If you take too much SINGULAIR, call your doctor.

For adults and children 12 months of age and older with asthma:

- Take SINGULAIR 1 time each day, in the evening. Continue to take SINGULAIR every day for as long as your healthcare provider prescribes it, even if you have no asthma symptoms.
- Tell your healthcare provider right away if your asthma symptoms get worse, or if you need to use your rescue inhaler medicine more often for asthma attacks.
- **Do not take SINGULAIR if you need relief right away from a sudden asthma attack.** If you get an asthma attack, you should follow the instructions your healthcare provider gave you for treating asthma attacks.
- Always have your rescue inhaler medicine with you for asthma attacks.
- Do not stop taking or lower the dose of your other asthma medicines unless your healthcare provider tells you to.

For patients 15 years of age and older for the prevention of exercise-induced asthma:

- Take SINGULAIR at least 2 hours before exercise.
- Always have your rescue inhaler medicine with you for asthma attacks.
- If you take SINGULAIR every day for chronic asthma or allergic rhinitis, **do not** take another dose to prevent exercise-induced asthma. Talk to your healthcare provider about your treatment for exercise-induced asthma.
- **Do not take 2 doses of SINGULAIR within 24 hours (1 day).**

For adults and children 2 years of age and older with seasonal allergic rhinitis, or for adults and children 6 months of age and older with perennial allergic rhinitis:

- Take SINGULAIR 1 time each day, at about the same time each day.

How should I give SINGULAIR oral granules to my child?

Give SINGULAIR oral granules to your child exactly as instructed by your healthcare provider.

Do not open the packet until ready to use.

SINGULAIR 4-mg oral granules can be given:

- right in the mouth; or
- dissolved in 1 teaspoonful (5 mL) of cold or room temperature baby formula or breast milk; or
- mixed with 1 spoonful of one of the following soft foods at cold or room temperature: applesauce, mashed carrots, rice, or ice cream.

Give the child all of the mixture right away, within 15 minutes.

Do not store any leftover SINGULAIR mixture (oral granules mixed with food, baby formula, or breast milk) for use at a later time. Throw away any unused portion.

Do not mix SINGULAIR oral granules with any liquid drink other than baby formula or breast milk. Your child may drink other liquids after swallowing the mixture.

What is the dose of SINGULAIR?

The dose of SINGULAIR prescribed for your or your child's condition is based on age:

- 6 to 23 months: one packet of 4-mg oral granules.
- 2 to 5 years: one 4-mg chewable tablet or one packet of 4-mg oral granules.
- 6 to 14 years: one 5-mg chewable tablet.
- 15 years and older: one 10-mg tablet.

What should I avoid while taking SINGULAIR?

If you have asthma and aspirin makes your asthma symptoms worse, continue to avoid taking aspirin or other medicines called non-steroidal anti-inflammatory drugs (NSAIDs) while taking SINGULAIR.

What are the possible side effects of SINGULAIR?

SINGULAIR may cause serious side effects.

- **Behavior and mood-related changes.** Tell your healthcare provider right away if you or your child have any of these symptoms while taking SINGULAIR:
  - agitation including aggressive behavior or hostility
  - bad or vivid dreams
  - depression
  - disorientation (confusion)
  - feeling anxious
  - hallucinations (seeing or hearing things that are not really there)
  - irritability
  - restlessness
  - sleep walking
  - suicidal thoughts and actions (including suicide)
  - tremor
  - trouble sleeping
- **Increase in certain white blood cells (eosinophils) and possible inflamed blood vessels throughout the body (systemic vasculitis).** Rarely, this can happen in people with asthma who take SINGULAIR. This usually, but not always, happens in people who also take a steroid medicine by mouth that is being stopped or the dose is being lowered.
  Tell your healthcare provider right away if you get one or more of these symptoms:
  - a feeling of pins and needles or numbness of arms or legs

- a flu-like illness
- rash
- severe inflammation (pain and swelling) of the sinuses (sinusitis)

The most common side effects with SINGULAIR include:

- upper respiratory infection
- fever
- headache
- sore throat
- cough
- stomach pain
- diarrhea
- earache or ear infection
- flu
- runny nose
- sinus infection

Other side effects with SINGULAIR include:

- increased bleeding tendency
- allergic reactions [including swelling of the face, lips, tongue, and/or throat (which may cause trouble breathing or swallowing), hives and itching]
- dizziness, drowsiness, pins and needles/numbness, seizures (convulsions or fits)
- palpitations
- nose bleed, stuffy nose
- diarrhea, heartburn, indigestion, inflammation of the pancreas, nausea, stomach or intestinal upset, vomiting
- hepatitis
- bruising, rash
- joint pain, muscle aches and muscle cramps
- tiredness, swelling

Tell your healthcare provider if you have any side effect that bothers you or that does not go away. These are not all the possible side effects of SINGULAIR. For more information ask your healthcare provider or pharmacist.

Call your healthcare provider for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

How should I store SINGULAIR?

- Store SINGULAIR at 59°F to 86°F (15°C to 30°C).
- Keep SINGULAIR in the container it comes in.
- Keep SINGULAIR in a dry place and away from light.

General Information about the safe and effective use of SINGULAIR

Medicines are sometimes prescribed for purposes other than those mentioned in Patient Information Leaflets. Do not use SINGULAIR for a condition for which it was not prescribed. Do not give SINGULAIR to other people even if they have the same symptoms you have. It may harm them. **Keep SINGULAIR and all medicines out of the reach of children.**

This leaflet summarizes information about SINGULAIR. If you would like more information, talk to your healthcare provider. You can ask your pharmacist or healthcare provider for information about SINGULAIR that is written for health professionals. For more information, go to www.singulair.com or call the Merck National Service Center at 1-800-NSC-Merck (1-800-672-6372).

What are the ingredients in SINGULAIR?

Active ingredient: montelukast sodium

Inactive ingredients:

- 4-mg oral granules: mannitol, hydroxypropyl cellulose, and magnesium stearate.
- 4-mg and 5-mg chewable tablets: mannitol, microcrystalline cellulose, hydroxypropyl cellulose, red ferric oxide, croscarmellose sodium, cherry flavor, aspartame, and magnesium stearate.

  People with Phenylketonuria: SINGULAIR 4-mg chewable tablets contain 0.674 mg of phenylalanine, and SINGULAIR 5-mg chewable tablets contain 0.842 mg of phenylalanine.
- 10-mg tablet: microcrystalline cellulose, lactose monohydrate, croscarmellose sodium, hydroxypropyl cellulose, and magnesium stearate. The film coating contains: hydroxypropyl methylcellulose, hydroxypropyl cellulose, titanium dioxide, red ferric oxide, yellow ferric oxide, and carnauba wax.

Dist. by: Merck Sharp & Dohme Corp., a subsidiary of
MERCK & CO., INC., Whitehouse Station, NJ 08889, USA

Issued July 2010
US Patent No.: 5,565,473

9989619

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

020829Orig1s055

OTHER REVIEW(S)

REGULATORY PROJECT MANAGER LABELING REVIEW

Division of Pulmonary and Allergy Products

Application Number: NDA 20-829/S-055
NDA 20-830/S-056
NDA 21-409/S-031

Name of Drug: Singulair Tablets, Chewable Tablets and Oral Granules

Applicant: Merck Sharp & Dohme Corp.

Material Reviewed:

Submission Date: April 14, 2010, May 05, 2010 and July 01, and 12, 2010

Receipt Date(s): April 14, 2010, May 05, 2010 and July 01, and 12, 2010

Type of Labeling Reviewed: WORD/SPL

Background and Summary

These Changes Being Effected labeling Supplements submitted April 14, 2010 and amended on May 05, and July 01, and 12, 2010, provide for the addition of the term "disorientation" to the package insert and the term "disorientation (confusion) to the patient package insert.

Package Insert

1. The term "disorientation" was added to Section 5 WARNINGS AND PRECAUTIONS, under subsection 5.4 Neuropsychiatric Events and to Section 6 ADVERSE REACTIONS, subsection 6.2 Post-Marketing Experience, to the list of psychiatric disorders.

2. In the Highlights section, the addition of new section "RECENT MAJOR CHANGES" with date has been incorporated after the product name.

Patient Package Insert

3. The term disorientation (confusion) was added to the list of behavior and mood-related changes.

The most recently approved package insert was approved on April 26, 2010.

Review

The SPL version (PLR format) of the package insert (9989619) proposed in these CBE labeling supplements was compared to the most recently approved Package Insert and Patient Package Insert Labeling. A fax was sent to Merck recommending the addition of the term "confusion" after the term disorientation to the PPI for a more patient-friendly language. Merck accepted the recommendation. No changes were made to the labeling other than those provided for by these supplements. These supplements were reviewed by Jennifer Pippins, M.D, MPH, Clinical Reviewer, (reviewed July 13, 2010) and were recommended for approval.

Recommendations

Approval

Sadaf Nabavian, Pharm.D.
REGULATORY PROJECT MANAGER

Supervisory Comment/Concurrence:

Sandy Barnes
Chief, Project Management Staff

Drafted: SNabavian/ Revised/Initialed: 07/29/2010
SBarnes/08/04/2010
Finalized: SNabavian/08/10/2010
Filename: CSO Labeling Review Template (updated 1-16-07).doc
CSO LABELING REVIEW

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

SADAF NABAVIAN
08/10/2010

SANDRA L BARNES
09/29/2010

MEDICAL OFFICER REVIEW

Division Of Pulmonary and Allergy Drug Products (HFD-570)

APPLICATION:	NDA 20-829, 20-830, and 21-409	**TRADE NAME:**	Singular
APPLICANT/SPONSOR:	Merck	**USAN NAME:**	Montelukast
MEDICAL OFFICER:	Jennifer Rodriguez Pippins, MD, MPH		
TEAM LEADER:	Susan Limb, MD	**CATEGORY:**	Tablets, Chewable Tablets, and Oral Granules
DATE:	July 13, 2010	**ROUTE:**	Oral

SUBMISSIONS REVIEWED IN THIS DOCUMENT

Document Date	CDER Stamp Date	Submission	Comments
July 12, 2010	July 12, 2010	NDA 20-829, SD# 337	Amendment to CBE labeling supplement
July 12, 2010	July 12, 2010	NDA 20-830, SD# 334	Amendment to CBE labeling supplement
July 12, 2010	July 12, 2010	NDA 21-409, SD# 216	Amendment to CBE labeling supplement
July 1, 2010	July 1, 2010	NDA 20-829, SD# 336	Response to IR
July 1, 2010	July 1, 2010	NDA 20-830, SD# 333	Response to IR
July 1, 2010	July 1, 2010	NDA 21-409, SD# 215	Response to IR
May 5, 2010	May 5, 2010	NDA 20-829, SD# 333	Amendment to CBE labeling supplement
May 5, 2010	May 5, 2010	NDA 20-830, SD #331	Amendment to CBE labeling supplement
May 5, 2010	May 5, 2010	NDA 21-409, SD# 213	Amendment to CBE labeling supplement

RELATED APPLICATIONS

Document Date	Application Type	Comments
April 14, 2010	NDA 20-829, SD # 331	CBE labeling supplement
April 14, 2010	NDA 20-830, SD # 329	CBE labeling supplement
April 14, 2010	NDA 21-409, SD # 212	CBE labeling supplement

REVIEW SUMMARY:

MEDICAL OFFICER REVIEW

Division Of Pulmonary and Allergy Drug Products (HFD-570)

This is a medical officer review of a Changes Being Effected (CBE) Supplement submitted for the addition of the term "disorientation" to the labeling for Singulair Tablets (NDA 20-829), Chewable Tables (NDA 20-830), and Oral Granules (NDA 21-409). The original labeling supplement was submitted on April 14, 2010. Following the April 26, 2010, approval of the labeling conversion to the Physician Labeling Rule (PLR) format, the Applicant submitted an amendment to the CBE labeling supplement dated May 5, 2010, which submitted the proposed changes in the PLR format. The Applicant provided responses to an Information Request (IR) in a July 1, 2010, submission.

The Applicant proposes the addition of the term "disorientation" to the package insert (PI), in WARNINGS AND PRECAUTIONS under the subsection Neuropsychiatric Events, as well as to the Post-Marketing Experience subsection of ADVERSE REACTIONS, where it is grouped with related terms under the System Organ Classification of psychiatric disorders. In addition to the changes submitted for the PI, the Applicant also proposes the addition of the term "disorientation" to the patient package insert (PPI) under the section titled, "What are the possible side effects of SINGULAIR?" in the "Behavior and mood-related changes" subsection. The list of 84 Merck Worldwide Adverse Experience System (WAES) reports previously submitted to the FDA and 55 WAES reports not previously submitted supporting the addition of the term to the PI and PPI are provided in the supplement.

Both the Division of Pharmacovigilance I (DPV I) and the Division of Risk Management (DRISK) in the Office of Surveillance and Epidemiology were consulted regarding this submission, and both Divisions supported the addition of the term "disorientation." In addition, DRISK recommended the addition of the patient-friendly term "confusion" as a parenthetical statement to the PPI. The Applicant submitted this revision in a submission dated July 12, 2010.

Upon clinical review, the changes to the PI and PPI appear appropriate. No additional clinical issues are identified. A detailed description of the proposed changes is provided and full copies of the agreed upon versions of the PI and PPI are attached. The recommendation for this labeling supplement is Approval.

OUTSTANDING ISSUES: None

RECOMMENDED REGULATORY ACTION

NDA LABEL SUPPLEMENT: X APPROVAL ___ COMPLETE RESPONSE

1. Background

This is a medical officer review of a Changes Being Effected (CBE) Supplement submitted for the addition of the term "disorientation" to the labeling for Singulair Tablets (NDA 20-829), Chewable Tables (NDA 20-830), and Oral Granules (NDA 21-409). The original labeling supplement was submitted on April 14, 2010. Following the April 26, 2010, approval of the labeling conversion to the Physician Labeling Rule (PLR) format, the Applicant submitted an amendment to the CBE labeling supplement dated May 5, 2010, which submitted the proposed changes in the PLR format.

2. Originally Proposed Changes

The Applicant proposes the addition of the term "disorientation" to the package insert (PI), in WARNINGS AND PRECAUTIONS under the subsection Neuropsychiatric Events, as well as to the Post-Marketing Experience subsection of ADVERSE REACTIONS, where it is grouped with related terms under the System Organ Classification of psychiatric disorders, as follows:

PI

5 WARNINGS AND PRECAUTIONS

5.4 Neuropsychiatric Events

Neuropsychiatric events have been reported in adult, adolescent, and pediatric patients taking SINGULAIR. Post-marketing reports with SINGULAIR use include agitation, aggressive behavior or hostility, anxiousness, depression, disorientation, dream abnormalities, hallucinations, insomnia, irritability, restlessness, somnambulism, suicidal thinking and behavior (including suicide), and tremor. The clinical details of some post-marketing reports involving SINGULAIR appear consistent with a drug-induced effect.

Patients and prescribers should be alert for neuropsychiatric events. Patients should be instructed to notify their prescriber if these changes occur. Prescribers should carefully evaluate the risks and benefits of continuing treatment with SINGULAIR if such events occur *[see Adverse Reactions (6.2)].*

6 ADVERSE REACTIONS

6.2 Post-Marketing Experience

The following adverse reactions have been identified during post-approval use of SINGULAIR. 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.

Immune system disorders: hypersensitivity reactions including anaphylaxis, hepatic esoinophilic infiltration.

Psychiatric disorders: agitation including aggressive behavior or hostility, anxiousness, depression, disorientation, dream abnormalities, hallucinations, insomnia, irritability, restlessness, somnambulism, suicidal thinking and behavior (including suicide), tremor *[see Warnings and Precautions (5.4)].*

Nervous system disorders: drowsiness, paraesthesia/hypoesthesia, seizures.

Cardiac disorders: palpitations.

Respiratory, thoracic and mediastinal disorders: epistaxis.

Gastrointestinal disorders: diarrhea, dyspepsia, nausea, pancreatitis, vomiting.

Hepatobiliary disorders: Cases of cholestatic hepatitis, hepatocellular liver-injury, and mixed-pattern liver injury have been reported in patients treated with SINGULAIR. Most of these occurred in combination with other confounding factors, such as the use of other mediations, or when SINGULAIR 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 nodosum, pruritus, urticaria.

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

General disorders and administration site conditions: edema.

Patients with asthma on therapy with SINGULAIR 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 usually, but not always, have been associated with the reduction of oral corticosteroid therapy. Physicians should be alert to eosinophilia, vasculitic rash, worsening pulmonary symptoms, cardiac complications, and/or neuropathy presenting in their patients *[see Warnings and Precautions (5.5)].*

In addition to the changes submitted for the PI, the Applicant also proposes the addition of the term "disorientation" to the patient package insert (PPI) under the section titled, "What are the possible side effects of SINGULAIR?" in the "Behavior and mood-related changes" subsection as follows:

PPI

- **Behavior and mood-related changes.** Tell your healthcare provider right away if you or your child have any of these symptoms while taking SINGULAIR:
  - agitation including aggressive behavior or hostility
  - bad or vivid dreams
  - depression
  - disorientation
  - feeling anxious
  - hallucinations (seeing or hearing things that are not really there)
  - irritability
  - restlessness
  - sleep walking
  - suicidal thoughts and actions (including suicide)
  - tremor
  - trouble sleeping

The list of 84 Merck Worldwide Adverse Experience System (WAES) reports previously submitted to the FDA and 55 WAES reports not previously submitted supporting the addition of the term to the PI and PPI are provided in the supplement.

3. Applicant's Response to Information Request

On June 15, 2010, the Division requested additional information (search strategy, case inclusion/exclusion criteria, causality assessment, and assessment of event severity) in order to facilitate review of this CBE supplement. The Applicant replied with an additional submission dated July 1, 2010. The Applicant's search strategy was described as including three MedDRA preferred terms: disorientation, confusional state, and memory impairment. Reports included in the review were ones originating from health care providers, regulatory agencies, and consumers received from 1997-2009. A total of 139 reports were identified including the terms confusional state (70), disorientation (44), and memory impairment (35).

Regarding causality, the Applicant stated that confounding factors (e.g. concurrent medical conditions and/or concomitant medications) were described in 34 reports. Nine reports documented positive rechallenge, supporting an association between montelukast and the events.

Regarding severity, the Applicant states that 110 of the 139 reports (79%) were non-serious. Reports meeting criteria for "serious" are described in Table 1.

Table 1. Reports of disorientation with montelukast meeting serious criteria

Serious Criteria	Total Reports
Hospitalized	12
Died	1
Disabling	3
Life threatening	1
Other Important medical event	15
Overdose	2
Total reports	29

The Applicant states that 20 of the 29 serious reports (70%) contained limited information. Further data was available for the 9 remaining reports:

1) 0701USA02524

This report was for a fatality. The Applicant states that the cause of death was hepatotoxicity which was associated with a confusional state.

2) 0603USA01443, 0307FRA00070, 0703SWE00051, 0803USA04995, 0501USA01213, 0412USA01356, and 00125624 (7 reports total)

The Applicant describes these reports as listing disorientation as a symptom of other adverse drug reactions including Churg-Strauss Syndrome, intentional multidrug overdose, metabolic encephalopathy, hypoglycemia, depression, pneumonia, and an influenza-like illness.

3) 0309USA02457

The Applicant describes this report as documenting disorientation in the context of hallucinations and abnormal dreams, thought to be due to a possible drug interaction between montelukast and levofloxacin.

4. Consultations

Both the Division of Pharmacovigilance I (DPV I) and the Division of Risk Management (DRISK) in the Office of Surveillance and Epidemiology were consulted regarding this submission. Both DPV and DRISK supported the addition of the term “disorientation.”

DPV conducted a search of the AERS data which identified 90 reports of disorientation-type events with montelukast; 50 of these cases were further identified as having a probable or possible association to montelukast exposure. Forty-five of the 50 cases reported a serious outcome, but there were no deaths. Four cases reported positive rechallenge. The reports included the following MedDRA preferred terms: confusional state (28), disorientation (13), delirium (6), incoherent (4), altered state of consciousness (2), and “feeling drunk” (1). The DPV review notes that the term “confusional state” was reported more frequently than “disorientation”, however, the review states that the latter term “may be more clinically meaningful to healthcare providers.” The events frequently occurred with other neuropsychiatric events, of which amnesia was the only unlabeled event. DPV conducted a separate review of 32 additional cases of amnesia which did not identify a strong association with montelukast.

DRISK recommended revised patient-friendly language for the PPI:

Merck’s proposed language:

- disorientation

DRISK revised patient-friendly language:

- disorientation (confusion)

5. Discussion and Recommendations

The DPV review noted that the term “confusional state” was reported more frequently than “disorientation” which is consistent with information presented in the Applicant’s July 1, 2010, submission. DPARP concludes that the term “disorientation” is appropriate for both the PI and PPI; in addition, DPARP concurs with DRISK’s recommendation to add the patient-friendly term “confusion”, in addition to “disorientation”, as a parenthetical statement to the PPI. The Applicant submitted a revised version of the PPI including the term “confusion” on July 12, 2010.

The DPV review also noted the occurrence of events described as “amnesia” (an unlabeled event), and the Applicant’s July 1, 2010, submission documented events described as “memory impairment.” The DPV review of an additional 32 cases of amnesia did not identify a strong association with montelukast. Given the lack of evidence for an association, DPARP does not recommend that any terms related to memory impairment be added to the product label at this time.

Full copies of the agreed upon versions of the PI and PPI are attached. The recommendation for this labeling supplement is Approval.

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-20830	SUPPL-56	MERCK AND CO INC	SINGULAIR(MONTELUKAST SODIUM)CHEWABLE TA
NDA-21409	SUPPL-31	MERCK RESEARCH LABORATORIES DIV MERCK CO INC	SINGULAIR(MONTELUKAST SODIUM)4MG GRANULE
NDA-20829	SUPPL-55	MERCK RESEARCH LABORATORIES DIV MERCK CO INC	SINGULAIR (MONTELUKAST SODIUM) TABS

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

JENNIFER R PIPPINS
07/13/2010

SUSAN L LIMB
07/13/2010

Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology

Date:	June 30, 2010
To:	Badrul Chowdhury, MD, Ph.D., Director Division of Pulmonary, Allergy and Rheumatology Products
Through:	Mark Avigan, MD, CM, Director Susan Lu, RPh, Team Leader Division of Pharmacovigilance I (DPV I) Office of Surveillance and Epidemiology (OSE)
From:	Melinda Wilson, Pharm.D, Safety Evaluator Division of Pharmacovigilance I (DPV I) Office of Surveillance and Epidemiology (OSE)
Subject:	Labeling Submission for Singulair® (montelukast sodium) and 'disorientation'
Drug Name(s):	Singulair® (montelukast sodium)
Application Type/Number:	NDA 20-829, 20-830, 21-409
Applicant/sponsor:	Merck & CO., INC.
OSE RCM #:	2010-1209

CONTENTS-

EXECUTIVE SUMMARY

This review summarizes disorientation-type events reported in the FDA's Adverse Event Reporting System (AERS) database associated with montelukast in response to the Sponsor's proposal to add 'disorientation' to the WARNINGS AND PRECAUTIONS and ADVERSE REACTIONS sections of the Prescribing Information for *Singulair*. A search of the AERS database on June 7, 2010 identified 90 reports of disorientation-type events (disorientation, altered consciousness, confusional state, delirium, feeling drunk or incoherent) with montelukast. Upon further evaluation, we identified 50 cases with probable (17) or possible (33) association to montelukast exposure.

Forty-five of 50 cases reported a serious outcome. Although there were no deaths, other serious important medical events (28) occurred most frequently followed by hospitalizations (13) disability (4) and life-threatening (4) events. Thirty-seven cases reported positive dechallenges and four reported positive rechallenges. The occurrence of disorientation-type events did not appear to be influenced by age, gender, or dose. The reported events (MedDRA preferred terms, non-mutually exclusive) included: confusional state (28), disorientation (13), delirium (6), incoherent (4), altered state of consciousness (2), and feeling drunk (1). Although the term 'disorientation' was not the most frequently reported term in this series, it is similar to the most commonly reported term 'confusion' and may be more clinically meaningful to healthcare providers.

Disorientation-type events frequently occurred with other neuropsychiatric events such as depression/depressed mood, nightmare/sleep terror, hallucination, agitation, anxiety, abnormal behavior, amnesia, dizziness, and insomnia. Specifically, 5 cases reported disorientation after awakening from a nightmare, 8 described disorientation as part of a hallucination and 1 patient reported disorientation after awakening from somnambulism. Among the neuropsychiatric events, amnesia is the only unlabeled event. A separate review of 32 additional cases of amnesia did not identify a strong association with montelukast due to confounding by disease state and poor documentation of amnesia events.

Due to the identification of serious outcomes associated with disorientation-type events among patients receiving *Singulair* and the frequent occurrence with other labeled neuropsychiatric events, we support the Sponsor's proposal to include 'disorientation' in the Prescribing Information for *Singulair*.

1 BACKGROUND

1.1 INTRODUCTION

The Division of Pulmonary, Allergy, and Rheumatology Products (DPARP) received a Changes Being Effected (CBE) supplement for the addition of the term "disorientation" to the labeling for *Singulair* Tablets (NDA 20-829), Chewable Tablets (NDA-20-830), and Oral Granules (NDA-21-409).[1] The sponsor proposed the addition of this term to the WARNINGS AND PRECAUTIONS section ,under the subsection Neuropsychiatric events and to the Post-Marketing Experience subsection of ADVERSE REACTIONS under Psychiatric Disorders. They also proposed adding this term to the Patient Package Insert (PPI) under the section titled, "What are the possible side effects of *Singulair*?", under the subsection "Behavior and mood-related changes". The sponsor provided case numbers for 84 World Wide Adverse Experience System (WAES) reports of disorientation previously submitted to the FDA and 55 WAES reports not

previously submitted in support of this proposal. DPARP requested that the Division of Pharmacovigilance I (DPV I) provide comments on the proposed labeling changes.

1.2 REGULATORY HISTORY

Singulair was approved on February 20, 1998 for the prophylaxis and chronic treatment of asthma in patients 15 years and older. Subsequent indications include: relief of symptoms of seasonal allergic rhinitis in adults and pediatric patients 2 years of age and older (12/31/2002), relief of symptoms of perennial allergic rhinitis (PAR) in adults and pediatric patients 6 months of age and older (7/27/2005) and prevention of exercise-induced bronchoconstriction in patients 15 years of age and older (4/13/2007). It is available as 5-mg and 10-mg film-coated tablets , 4-mg and 5-mg chewable tablets and 4-mg oral granules.

In 2008, the Office of Surveillance and Epidemiology (OSE) completed a post-marketing review of AERS reports of mood, cognitive, perception, sleep and movement adverse events associated with *Singulair*.[2] Of 400 cases of neuropsychiatric events reported in AERS from approval on February 20, 1998 through March 26, 2008, there were 39 (10%) cases grouped in the cognitive disorders category. This category included the Preferred Terms (PT) disorientation, memory impairment, impaired concentration or mental acuity, and confusion. These events were reported more frequently among patients ≥16 years of age (17 cases, 14%) than younger patients less than 16 years of age (9 cases, 11%). The review did not provide further evaluation of the cognitive disorder event category or individual events such as disorientation or confusion. Instead, the review focused on more frequently reported events including sleep disturbances (176), disruptive behaviors/hyperactivity (144) and serious events such as fatalities and seizures.

1.3 PRODUCT LABELING

The previous OSE review supported the addition of the following PRECAUTION and Post-Marketing Experience to the Psychiatric disorders subsection in the ADVERSE REACTIONS section of *Singulair* PI in 2009:[3]

> PRECAUTIONS
> *Neuropsychiatric Events*
>
> Neuropsychiatric events have been reported in adult, adolescent, and pediatric patients taking SINGULAIR. Post-marketing reports with SINGULAIR use include agitation, aggressive behavior or hostility, anxiousness, depression, dream abnormalities, hallucinations, insomnia, irritability, restlessness, somnambulism, suicidal thinking and behavior (including suicide) and tremor. The clinical details of some post-marketing reports involving SINGULAIR appear consistent with a drug-induced effect.
>
> Patients and prescribers should be alert for neuropsychiatric events. Patients should be instructed to notify their prescriber if these changes occur. Prescribers should carefully evaluate the risks and benefits of continuing treatment with SINGULAIR if such events occur (see ADVERSE REACTIONS, Post-Marketing Experience
>
> ADVERSE EVENTS
> Post-Marketing Experience
>
> Psychiatric disorders: agitation, including aggressive behavior or hostility, anxiousness, depression, dream abnormalities, hallucinations, insomnia, irritability, restlessness, somnambulism, suicidal thinking and behavior (including suicide) tremor (see PRECAUTIONS, Neuropsychiatric Events).

2 METHODS AND MATERIALS

2.1 SEARCH STRATEGY

We searched AERS on June 7, 2010 using the following criteria:

- active ingredient montelukast or montelukast sodium or trade name *Singulair*
- MedDRA preferred terms (PTs) altered consciousness, confusional state, delirium, disorientation, feeling drunk or incoherent

Using the WAES report numbers the sponsor identified as expedited 15-day or periodic reports submitted to the FDA, we searched AERS to identify additional reports. We also searched AERS on June 21, 2010 for PT amnesia and the active ingredient montelukast or montelukast sodium or the trade name *Singulair*.

2.1.1 Case selection criteria

We categorized the association between montelukast and the disorientation event using the criteria in Table 1.

Table 1. Association Categories and Criteria

Association term	Assessment Criteria
Probable	Disorientation event occurring in a reasonable time relationship to the administration of montelukast. The event is unlikely attributed to concurrent disease or other drugs and the patient experienced a positive response to withdrawal of montelukast.
Possible	Disorientation event occurring in a reasonable time relationship to the administration of montelukast. Other factors present that could have plausibly contributed to the event but were not the most likely explanation. Information on drug withdrawal may be lacking or unclear.
Unlikely	Disorientation event occurring in an improbable time relationship to the administration of montelukast or the event was more likely related to other causes
Unassessable	Report suggesting a disorientation event occurred in relationship to the administration of montelukast, however the event cannot be assessed due to insufficient or contradictory information.

3 RESULTS

3.1 AERS CASE SERIES

The AERS search identified 90 reports of disorientation-type events (disorientation, altered consciousness, confusional state, delirium, feeling drunk or incoherent) associated with the use of montelukast. Four duplicate reports were excluded. We categorized 86 cases according to the criteria described in Table 1 as probable (17), possible (33), unlikely (24) and unassessable (12)..

The following table describes clinical characteristics of disorientation-type events with a probable or possible association with montelukast (50). Appendix 1 includes the entire case series of disorientation-type events (86).

Table 2: Clinical Characteristics of Disorientation-Type Events with Probable or Possible Association with Montelukast Use as of June 7, 2010	
Number of cases	50
Age (years) n = 40	Mean= 26.5 years Median=13.5 years Range= 1 year to 89 years
Gender N=48	Female =28 Male = 20
Report type and FDA Receipt year	• Expedited (27), Direct (21) Periodic (2) • Events reported from 1998-2010, with the most frequent reporting in 2008
Reported Outcomes	Disability (4), Hospitalization (13), Life-threatening (4) , Other Medically Serious (28)
MedDRA Preferred term[1]	Confusional state (28), disorientation (13), delirium (6), incoherent (4), Altered state of consciousness (2), feeling drunk (1)
Average Daily Dose n=40	Mean=7.5 mg, Mode= 10 mg Range=4 mg to 10 mg
Latency (time to onset of symptoms from initiation of treatment)	Mean = 49.3 days Mode= 1 day Range= 2 hours to 2 years
Dechallenge or Rechallenge results	Positive Dechallenge (37) Positive Rechallenge (4)
Most frequently reported concurrent neuropsychiatric events (in descending frequency)[2]	Depression/depressed mood (12), nightmare/sleep terror (11), hallucination (9), agitation (8), anxiety (8), abnormal behavior (7), amnesia (7), dizziness (7), insomnia (7)
[1]Four cases reported multiple events (disorientation and confusional state [1], incoherent and confusional state [2], disorientation and delirium [1]) [2] 5 cases reported disorientation after awakening from a nightmare, 8 described disorientation as part of a hallucination and 1 patient reported disorientation after awakening from somnambulism.	

3.2 WAES REPORTS

We reconciled the manufacturer control numbers from the 90 cases identified by the AERS search of disorientation-type PTs with the 84 WAES report numbers the Sponsor identified as either expedited 15-day or periodic reports submitted to the FDA. This process identified 25 of the 84 WAES reports. Using the remaining 59 WAES report numbers, we searched the manufacturer control number field in AERS but did not identifiy additional cases.

3.3 BEST REPRESENTATIVE CASES

Appendix 2 describes four cases of disorientation-type events with positive rechallenges. Of note, two of these cases report disorientation after awakening from a nightmare.

3.4 UNLABELED NEUROPSYCHIATRIC EVENT: AMNESIA

Forty-four (88%) cases reported a concomitant neuropsychiatric event. The most common neuropsychiatric events included depression/depressed mood, nightmare/sleep terror,

hallucination, agitation, anxiety, abnormal behavior, amnesia, dizziness, and insomnia. All of these events are currently included in the Prescribing Information for *Singulair* except for amnesia.

On June 21, 2010, a search of the AERS database for the PT amnesia and the active ingredient montelukast or montelukast sodium or the trade name *Singulair* identified 42 cases. The previous case series of disorientation type events identified ten cases, leaving 32 additional unique cases for further evaluation. Using the same criteria presented in Table 1 we identified probable(2), possible (14), unassessable(6) and unlikely(10) cases. We provide further discussion of the cases with a possible or probable association below (16). Appendix 2 includes a listing of all ISR numbers identified in this case series.

Serious outcomes among the probable and possible cases included disabilities (3), hospitalizations(3), life-threatening events(3), and other serious important medical events(9). Only three cases described amnesia without other concurrent medical events. Neuropsychiatric events were most commonly reported with amnesia and included: depression (5), headache (5), abnormal behaviour (4) and aggression (4). The average age was 24.6 years (median 12.5, range 3-74 years) with eight females and six males (2 unknown). One case (ISR #5785612) described a positive rechallenge however the case contained limited information for assessment. Due to poor documentation of amnesia events and confounding by other disease states, a drug-event relationship could not be established at this time.

4 DISCUSSION

The AERS search identified 86 cases of disorientation-type events (disorientation, altered consciousness, confusional state, delirium, feeling drunk or incoherent) associated with the use of montelukast. After review, 50 cases were assessed as having a probable (17) or possible (33) association with montelukast exposure. Thirty-seven cases cited a positive dechallenge and four cases also cited a positive rechallenge.

Although no deaths were reported in this case series, 45 cases (90%) indicated a serious outcome Hospitalization and life-threatening events were more common among patients older than 18 years. Disability occurred with the same frequency among patients older than 17 years and those 7 to 16 years with no reports of disability among patients six years and younger.

The most commonly reported time to onset was within one day of initiation (seven cases, 14%). Although the median time to onset was 49.3 days, 17 (34%) of all cases occurred within seven days of initiation and 50% of all cases were reported within 14 days. This temporal association supports the link between montelukast administration and disorientation-type events.

The previous OSE review of neuropsychiatric events suggested patients six years and younger and those 16 and older were more likely to experience cognitive disorders. This review found that among the pediatric patients, those 7-16 years (12) reported disorientation type events at about the same rate as those six and younger (10). Taken as a group, disorientation-type events were evenly distributed among patients 16 and younger (22) and those older than 17 years (18), with 10 cases reporting an unknown age range. Thus, age did not appear to influence the reporting rate.

Disorientation-type events occurred across the dose range. Adult patients were more likely to use the 10 mg dose (14) and pediatric patients were more likely to use either the 4 mg or 5 mg dose (18) and roughly equal numbers of events were reported with the 10 mg dose versus the two lower doses combined. Only two patients under the age of 18 (ISR# 4212870, 6204164) received the 10 mg dose, yet considering their ages and weight, the higher dose may have been appropriate. One 53 year old female reported delirium after her dose increased from 5 mg to 10

mg and did not report this event after the dose was decreased (ISR#3329700). The dose of montelukast did not appear to influence the occurrence of disorientation-type events.

Although the sponsor proposes adding the term 'disorientation', only 13 (26%) of the cases specifically listed this term. Instead, confusional state occurred 28 times in the case series as the most commonly used term. Considering almost half of the reports originated from consumers and the events are coded according to the terms used in the reporter's narrative, the term confusion may be used more frequently in the lay vernacular. Although the term disorientation was not the most frequently reported term, it is similar to the most commonly reported term confusion and may be more clinically meaningful to healthcare providers.

The 2008 OSE review of neuropsychiatric events identified only 39 events within the cognitive disorders category which included the terms disorientation, confusion, memory impairment and impairment in concentration or mental acuity. Nineteen (38%) of the 50 events described in this review were reported in 2008, the same year as the first OSE review of neuropsychiatric events. In 2009, the same year as the inclusion of neuropsychiatric events in the label, the second highest reporting (nine cases, 18%) rate occurred. With the exception of 2008-2009, the reporting rate consistently ranged from one to three reports per year from 1998-2010. While the timeframe suggests reporting may be stimulated by media attention, the presence of cases with a positive rechallenge/ dechallenge and the serious nature of these events contribute to the validity of the association between montelukast and disorientation-type events.

Although the sponsor indicated that 84 WAES reports of disorientation had been previously submitted to FDA, a search of the AERS database identified only 25 of 84 reports. From our review, plausible explanations include: (a)sponsor change in reporting nomenclature, (b) differences between sponsor's electronic submission (e-sub) report numbers and report numbers provided in the CBE, and (c) the manufacturer control number search field in AERS requires an exact match to identify cases. Since the sponsor did not provide an analysis of the cases in the CBE, DPARP submitted an information request to the Sponsor during the week of June 15, 2010 requesting additional information regarding their search strategy, adjudication, and assessment of severity of these cases.

5 CONCLUSIONS

We identified 86 cases of disorientation-type events associated with montelukast in the AERS database. Reported events included disorientation, altered consciousness, confusional state, delirium, feeling drunk or incoherent. After review, 50 cases were assessed as having a probable or possible association to montelukast. The drug-event relationship is supported by temporal relationship to montelukast administration (50% of all cases occurred within 14 days), positive dechallenges in the majority of cases (82%) and 4 cases of positive rechallenge.

Although the term disorientation was not the most frequently reported term in this case series, it is similar to the most commonly reported term confusion and may be more clinically meaningful to healthcare providers. It would be appropriate to use the term disorientation to represent disorientation-type events (disorientation, altered consciousness, confusional state, delirium, feeling drunk or incoherent) in the label.

Disorientation-type events frequently occurred with other neuropsychiatric events such as depression/depressed mood, nightmare/sleep terror, hallucination, agitation, anxiety, abnormal behavior, amnesia, dizziness, and insomnia. Specifically, 5 cases reported disorientation after awakening from a nightmare, 8 described disorientation as part of a hallucination and 1 patient reported disorientation after awakening from somnambulism. Among these neuropsychiatric events, amnesia is the only unlabeled event. A review of 32 additional cases of amnesia did not

identify a strong association with montelukast due to confounding by disease state and poor documentation of amnesia events.

6 RECOMMENDATIONS

We agree with the Sponsor's proposal to add the term 'disorientation' to the WARNINGS AND PRECAUTIONS and ADVERSE REACTIONS sections of the Prescribing Information for *Singulair.*

The strength of evidence from the amnesia case series do not alone support changes to the label at this time.

7 REFERENCES

[1] Merck&CO., INC. NDA 20-829, 20-830, and 21-709 Labeling Supplement – Changes Being Effected. April 14, 2010.

[2] Green, L., Mosholder, A., Money, D. Office of Surveillance and Epidemiology. AERS Postmarketing Safety Review: Mood, Cognitive, Perception, Sleep and Movement Adverse Events. RCM 2008-474. Dec 19 2008.

[3] Singulair (montelukast sodium) Prescribing Information. Merck &CO., INC. Whitehouse Station, NJ. August 2009 and April 2010.

8 APPENDIX

Appendix 1. Disorientation-type cases (n=86)

ISR #	Manufacturer Control Number	Received Date	AGE (years)	Sex	Outcome[1]	Event of Interest	Other Neuropsychiatric Event	Case Categorization	Onset	rechallenge or dechallenge	Singulair Dose
5607004	JP-MERCK-0801USA04313	29-Jan-08	4	Male	OT	DELIRIUM	AGITATION, INSOMNIA, CRYING	Possible	<1 day	dechallenge	4 mg
4864746	GB-MERCK-0512GBR00100	22-Dec-05	58	Female	OT	CONFUSIONAL STATE	ANXIETY, DEPRESSED MOOD, DEPRESSION, DIZZINESS, FEAR, INSOMNIA, RESTLESSNESS	Possible	1 day	dechallenge	
5364313	NL-MERCK-0706NLD00013	20-Jun-07	7	Male	OT	CONFUSIONAL STATE		Probable	1 day	dechallenge	5 mg
6279688	AT-MERCK-0907AUT00008	23-Jul-09	3	Female	OT	CONFUSIONAL STATE	NIGHTMARE, SLEEP DISORDER	Probable	1 day	dechallenge	4 mg
5583592	PL-MERCK-0712POL00006	7-Jan-08	4	Female	OT	DELIRIUM	TREMOR	Probable	1 day	dechallenge	4 mg
6034581	JP-MERCK-0812USA02220	12-Jan-09	3	Female	OT	DELIRIUM	ABNORMAL BEHAVIOUR, AGITATION	Probable	1 day	dechallenge possible rechallenge	4 mg
6294961	CTU 387072	31-Jul-09	35	Female	OT	FEELING DRUNK	ANXIETY, DISTURBANCE IN ATTENTION, PSYCHOMOTOR HYPERACTIVITY, TREMOR	unassessable	1 hour	dechallenge	10 mg
6461846	ES-MERCK-0911ESP00036	30-Nov-09	49	Female	OT	CONFUSIONAL STATE	DEPERSONALISATION, NIGHTMARE	Probable	1 week	rechallenge	10 mg
5746405	CTU 337319	20-May-08	9	Male	OT	DISORIENTATION	AMNESIA, LOSS OF CONSCIOUSNESS, MOOD SWINGS, NIGHTMARE	Possible	1 year	dechallenge	5mg
6595166	GB-MERCK-1002GBR00059	22-Feb-10	43	Male	HO	CONFUSIONAL STATE	AGITATION, PARANOIA, HALLUCINATION, AUDITORY, ANXIETY	Possible	1.5 mos	dechallenge	10 mg

ISR #	Manufacturer Control Number	Received Date	AGE (years)	Sex	Outcome[1]	Event of Interest	Other Neuropsychiatric Event	Case Categorization	Onset	rechallenge or dechallenge	Singulair Dose
5690105	CTU 330611	31-Mar-08	7	Male	OT	CONFUSIONAL STATE	ABNORMAL BEHAVIOUR, CRYING, DEPRESSED MOOD, DISTURBANCE IN ATTENTION, EDUCATIONAL PROBLEM, ELEVATED MOOD, NIGHTMARE, SOMNOLENCE	Probable	1.5 weeks	dechallenge	5 mg
6190794	CTU 376928	13-May-09	39	Female	OT	CONFUSIONAL STATE	ABNORMAL BEHAVIOUR, MOOD ALTERED, MIDDLE INSOMNIA, DIZZINESS, ANXIETY, ABNORMAL DREAMS	unlikely	10 days	no information	10 mg
5354168	SI-MERCK-0412HUN00017	12-Jun-07	3.8	Female	OT	CONFUSIONAL STATE	FEAR, SLEEP DISORDER, HALLUCINATIONS, MIXED, TIC	Probable	11 days	dechallenge	4 mg
5706800	CTU 332369	15-Apr-08	U	Female	OT	FEELING DRUNK	CEREBRAL DISORDER, DISTURBANCE IN ATTENTION, DIZZINESS, HALLUCINATION, MENTAL DISORDER, THINKING ABNORMAL	Probable	1-2 days	dechallenge	10 mg
3651572	WAES 00125624	19-Jan-01	6	Male	OT	DISORIENTATION	AKATHISIA, HALLUCINATION, MEMORY IMPAIRMENT, RESTLESSNESS	Probable	1-2 hours after onset	rechallenge	5 mg
6263054	CTU 384130	8-Jul-09	1.3	Female	OT	DISORIENTATION	NIGHTMARE, SCREAMING, MIDDLE INSOMNIA	Possible	14 days	dechallenge	4 mg
5873859	CTU 348265	3-Sep-08	U	Female	HO	CONFUSIONAL STATE	AGGRESSION, AMNESIA, ANGER, ANXIETY, CRYING, FEELING ABNORMAL, MOOD ALTERED, NERVOUSNESS, NIGHTMARE	Possible	14 days	dechallenge	10 mg
6004326	CTU 359209	15-Dec-08	31	Female	LT	ALTERED STATE OF CONSCIOUSNESS	DEPRESSION, STRESS, SUICIDAL IDEATION	Possible	15 days	dechallenge	10 mg
6538493	FR-MERCK-0912FRA00089	14-Jan-10	14	Male	HO	CONFUSIONAL STATE, INCOHERENT		Possible	18 days	dechallenge	5 mg
6614436	CTU 410117	3-Mar-10	U	Unk		CONFUSIONAL STATE	ABNORMAL BEHAVIOUR, AMNESIA	Probable	2 days	dechallenge	4 mg
5743827	CTU 337161	19-May-08	50	Female	OT	CONFUSIONAL STATE		Probable	2 days	dechallenge	10 mg

ISR #	Manufacturer Control Number	Received Date	AGE (years)	Sex	Outcome[1]	Event of Interest	Other Neuropsychiatric Event	Case Categorization	Onset	rechallenge or dechallenge	Singulair Dose
4212870	WAES 0309USA02457	20-Oct-03	13	Male	DS	DISORIENTATION	ABNORMAL DREAMS, DIZZINESS, HALLUCINATION, VISUAL, TREMOR	Probable	2 days, 3 doses	dechallenge	10 mg
6204164	JP-MERCK-0904USA01231	27-May-09	16	Male	OT	ALTERED STATE OF CONSCIOUSNESS		Possible	2 mos	dechallenge	10 mg
3541945	WAES 98121094	23-Mar-00	6	Female		DISORIENTATION	ANXIETY, PARASOMNIA	Possible	2 weeks	dechallenge	
3118403	WAES 98062009	17-Aug-98	U	Female	HO	CONFUSIONAL STATE	AGITATION, HALLUCINATION	Possible	2 weeks	dechallenge	10 mg
6181050	CTU 375770	4-May-09	4	Male	OT	CONFUSIONAL STATE	ABNORMAL BEHAVIOUR, ABNORMAL DREAMS, AGGRESSION, DISTURBANCE IN SOCIAL BEHAVIOUR, INSOMNIA, MOOD SWINGS, MORBID THOUGHTS	unassessable	2 years	no information	4 mg
5774113	US-MERCK-0310USA00013	16-Jun-08	12	Male	OT	INCOHERENT	DEPRESSED MOOD, DEPRESSION, SUICIDAL IDEATION, HALLUCINATION, PSYCHOMOTOR HYPERACTIVITY	Probable	20 days	dechallenge	5 mg
5160587	KW-MERCK-0610USA14295	29-Nov-06	1	Male	HO	DISORIENTATION	SENSORY LEVEL ABNORMAL, SOMNOLENCE	Possible	21 days	dechallenge	4 mg
3329700	WAES 99073625	18-Aug-99	53	Female	HO	DELIRIUM		Possible	3 days	no information	5 mg increased to 10 mg
5755057	CTU 338122	28-May-08	U	Unk		INCOHERENT	ABNORMAL BEHAVIOUR, AGGRESSION, ANXIETY, EDUCATIONAL PROBLEM	Possible	3 mos	dechallenge	
5897792	CTU 350685	24-Sep-08	7	Female	OT	CONFUSIONAL STATE	ABNORMAL BEHAVIOUR, ANGER, CRYING, DEPRESSED MOOD, FEAR, FEELING ABNORMAL, MOOD SWINGS	Probable	4 days	rechallenge	
4527269	CTU 234260	14-Dec-04	52	Male	OT	CONFUSIONAL STATE	DIZZINESS	Possible	45 days	dechallenge	10 mg
3374206	WAES 99096768	15-Oct-99	57	Male	HO	CONFUSIONAL STATE	AKATHISIA, ANXIETY, RESTLESSNESS	Possible	5 mos	dechallenge	10 mg
6268955	CTU 385038	14-Jul-09	61	Male	DS	CONFUSIONAL STATE	AGITATION, ANGER, DEPRESSION, FEELING ABNORMAL, SUICIDAL IDEATION, OBSESSIVE-COMPULSIVE	unassessable	5 mos	no information	10 mg

							DISORDER, MENTAL STATUS CHANGES				
6073892	PR-MERCK-0902USA01437	11-Feb-09	11	Female	HO	DELIRIUM	NIGHTMARE, SUICIDAL IDEATION	Possible	6 mos	dechallenge	5 mg
ISR #	**Manufacturer Control Number**	**Received Date**	**AGE (years)**	**Sex**	**Outcome[1]**	**Event of Interest**	**Other Neuropsychiatric Event**	**Case Categorization**	**Onset**	**rechallenge or dechallenge**	**Singulair Dose**
3099380	WAES 98069113	29-Jun-98	52	Female	LT, HO, DS	CONFUSIONAL STATE	AGITATION	Possible	7 days	dechallenge	10 mg
6149311	CTU 372374	6-Apr-09	U	Female	OT	DISORIENTATION	DIZZINESS, FEELING ABNORMAL, MIDDLE INSOMNIA, PARANOIA	Possible	7 days	dechallenge	10 mg
5179274	PL-MERCK-0612POL00006	19-Dec-06	18	Male	LT	DISORIENTATION		Probable	7 days	dechallenge	10 mg
6656233	US-MERCK-1003USA00223	29-Mar-10	41	Male	OT	CONFUSIONAL STATE	IRRITABILITY, THINKING ABNORMAL, DEPRESSION	unassessable	7 days	no information	
3457484	WAES 00028102	14-Feb-00	89	Male	DS	DELIRIUM, DISORIENTATION	AGITATION	Probable	9 days	dechallenge	10 mg
3574139	WAES 00042306	21-Jun-00	19	Female		CONFUSIONAL STATE	ASTHENIA	unlikely	9 ms	no information	
3240615	WAES 99021085	14-Apr-99	10	Female	LT	CONFUSIONAL STATE	AGGRESSION, AMNESIA, GRAND MAL CONVULSION	unlikely	After dose incrs.	no information	5 mg increased to 10 mg
5714130	CTU 333158	22-Apr-08	U	Female	LT	CONFUSIONAL STATE	ABNORMAL DREAMS, INSOMNIA, MAJOR DEPRESSION, MENTAL DISORDER, SLEEP TERROR, SOMNOLENCE	Possible	over 2 years	dechallenge	10 mg
5933983	CTU 354070	28-Oct-08	38	Female	HO	CONFUSIONAL STATE	AGGRESSION, AGITATION, AMNESIA, ANGER, HALLUCINATION, MANIA	Possible	over course of 3 weeks	dechallenge	10 mg
3592276	WAES 00051196	21-Sep-00	68	Male		CONFUSIONAL STATE	DIZZINESS	Possible	up to 13 days	dechallenge	10 mg
5707153	CTU 332213	14-Apr-08	6	Male	OT	CONFUSIONAL STATE	NERVOUS SYSTEM DISORDER, INSOMNIA, IMPULSIVE BEHAVIOUR, EMOTIONAL DISORDER, DEPRESSION, ANGER, AGGRESSION, ABNORMAL BEHAVIOUR	Possible		dechallenge	5 mg
5127827	US-MERCK-0603USA01443	16-Oct-06	13	Male	DS	CONFUSIONAL STATE	AMNESIA, HALLUCINATION, DEPRESSED LEVEL OF CONSCIOUSNESS	Possible		dechallenge	

3882427	WAES 0202USA00018	12-Mar-02	32	Female	HO, OT	DISORIENTATION	ABNORMAL DREAMS, FEELING ABNORMAL, DIZZINESS	Possible		dechallenge	10 mg
ISR #	**Manufacturer Control Number**	**Received Date**	**AGE (years)**	**Sex**	**Outcome[1]**	**Event of Interest**	**Other Neuropsychiatric Event**	**Case Categorization**	**Onset**	**rechallenge or dechallenge**	**Singulair Dose**
4770186	CA-MERCK-0509USA01132	15-Sep-05	78	Male	OT	DISORIENTATION	LOSS OF CONSCIOUSNESS	Possible		dechallenge	
5690119	CTU 330499	31-Mar-08	10	Male	OT	CONFUSIONAL STATE	ANXIETY, EMOTIONAL DISORDER, FEELING ABNORMAL, MOOD ALTERED, OBSESSIVE-COMPULSIVE DISORDER, SOMNOLENCE	Possible		no information	
5690159	CTU 330669	31-Mar-08	19	Female	HO, OT	CONFUSIONAL STATE	FEAR, HALLUCINATION, INSOMNIA, MENTAL DISORDER, PSYCHOTIC DISORDER	Possible		no information	
6291852	CA-MERCK-0907CAN00113	30-Jul-09	34	Female	OT	CONFUSIONAL STATE	AMNESIA, APATHY, DEPRESSION, ANGER	Possible		no information	10 mg
5690089	CTU 330542	31-Mar-08	74	Female	OT	CONFUSIONAL STATE, DISORIENTATION	DEPRESSION, JUDGEMENT IMPAIRED	Possible		no information	
3305622	WAES 99073503	16-Jul-99	U	Female	HO	CONFUSIONAL STATE	AGGRESSION, AGITATION	Possible		dechallenge	10 mg
5690658	CTU 330283	31-Mar-08	U	Female	OT	CONFUSIONAL STATE	ABNORMAL BEHAVIOUR, AMNESIA, ANXIETY, APATHY, CRYING, DEPRESSION, DISTURBANCE IN ATTENTION	Possible		no information	
5690683	CTU 330469	31-Mar-08	U	Female		CONFUSIONAL STATE, INCOHERENT	NIGHTMARE, SLEEP TERROR, MOOD SWINGS, CRYING	Possible		no information	4 mg
6303666	CTU 388026	7-Aug-09	7	Female	OT	DISORIENTATION	RESTLESSNESS, SCREAMING	Probable		rechallenge	5 mg
6102217	CTU 368030	3-Mar-09	22	Female	OT	CONFUSIONAL STATE		unassessable		no information	
6739029	CTU 419240	24-May-10	7	Male	OT	CONFUSIONAL STATE	AGGRESSION, ANGER, CONVULSION, HALLUCINATION, VISUAL, MEMORY IMPAIRMENT	unassessable		no information	
6754269	US-MERCK-1005USA03906	3-Jun-10	13	Female	OT	CONFUSIONAL STATE	DEPRESSION, EMOTIONAL DISORDER, HALLUCINATION, HEART RATE	unassessable		no information	

							DECREASED, MOOD SWINGS, NIGHTMARE, SUICIDAL IDEATION				
ISR #	**Manufacturer Control Number**	**Received Date**	**AGE (years)**	**Sex**	**Outcome[1]**	**Event of Interest**	**Other Neuropsychiatric Event**	**Case Categorization**	**Onset**	**rechallenge or dechallenge**	**Singulair Dose**
6439786	US-MERCK-0911USA01696	13-Nov-09	20	Male	HO	INCOHERENT		unassessable		no information	
4239435	WAES 0310USA00013	21-Nov-03	12	Male	OT	INCOHERENT	DEPRESSION, SUICIDAL IDEATION, DEPRESSED MOOD, HALLUCINATION, PSYCHOMOTOR HYPERACTIVITY	unassessable		no information	
5763848	CTU 339278	6-Jun-08	4	Female	OT	CONFUSIONAL STATE	ABNORMAL BEHAVIOUR, AGGRESSION, DEPRESSED MOOD, EMOTIONAL DISORDER, FEELING ABNORMAL, HALLUCINATIONS, MIXED, MOOD SWINGS, SCREAMING, SLEEP TERROR	unassessable		no information	
5929109	CTU 353649	23-Oct-08	73	Male	OT	CONFUSIONAL STATE	ABNORMAL DREAMS, ANGER, HALLUCINATION, VISUAL, INITIAL INSOMNIA, SUICIDAL IDEATION	unassessable		no information	10 mg
6012657	US-MERCK-0812USA00968	18-Dec-08	U	Female	LT	CONFUSIONAL STATE	ABNORMAL DREAMS, INSOMNIA, MAJOR DEPRESSION, MENTAL DISORDER, SLEEP TERROR, SOMNOLENCE	unassessable		no information	
3172211	WAES 98125094	21-Dec-98	30	Female	HO	CONFUSIONAL STATE		unlikely		dechallenge	10 mg
4161840	WAES 0307FRA00070	5-Aug-03	60	Female	HO	CONFUSIONAL STATE	BALANCE DISORDER, ENCEPHALOPATHY	unlikely		dechallenge	
6732414	JP-MERCK-1004USA01701	19-May-10	4	Female	HO	ALTERED STATE OF CONSCIOUSNESS		unlikely		no information	
3470456	WAES 00022295	6-Mar-00	78	Male	HO	CONFUSIONAL STATE, DISORIENTATION		unlikely		no information	
3647941	WAES 00090040	26-Dec-00	40	Female		CONFUSIONAL STATE	MEMORY IMPAIRMENT	unlikely		no information	
3927212	WAES 0205FRA00028	31-May-02	50	Male	HO	CONFUSIONAL STATE		unlikely		no information	

4171627	CTU 200173	18-Aug-03	62	Female	RI	CONFUSIONAL STATE	ASTHENIA, FEELING ABNORMAL, INSOMNIA	unlikely		no information	
ISR #	**Manufacturer Control Number**	**Received Date**	**AGE (years)**	**Sex**	**Outcome[1]**	**Event of Interest**	**Other Neuropsychiatric Event**	**Case Categorization**	**Onset**	**rechallenge or dechallenge**	**Singulair Dose**
4285016	WAES 0312USA02233	4-Feb-04	45	Male	HO, DC, OT	CONFUSIONAL STATE		unlikely		no information	
4319640	WAES 0402USA01401	19-Mar-04	38	Male	LT, HO, DS, OT	CONFUSIONAL STATE	AMNESIA	unlikely		no information	
4552845	US-MERCK-0412USA01356	14-Jan-05	14	Female	HO, OT	CONFUSIONAL STATE	SUICIDE ATTEMPT	unlikely		no information	
4577060	US-MERCK-0402USA01401	10-Feb-05	38	Male	LT, HO, DS, OT	CONFUSIONAL STATE	AMNESIA	unlikely		no information	
4645445	US-MERCK-0502USA03308	26-Apr-05	64	Male	HO, DS	CONFUSIONAL STATE, DELIRIUM	HALLUCINATION, MENTAL STATUS CHANGES, PARANOIA, SOMNOLENCE	unlikely		no information	
4677502	CTU 249780	27-May-05	67	Female	DE	CONFUSIONAL STATE		unlikely		no information	
5291353	NL-MERCK-0704NLD00003	9-Apr-07	5	Female	HO	CONFUSIONAL STATE		unlikely		no information	
6266037	SE-MERCK-0703SWE00051	13-Jul-09	4	Male	HO	CONFUSIONAL STATE	ABNORMAL BEHAVIOUR, AGGRESSION, ANXIETY, APATHY, DEMENTIA, DEPRESSED MOOD, DEPRESSION	unlikely		no information	4 mg
5088128	2006025135	27-Jul-06	81	Female	OT	DISORIENTATION		unlikely		no information	
6756634	US-MERCK-1005USA03367	4-Jun-10	9	Female	OT	DISORIENTATION	AGGRESSION, CONVULSION, DEPRESSION, DISTURBANCE IN ATTENTION, EDUCATIONAL PROBLEM, OPPOSITIONAL DEFIANT DISORDER, PERSONALITY CHANGE, SELF ESTEEM DECREASED, SUICIDAL IDEATION	unlikely		no information	
4076856	WAES 0302MYS00012	24-Mar-03	79	Female	HO, DS	DISORIENTATION, CONFUSIONAL STATE		unlikely		no information	

3106859	WAES 98060800	20-Jul-98	69	Male	HO	CONFUSIONAL STATE	CONVULSION	unlikely		no information	10 mg
ISR #	**Manufacturer Control Number**	**Received Date**	**AGE (years)**	**Sex**	**Outcome[1]**	**Event of Interest**	**Other Neuropsychiatric Event**	**Case Categorization**	**Onset**	**rechallenge or dechallenge**	**Singulair Dose**
4085186	WAES 0303USA01250	4-Apr-03	53	Female	HO, OT	INCOHERENT	CONVULSION, LOSS OF CONSCIOUSNESS, MEMORY IMPAIRMENT	unlikely		no information	
4441806	US-MERCK-0407USA00328	7-Sep-04	87	Female	HO, OT	CONFUSIONAL STATE		unlikely		no information	
[1]DS (disability) OT (Other), LT (life-threatening), HO (hospitalization)											

Appendix 2: Best Respresentative Cases (n=4)

***ISR#3651572, Manufacturer control # WAES 00125624*, Germany, November 2000**: A six year-old male began therapy with montelukast 5 mg tablets in November 2000. Concomitant therapy included theophylline and unspecified corticosteroids. Approximately one to two hours after administration of montelukast, he developed restlessness, vomiting, disorientation and hallucinations. Montelukast was discontinued after three days of treatment and the patient recovered. In December 2000, the patient was hospitalized for an asthma exacerbation and after initial treatment with prednisone, terbutaline, fenoterol hydrobromide and ipratropium a second trial with montelukast 5 mg was initiated. Similar to the initial reaction, one to two hours after oral administration of montelukast the patient experienced restlessness, vomiting with heavy retching, disorientation ("he did not recognize his mother") and hallucinations ("fighting with imaginary enemies). Montelukast was discontinued the same day. The following morning, the patient did not remember the incidents of the night and he was exhausted but fully oriented and behaved 'as usual'. The patient was later diagnosed with an atypical pneumonia which resolved following a course of amoxicillin. His respiratory condition improved and he was released from the hospital after eight days of treatment.

Reviewer's comments: While the acute infection could be associated with disorientation, the reoccurrence of the exact same adverse events following the first dose and resolution after discontinuation provide stronger evidence of a causal association with montelukast. The reporting physician indicated this event was a seriously important medical event and the sponsor identified this case number in the CBE.

ISR #5897792, Direct report, US, September 2008: The mother of a seven year-old female observed mood swings ranging from angry rages to uncontrollable sobbing and sadness within four days after her daughter started montelukast for the treatment of seasonal allergies. The patient was not able to identify the cause of her mood swings and was 'scared and confused' by her own behavior. After three weeks of therapy she stopped

montelukast and reported a return to normal behavior within 24 to 36 hours. Two years prior, the patient also received montelukast and exhibited similar behavior. The mother believed the child was 'out of control' but did not attribute the behavior to montelukast therapy and instead took parenting classes to help manage the child's behavior. When the child entered kindergarten after approximately nine months of treatment the mother stopped the montelukast and her behavior improved. The patient received both cetirizine 5 mg and mometasone furoate nasal spray concomitantly during both occurrences. The reporter did not provide the dose of montelukast. The child's sister also received montelukast and experienced similar, although less severe, changes in behavior which also abated following discontinuation.

Reviewer's comment: Although this case presents a positive rechallenge, it is potentially confounded by recall bias of the initial event and a lack of detail describing the patient's 'confusion'. The reporter indicated this event was a seriously important medical event.

ISR#6303666, Direct report, US, August 2009: This case involves a seven year-old female who took montelukast 5 mg from August to February for seasonal asthma. In August 2008, the patient's mother reported that "each night when her daughter took montelukast she would seem to wake up several hours later screaming not knowing where she was or who anyone was". The patient discontinued montelukast in February 2009 and these events resolved. On August 1, 2009, the patient restarted montelukast and the insomnia, screaming, and disorientation returned. The patient did not know where she was and could not identify the people around her. Her mother reported she was in a 'trance like state' which was sometimes difficult to wake her from and she was very restless. After 4 days of treatment with montelukast, the mother notified the prescribing pulmonologist that she was discontinuing the medication.

Reviewer's comment: The reporter indicated this event was a seriously important medical event

ISR#6461846, Manufacturer control #ES-MERCK-0911ESP00036, Spain, November 2009: A 49 year-old female with a history of congenital pulmonary artery atresia initiated montelukast 10 mg on September 2, 2009 for the treatment of COPD. Long-standing concomitant therapy included fluticasone propionate and salmeterol xinafoate and the patient was involved in routine respiratory monitoring. A week after starting montelukast therapy the patient experienced nightmares, depersonalization and confusional awakening: the patient had strange dreams and woke up with depersonalization and feelings of strangeness. Montelukast therapy was discontinued after a total of 14 days of therapy and the adverse events resolved. At a later date, montelukast was reinitiated and within one week, the same symptoms reappeared.

Reviewer's comments: The report did not include start date for second course of montelukast. The reporting physician indicated this event was a serious important medical event. This is the only case in the series which described an off-label use for COPD. The manufacturer submitted this case electronically as an expedited 15-day report however we were not able to match with report number with those included in the CBE.

Appendix 3: Amnesia Cases (n=32)

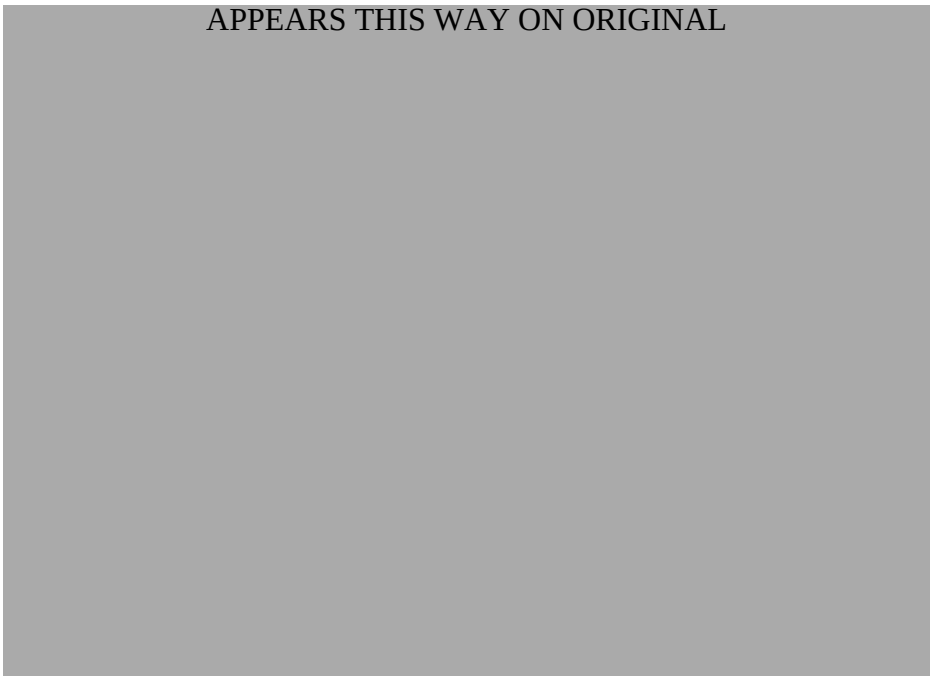
ISRNUM	RECVDATE	RPTYPE	AGE (years)	SEX	Outcome	Event Reactions	Case categorization	Comments	dechallenge rechallenge	onset (days)
5868819	2-Sep-08	Direct	13	Male	LT, DS	ABDOMINAL PAIN UPPER, ABNORMAL BEHAVIOUR, AGGRESSION, AMNESIA ,ANGER, DECREASED INTEREST, DEPRESSION, INSOMNIA, NIGHTMARE, SUICIDAL IDEATION,	possible	positive dechallenge, no other information	dechallenge	730
6016048	22-Dec-08	Expedited (15-Day)	U	Female	LT, OT	ABDOMINAL PAIN UPPER,ABNORMAL BEHAVIOUR,ABNORMAL DREAMS,AGGRESSION,AMNESIA,DEPRESSION,DIZZINESS,EMOTIONAL DISORDER,HEADACHE,INSOMNIA,MOOD SWINGS,MUSCLE SPASMS,	possible	event, but no additional information		
5994515	12-Dec-08	Expedited (15-Day)	47	Female	LT	ABNORMAL BEHAVIOUR,ABNORMAL DREAMS,AMNESIA,ANGER,MOOD ALTERED,SLEEP DISORDER,SUICIDAL IDEATION,	possible	event, but no additional information		
5755072	28-May-08	Direct	U	Unk		ABDOMINAL PAIN UPPER,AGGRESSION,AMNESIA,ANHEDONIA, CONVULSION, DEPRESSION, FEELING ABNORMAL, GASTROOESOPHAGEAL REFLUX DISEASE, MOOD SWINGS, PAIN IN EXTREMITY,	possible	positive dechallenge	dechallenge	730
5948271	10-Nov-08	Direct	42	Female	OT	ABNORMAL BEHAVIOUR, ALCOHOL USE, AMNESIA, LOSS OF CONSCIOUSNESS,	possible	concomitant alcohol consumption		3
5738661	13-May-08	Direct	U	Unk		AGGRESSION, AMNESIA, ANGER, BIPOLAR DISORDER,CRYING, DEPRESSION, DISTURBANCE IN ATTENTION, HAEMORRHAGE, IRRITABILITY, MIDDLE INSOMNIA, MOOD ALTERED, MYALGIA,	possible	positive dechallenge however possible comorbid AHDH/bipolar could contribute	dechallenge	
4955852	27-Mar-06	Direct	23	Male	HO, OT	AMNESIA,CHEST PAIN,COUGH, DEPRESSION, DIARRHOEA,FATIGUE, HEADACHE,MIGRAINE, NAUSEA,NIGHTMARE, OROPHARYNGEAL PAIN,SINUSITIS,	possible	stimulated reporting - based on effects listed on patient forum on web	dechallenge	7
5100240	8-Sep-06	Expedited	6	Female	DS, OT	AMNESIA,CONVULSION,DYSGEUSIA,	possible	unclear if seizure	dechallenge	112

ISRNUM	RECVDATE	RPTYPE	AGE (years)	SEX	Outcome	Event Reactions	Case categorization	Comments	dechallenge rechallenge	onset (days)
		(15-Day)						before or after memory impairment. Resolved with DC		
5746405	20-May-08	Direct	9	Male	OT	AMNESIA, DISORIENTATION, HEADACHE, LOSS OF CONSCIOUSNESS, MOOD SWINGS,NIGHTMARE,	possible	no information on resolution of memory problem with dechallenge	dechallenge	
4245759	4-Dec-03	Expedited (15-Day)	12	Female	HO	AMNESIA,DISTURBANCE IN ATTENTION, HEADACHE, NIGHTMARE, MEMORY IMPAIRMENT,MENTAL DISORDER,	possible	comments regarding possible comorbid psychiatric condition	dechallenge	56
6058787	28-Jan-09	Direct	74	Female	DS	AMNESIA,DRY MOUTH,JAUNDICE, SPEECH DISORDER,THINKING ABNORMAL,	possible		dechallenge	
5907070	2-Oct-08	Direct	8	Male		ABDOMINAL PAIN,AMNESIA, ANXIETY, ATTENTION DEFICIT/HYPERACTIVITY DISORDER, EDUCATIONAL PROBLEM, HEADACHE, MOOD ALTERED,PAIN IN EXTREMITY,	possible	comorbid ADHD? Positive dechallenge	dechallenge	
3759292	16-Jul-01	Expedited (15-Day)	52	Male	HO	AMNESIA,	possible	no other attributable factors however no discontinuation	no, event resolved on therapy	2
6646489	22-Mar-10	Direct	3 25	Male	OT	AMNESIA,	possible	although lacking significant additional information		
5785612	20-Jun-08	Direct	U	Female	OT	AMNESIA,CLUMSINESS, DISTURBANCE IN ATTENTION,	probable	positive rechallenge	rechallenge	7
5397083	25-Jul-07	Expedited (15-Day)	6	Female	OT	AMNESIA,	probable	positive dechallenge; no other concomitant medical event listed	dechallenge	28
5696212	4-Apr-08	Direct	U	Female	LT, OT	ABDOMINAL PAIN UPPER,ABNORMAL BEHAVIOUR,ABNORMAL DREAMS,AGGRESSION, AMNESIA,DEPRESSION,	unassessable	no clear description of amnesia - sleepwalking instead		

ISRNUM	RECVDATE	RPTYPE	AGE (years)	SEX	Outcome	Event Reactions	Case categorization	Comments	dechallenge rechallenge	onset (days)
						DIZZINESS,EMOTIONAL DISORDER,HEADACHE, INSOMNIA,MOOD SWINGS,MUSCLE SPASMS,				
6121205	12-Mar-09	Direct	8	Female	OT	ABDOMINAL PAIN UPPER,ABNORMAL BEHAVIOUR,AMNESIA, NAUSEA,NIGHTMARE, OPPOSITIONAL DEFIANT DISORDER,	unassessable	amnesia event unclear. No information on resolution with dechallenge		7
5710816	17-Apr-08	Direct	47	Female	LT	ABNORMAL BEHAVIOUR,ABNORMAL DREAMS,AMNESIA, ANGER,MOOD ALTERED,SLEEP DISORDER,SUICIDAL IDEATION,	unassessable	no clear description of amnesia.		
6290873	29-Jul-09	Direct	U	Female	OT, RI	ABNORMAL BEHAVIOUR,AFFECTIVE DISORDER,AGGRESSION,AMNESIA,ANGER,DEATH OF RELATIVE,DRUG INEFFECTIVE, EMOTIONAL DISORDER, EYE DISORDER, IMPATIENCE, POOR QUALITY SLEEP,TREMOR,	unassessable	unclear description of amnesia		
6684869	16-Apr-10	Expedited (15-Day)	13	Female	HO, OT	ABNORMAL BEHAVIOUR, AGITATION, DRUG ABUSE, SHOPLIFTING, SUBSTANCE ABUSE, AMNESIA, APATHY, DECREASED APPETITE, DISTURBANCE IN ATTENTION, INTENTIONAL SELF-INJURY, MOOD SWINGS, BIPOLAR DISORDER,	unassessable	incomplete information regarding memory loss and resolution. Case centers around suicidal ideation and psych events and little about memory.		
5904797	1-Oct-08	Expedited (15-Day)	U	Male	OT	DEPRESSED MOOD,SUICIDAL IDEATION, ABNORMAL BEHAVIOUR, AMNESIA,	unassessable			
5690116	31-Mar-08	Direct	U	Female	OT	ABNORMAL BEHAVIOUR, AFFECTIVE DISORDER, AMNESIA, ANXIETY, BALANCE DISORDER, CONDITION AGGRAVATED, CONVULSION, DEMENTIA, DEMENTIA ALZHEIMER'S TYPE, DEPRESSION, DISTURBANCE IN ATTENTION, DRUG INEFFECTIVE,	unlikely	comorbid conditions, including seizure disorder		
3136088	28-Sep-98	Expedited (15-Day)	10	Male	LT, HO	AMNESIA, APHASIA, BLOOD IMMUNOGLOBULIN E INCREASED, BREATH HOLDING, CONVULSION,	unlikely	hyperventilation leading to convulsion resulting		

ISRNUM	RECVDATE	RPTYPE	AGE (years)	SEX	Outcome	Event Reactions	Case categorization	Comments	dechallenge rechallenge	onset (days)
						ELECTROENCEPHALO-GRAM ABNORMAL, GAZE PALSY, HYPERVENTILATION, HYPOAESTHESIA, LOSS OF CONSCIOUSNESS, MUSCLE SPASMS, PAPILLOEDEMA,		in amnesia		
3860880	29-Jan-02	Expedited (15-Day)	7	Male	HO, OT	AMNESIA, BALANCE DISORDER, DEPRESSED LEVEL OF CONSCIOUSNESS, DISTURBANCE IN ATTENTION, GAIT DISTURBANCE, HYPONATRAEMIA, INAPPROPRIATE ANTIDIURETIC HORMONE SECRETION, METABOLIC ACIDOSIS,	unlikely	metabolic acidosis		
4314293	9-Mar-04	Expedited (15-Day)	51	Female	OT	AMNESIA, CARDIAC ARREST, PHARYNGITIS STREPTOCOCCAL, ADVERSE EVENT, EAR PAIN,	unlikely	concomitant benzodiazepine (and surgery) could be associated with memory loss. Long latency to onset of event		
6360619	15-Sep-09	Expedited (15-Day)	65	Female	LT, OT	AMNESIA, CARDIAC DISORDER, CONVULSION,	unlikely	seizure		
5111200	20-Sep-06	Direct	5	Female	OT	AGGRESSION, AMNESIA, COMPLEX PARTIAL SEIZURES, CRYING, DYSGRAPHIA, EMOTIONAL DISORDER, ENCEPHALITIS, FORMICATION, INTENTIONAL SELF-INJURY, SUICIDAL BEHAVIOUR,	unlikely	concomitant seizure disorder		
6038973	15-Jan-09	Expedited (15-Day)	6	Female	LT, HO, DS	AMNESIA, MYOSITIS, RESPIRATORY FAILURE, STATUS EPILEPTICUS, DRUG HYPERSENSITIVITY, MUSCLE SPASMS,	unlikely	seizure		
5725744	1-May-08	Expedited (15-Day)	52	Female	HO, OT	NIGHTMARE, SYNCOPE, ASTHMA, SINUSITIS, ABDOMINAL PAIN, AMNESIA, ANXIETY, DIARRHOEA, DISTURBANCE IN ATTENTION, DRY MOUTH, DYSGEUSIA, STRESS,	unlikely	significant concomitant medications which could contribute to memory loss, med hx suggest previous psych disorder		
4852615	13-Dec-05	Expedited (15-Day)	50	Female	HO, DS, OT	PAIN, VOMITING, ANTICONVULSANT DRUG LEVEL INCREASED, ACCIDENTAL	unlikely	cognitive dysfunction		

ISRNUM	RECVDATE	RPTYPE	AGE (years)	SEX	Outcome	Event Reactions	Case categorization	Comments	dechallenge rechallenge	onset (days)
						OVERDOSE, AMNESIA, COORDINATION ABNORMAL, HEADACHE, LETHARGY,		associated with carbamazepine; previous memory disorder		
5640942	27-Feb-08	Expedited (15-Day)	67	Male	HO, OT	AMNESIA, GRAND MAL CONVULSION,	unlikely	seizure		


APPEARS THIS WAY ON ORIGINAL

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-20830	SUPPL-56	MERCK AND CO INC	SINGULAIR(MONTELUKAST SODIUM)CHEWABLE TA
NDA-21409	SUPPL-31	MERCK RESEARCH LABORATORIES DIV MERCK CO INC	SINGULAIR(MONTELUKAST SODIUM)4MG GRANULE
NDA-20829	SUPPL-55	MERCK RESEARCH LABORATORIES DIV MERCK CO INC	SINGULAIR (MONTELUKAST SODIUM) TABS

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/s/

MELINDA WILSON
06/30/2010

SUSAN L LU
07/01/2010

MARK I AVIGAN
07/01/2010

Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology

Date:	June 24, 2010
To:	Badrul Chowdhury, M.D. Director Division of Pulmonary, Allergy and Rheumatology Products (DPARP)
Through:	Mary Willy, Ph.D., Deputy Director **Division of Risk Management** LaShawn Griffiths, MSHS-PH, BSN, RN Senior Patient Labeling Reviewer, Acting Team Leader **Division of Risk Management**
From:	Robin Duer, RN, BSN, MBA Patient Product Information Reviewer **Division of Risk Management**
Subject:	DRISK Review of Patient Labeling (Patient Package Insert)
Drug Name(s) and Application Type/Number(s):	SINGULAIR (montelukast sodium) tablets, NDA 20-829/ S-055 SINGULAIR (montelukast sodium) chewable tablets, NDA 20-830/S-056 SINGULAIR (montelukast sodium) oral granules, NDA 21-409/S-031
Applicant/sponsor:	Merck & Company, Inc.
OSE RCM #:	2010-1209

1 INTRODUCTION

This review is written in response to a request by the Division of Pulmonary, Allergy and Rheumatology Products (DPARP) for the Division of Risk Management (DRISK) to review the Applicant's proposed addition of "disorientation" to the approved PPI for SINGULAIR.

Merck submitted a Changes Being Effected (CBE) labeling supplement for SINGULAIR (montelukast sodium) on April 14, 2010. The purpose of this submission was to add the adverse event "disorientation" to the SINGULAIR Prescribing Information (PI) under the Warnings and Precautions section, Neuropsychiatric Events subsection and to the Adverse Reactions section, Post-Marketing Experience, Psychiatric Disorders subsection. Additionally, Merck added "disorientation" to the Patient Package Insert (PPI) in the "What are the possible side effects of SINGULAIR?" section under serious side effects, behavior and mood-related changes. This submission was based on 84 Merck's Worldwide Adverse Experience System (WAES) reports previously submitted to FDA and an additional 55 WAES reports not previously submitted.

On May 5, 2010 the applicant submitted an amendment to the CBE labeling supplement which included the PLR conversion of the SINGULAIR PI and PPI as approved on April 26, 2010.

2 MATERIAL REVIEWED

- SINGULAIR (montelukast sodium) Prescribing Information (PI) submitted May 5, 2010 and sent to DRISK on May 27, 2010
- SINGULAIR (montelukast sodium) Patient Package Insert (PPI) submitted May 5, 2010 and sent to DRISK on May 27, 2010
- DRISK review of SINGULAIR (montelukast sodium) patient labeling (Patient Package Insert) dated November 10, 2009

3 DISCUSSION

On June 9, 2010 DRISK asked DPARP if the reporting of disorientation was considered to be new safety information, and DPARP responded that neuropsychiatric events were already known as adverse events associated with SINGULAIR. DPARP did not consider the reported adverse event of disorientation to be new safety information.

DRISK completed a comprehensive review of the SINGULAIR PPI on November 10, 2009 for the PLR conversion of the PI, so only the proposed addition of "disorientation" was included in this review of the PPI.

4 RESULTS OF REVIEW

We have reviewed Merck's proposed change to the PPI and suggest the following patient-friendly language:

Merck's proposed added language under serious side effects, behavior and mood-related changes:

- disorientation

DRISK revised patient-friendly language:

- disorientation (confusion)

Please let us know if you have any questions.

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
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/s/

ROBIN E DUER
06/24/2010

MARY E WILLY
06/24/2010
I concur

DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE FOOD AND DRUG ADM NISTRATION	**REQUEST FOR CONSULTATION**

TO *(Division/Office)*: **Mail: OSE**			FROM: Ladan Jafari, SRPM/DPARP 301-796-1231	
DATE: 5/27/2010	IND NO.	NDA NO.20-829 and NDA No: 20-830, and NDA No: 21-409	TYPE OF DOCUMENT: :Labeling supplement	DATE OF DOCUMENT: Amendment dated May 5, 2010, to CBE supplements dated April 14, 2010.
NAME OF DRUG: Singulair	PRIORITY CONSIDERATION: S		CLASSIFICATION OF DRUG: Respiratory	DESIRED COMPLETION DATE: June 30, 2010
NAME OF FIRM: Merck				

REASON FOR REQUEST

I. GENERAL

☐ NEW PROTOCOL	☐ PRE--NDA MEETING	☐ RESPONSE TO DEFICIENCY LETTER
☐ PROGRESS REPORT	☐ END OF PHASE II MEETING	☐ FINAL PRINTED LABELING
☐ NEW CORRESPONDENCE	☐ RESUBMISSION	☐ LABELING REVISION
☐ DRUG ADVERTISING	☐ SAFETY/EFFICACY	☐ ORIGINAL NEW CORRESPONDENCE
☐ ADVERSE REACTION REPORT	☐ PAPER NDA	☐ FORMULATIVE REVIEW
☐ MANUFACTURING CHANGE/ADDITION	☐ CONTROL SUPPLEMENT	☐ OTHER *(SPECIFY BELOW)*:
☐ MEETING PLANNED BY		

II. BIOMETRICS

STATISTICAL EVALUATION BRANCH	STATISTICAL APPLICATION BRANCH
☐ TYPE A OR B NDA REVIEW ☐ END OF PHASE II MEETING ☐ CONTROLLED STUDIES ☐ PROTOCOL REVIEW ☐ OTHER (SPECIFY BELOW):	☐ CHEMISTRY REVIEW ☐ PHARMACOLOGY ☐ BIOPHARMACEUTICS ☐ OTHER (SPECIFY BELOW):

III. BIOPHARMACEUTICS

☐ DISSOLUTION	☐ DEFICIENCY LETTER RESPONSE
☐ BIOAVAILABILTY STUDIES	☐ PROTOCOL-BIOPHARMACEUTICS
☐ PHASE IV STUDIES	☐ IN-VIVO WAIVER REQUEST

IV. DRUG EXPERIENCE

☐ PHASE IV SURVEILLANCE/EPIDEMIOLOGY PROTOCOL	☐ REVIEW OF MARKETING EXPERIENCE, DRUG USE AND SAFETY
☐ DRUG USE e.g. POPULATION EXPOSURE, ASSOCIATED DIAGNOSES	☐ SUMMARY OF ADVERSE EXPERIENCE
☐ CASE REPORTS OF SPECIFIC REACTIONS (List below)	☐ POISON RISK ANALYSIS
☐ COMPARATIVE RISK ASSESSMENT ON GENERIC DRUG GROUP	

V. SCIENTIFIC INVESTIGATIONS

☐ CLINICAL	☐ PRECLINICAL

COMMENTS/SPECIAL INSTRUCTIONS: The following submissions are available electronically in the EDR.

DPARP request input regarding a Changes Being Effected (CBE) Supplement submitted for the addition of the term "disorientation" to the labeling for Singulair Tablets (NDA 20-829), Chewable Tables (NDA 20-830), and Oral Granules (NDA 21-409). The original labeling supplement was submitted on April 14, 2010. Following the April 26, 2010, approval of the labeling conversion to the Physician Labeling Rule (PLR) format, the Applicant submitted an amendment to the CBE labeling supplement dated May 5, 2010, which submitted the proposed changes in the PLR format.

The Applicant proposes the addition of the term "disorientation" to the package insert (PI), in WARNINGS AND PRECAUTIONS under the subsection Neuropsychiatric Events, as well as to the Post-Marketing Experience subsection of ADVERSE REACTIONS, where it is grouped with related terms under the System Organ Classification of psychiatric disorders. In addition to the changes submitted for the PI, the Applicant also proposes the addition of the term "disorientation" to the patient package insert (PPI) under the section titled, "What are the possible side effects of SINGULAIR?" in the "Behavior and mood-related changes" subsection. The list of 84

Merck Worldwide Adverse Experience System (WAES) reports previously submitted to the FDA and 55 WAES reports not previously submitted supporting the addition of the term to the PI and PPI is provided in the supplement. The proposed changes to the PI and PPI appear appropriate to DPARP.

Consult Question:

1) Does OSE concur with the proposed changes to the PI and PPI?

SIGNATURE OF REQUESTER: Ladan Jafari	METHOD OF DELIVERY (Check one) ☐ MAIL ☐ HAND
SIGNATURE OF RECEIVER	SIGNATURE OF DELIVERER

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
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/s/

LADAN G JAFARI
05/27/2010