CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

020829Orig1s073

Trade Name:	**SINGULAIR**
Generic or Proper Name:	montelukast sodium
Sponsor:	Organon LLC
Approval Date:	April 29, 2020
Indication:	SINGULAIR is a leukotriene receptor antagonist indicated for: Prophylaxis and chronic treatment of asthma in patients 12 months of age and older. Acute prevention of exercise-induced bronchoconstriction (EIB) in patients 6 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. Reserve use for patients who have an inadequate response or intolerance to alternative therapies.

CENTER FOR DRUG EVALUATION AND RESEARCH

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APPROVAL LETTER

NDA 20829/S-073
NDA 20830/S-075
NDA 21409/S-051

SUPPLEMENT APPROVAL

Merck Sharp & Dohme Corp.
126 E. Lincoln Ave.
P.O. Box 2000
RY34-B295
Rahway, NJ 07065

Attention: Eleftheria Tsatsos
Senior Scientist, Regulatory Liaison

Dear Ms. Tsatsos:

Please refer to your supplemental new drug applications (sNDA) dated April 3, 2020, received April 3, 2020, and your amendments, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Singulair (montelukast) Tablets, Granules, and Chewable Tablets.

We also refer to our letter dated March 4, 2020, notifying you, under Section 505(o)(4) of the FDCA, of new safety information that we believe should be included in the labeling for Singulair. This information pertains to the risk of neuropsychiatric adverse reactions.

These supplemental new drug applications provide for revisions to the labeling for Singulair, consistent with our March 4, 2020, Safety Labeling Change Notification Letter, and those additional revisions communicated on April 16, 2020.

APPROVAL & LABELING

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

WAIVER OF ½ PAGE LENGTH REQUIREMENT FOR HIGHLIGHTS

Please note that we have previously granted a waiver of the requirements of 21 CFR 201.57(d)(8) regarding the length of Highlights of Prescribing Information.

CONTENT OF LABELING

As soon as possible, but no later than 14 days from the date of this letter, submit the content of labeling [21 CFR 314.50(l)] in structured product labeling (SPL) format using the FDA automated drug registration and listing system (eLIST), as described at FDA.gov.[1] Content of labeling must be identical to the enclosed labeling (text for the Prescribing Information, Instructions for Use, and Medication Guide), with the addition of any labeling changes in pending "Changes Being Effected" (CBE) supplements, as well as annual reportable changes not included in the enclosed labeling.

Information on submitting SPL files using eList may be found in the guidance for industry *SPL Standard for Content of Labeling Technical Qs and As*.[2]

The SPL will be accessible from publicly available labeling repositories.

Also within 14 days, amend all pending supplemental applications that include labeling changes for this NDA, including 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 Microsoft Word format, that includes the changes approved in this supplemental application, as well as annual reportable changes. To facilitate review of your submission(s), provide a highlighted or marked-up copy that shows all changes, as well as a clean Microsoft Word version. The marked-up copy should provide appropriate annotations, including supplement number(s) and annual report date(s).

CARTON AND CONTAINER LABELING

Submit final printed carton and container labeling that are identical to the enclosed carton and container labeling as soon as they are available, but no more than 30 days after they are printed. Please submit these labeling electronically according to the guidance for industry *Providing Regulatory Submissions in Electronic Format — Certain Human Pharmaceutical Product Applications and Related Submissions Using the eCTD Specifications*. For administrative purposes, designate this submission "**Final Printed Carton and Container Labeling for approved NDA 20829/S-073, NDA 20830/S-075, and NDA 21409/S-051**." Approval of this submission by FDA is not required before the labeling is used.

[1] http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm
[2] We update guidances periodically. For the most recent version of a guidance, check the FDA Guidance Documents Database https://www.fda.gov/RegulatoryInformation/Guidances/default.htm.

REPORTING REQUIREMENTS

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}

Sally M. Seymour, MD
Director
Division of Pulmonology, Allergy, and Critical Care
Office of Immunology and Inflammation
Center for Drug Evaluation and Research

ENCLOSURE(S):

- Content of Labeling
  - Prescribing Information
  - Medication Guide
  - Instructions for Use
- Carton and Container Labeling

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

SALLY M SEYMOUR
04/29/2020 02:59:11 PM

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

020829Orig1s073

LABELING

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

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

- **Serious neuropsychiatric events have been reported in patients taking SINGULAIR (5.1).**
- **Discuss benefits and risks of SINGULAIR with patients and caregivers (5.1).**
- **Monitor for neuropsychiatric symptoms in patients taking SINGULAIR (5.1).**
- **Discontinue SINGULAIR immediately if neuropsychiatric symptoms occur (5.1).**
- **Because the benefits of SINGULAIR may not outweigh the potential risk of neuropsychiatric symptoms in patients with allergic rhinitis, reserve use for patients who have an inadequate response or intolerance to alternative therapies (1.3, 5.1).**

----------RECENT MAJOR CHANGES----------

Boxed Warning	04/2020
Indications and Usage, Allergic Rhinitis (1.3)	04/2020
Dosage and Administration, Asthma (2.1), Allergic Rhinitis (2.3), Asthma and Allergic Rhinitis (2.4)	04/2020
Warnings and Precautions, Neuropsychiatric Events (5.1)	04/2020

----------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 6 years of age and older (1.2).
- Relief of symptoms of allergic rhinitis (AR): seasonal allergic rhinitis (SAR) in patients 2 years of age and older, and perennial allergic rhinitis (PAR) in patients 6 months of age and older. Reserve use for patients who have an inadequate response or intolerance to alternative therapies (1.3).

----------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): One tablet at least 2 hours before exercise for patients 6 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) (2):

- 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----------

- Tablets: 10 mg (3)
- Chewable tablets: 5 mg and 4 mg (3)
- Oral granules: 4 mg (3)

----------CONTRAINDICATIONS----------

Hypersensitivity to any component of this product (4).

----------WARNINGS AND PRECAUTIONS----------

- Do not prescribe SINGULAIR to treat an acute asthma attack (5.2).
- Advise patients to have appropriate rescue medication available (5.2).
- Inhaled corticosteroid may be reduced gradually. Do not abruptly substitute SINGULAIR for inhaled or oral corticosteroids (5.3).
- Patients with known aspirin sensitivity should continue to avoid aspirin or non-steroidal anti-inflammatory agents while taking SINGULAIR (5.4).
- Systemic eosinophilia, sometimes presenting with clinical features of vasculitis consistent with Churg-Strauss syndrome, has been reported. These events have been sometimes 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 Medication Guide.

Revised: 04/2020

FULL PRESCRIBING INFORMATION: CONTENTS*

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

FULL PRESCRIBING INFORMATION

WARNING: SERIOUS NEUROPSYCHIATRIC EVENTS

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

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

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

1 INDICATIONS AND USAGE

1.1 Asthma

SINGULAIR® is indicated for the prophylaxis and chronic treatment of asthma in adults and pediatric patients 12 months of age and older.

1.2 Exercise-Induced Bronchoconstriction (EIB)

SINGULAIR is indicated for prevention of exercise-induced bronchoconstriction (EIB) in patients 6 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. Because the benefits of SINGULAIR may not outweigh the risk of neuropsychiatric symptoms in patients with allergic rhinitis *[see Warnings and Precautions (5.1)]*, reserve use for patients who have an inadequate response or intolerance to alternative therapies.

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.

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

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)

For prevention of EIB, a single dose of SINGULAIR should be taken at least 2 hours before exercise. 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.

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 efficacy in patients younger than 6 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.

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.

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

2.4 Asthma and Allergic Rhinitis

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

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

2.5 Instructions for Administration of Oral Granules

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 MSD 117 on one side and SINGULAIR on the other.
- SINGULAIR 5-mg Chewable Tablets are pink, round, bi-convex-shaped tablets, with code MSD 275 on one side and SINGULAIR on the other.
- SINGULAIR 4-mg Chewable Tablets are pink, oval, bi-convex-shaped tablets, with code MSD 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 Neuropsychiatric Events

Serious neuropsychiatric (NP) events have been reported with use of SINGULAIR. These postmarketing reports have been highly variable and included, but were not limited to, agitation, aggressive behavior or hostility, anxiousness, depression, disorientation, disturbance in attention, dream abnormalities, dysphemia (stuttering), hallucinations, insomnia, irritability, memory impairment, obsessive-compulsive symptoms, restlessness, somnambulism, suicidal thoughts and behavior (including suicide), tic, and tremor. NP events have been reported in adult, adolescent, and pediatric patients with and without a previous history of psychiatric disorder. NP events have been reported mostly during SINGULAIR treatment, but some were reported after SINGULAIR discontinuation. Animal studies showed that montelukast distributes into the brain in rats *[see Clinical Pharmacology (12.3)]*; however, the mechanisms underlying SINGULAIR-associated NP events are currently not well understood. Based upon the available data, it is difficult to identify risk factors for or quantify the risk of NP events with SINGULAIR use.

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

Discuss the benefits and risks of SINGULAIR use with patients and caregivers when prescribing SINGULAIR. Advise patients and/or caregivers to be alert for changes in behavior or for new NP symptoms when taking SINGULAIR. If changes in behavior are observed, or if new NP symptoms or suicidal thoughts and/or behavior occur, advise patients to discontinue SINGULAIR and contact a healthcare provider immediately. In many cases, symptoms resolved after stopping SINGULAIR therapy; however, in some cases symptoms persisted after discontinuation of SINGULAIR. Therefore, continue to monitor and provide supportive care until symptoms resolve. Re-evaluate the benefits and risks of restarting treatment with SINGULAIR if such events occur.

5.2 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.

5.3 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.

5.4 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)]*.

5.5 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 have been sometimes 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.

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

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 Postmarketing 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, thrombocytopenia.

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

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

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

Cardiac disorders: palpitations.

Respiratory, thoracic and mediastinal disorders: epistaxis, pulmonary eosinophilia.

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

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 multiforme, erythema nodosum, pruritus, Stevens-Johnson syndrome/toxic epidermal necrolysis, urticaria.

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

Renal and urinary disorders: enuresis in children.

General disorders and administration site conditions: edema.

Patients with asthma on therapy with 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 have been sometimes 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, gemfibrozil, itraconazole, thyroid hormones, sedative hypnotics, non-steroidal anti-inflammatory agents, benzodiazepines, decongestants, and Cytochrome P450 (CYP) enzyme inducers *[see Clinical Pharmacology (12.3)].*

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

Available data from published prospective and retrospective cohort studies over decades with montelukast use in pregnant women have not established a drug-associated risk of major birth defects *[see Data]*. In animal reproduction studies, no adverse developmental effects were observed with oral administration of montelukast to pregnant rats and rabbits during organogenesis at doses approximately 100 and 110 times, respectively, the maximum recommended human daily oral dose (MRHDOD) based on AUCs *[see Data].*

The estimated background risk of major birth defects and miscarriage for the indicated population is unknown. All pregnancies have a background risk of birth defect, loss, or other adverse outcomes. In the

U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2-4% and 15-20%, respectively.

Clinical Considerations

Disease-associated maternal and/or embryo/fetal risk

Poorly or moderately controlled asthma in pregnancy increases the maternal risk of perinatal adverse outcomes such as preeclampsia and infant prematurity, low birth weight, and small for gestational age.

Data

Human Data

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

Animal Data

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

8.2 Lactation

Risk Summary

A published clinical lactation study reports the presence of montelukast in human milk. Data available on the effects of the drug on infants, either directly *[see Use in Specific Populations (8.4)]* or through breast milk, do not suggest a significant risk of adverse events from exposure to SINGULAIR. The effects of the drug on milk production are unknown. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for SINGULAIR and any potential adverse effects on the breastfed infant from SINGULAIR or from the underlying maternal condition.

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, 14.2)].*

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

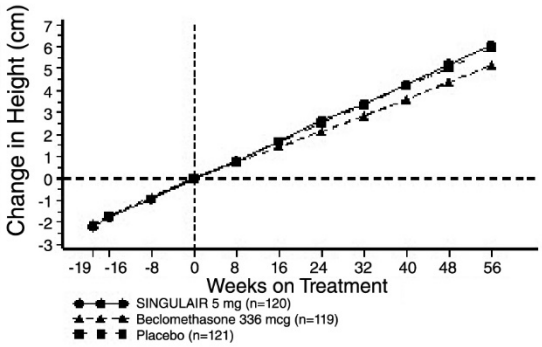
asthma and from pharmacokinetic data comparing systemic exposures in patients 6 months to 23 months of age to systemic exposures in adults.

The safety and effectiveness in pediatric patients below the age of 12 months with asthma, 6 months with perennial allergic rhinitis, and 6 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

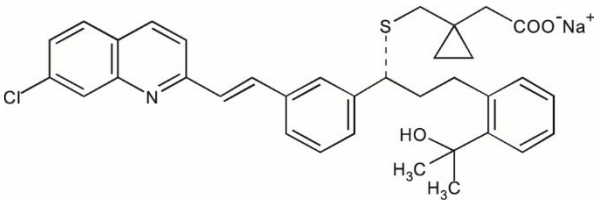
No specific information is available on the treatment of overdosage with SINGULAIR. In the event of overdose, it is reasonable to employ the usual supportive measures; e.g., remove unabsorbed material from the gastrointestinal tract, employ clinical monitoring, and institute supportive therapy, if required. 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 $\pm$ 1.0 hours to 6.4 $\pm$ 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. Orally administered montelukast distributes into the brain in rats.

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, 2C8, and 2C9 are involved in the metabolism of montelukast. At clinically relevant concentrations, 2C8 appears to play a major role in the metabolism of montelukast.

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.

Effect of Montelukast on Cytochrome P450 (CYP) Enzymes: 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). Based on further *in vitro* results in human liver microsomes, therapeutic plasma concentrations of montelukast do not inhibit CYP 3A4, 2C9, 1A2, 2A6, 2C19, or 2D6.

Cytochrome P450 (CYP) Enzyme Inhibitors: In vitro studies have shown that montelukast is a substrate of CYP 2C8, 2C9, and 3A4. Co-administration of montelukast with itraconazole, a strong CYP 3A4 inhibitor, resulted in no significant increase in the systemic exposure of montelukast. Data from a clinical drug-drug interaction study involving montelukast and gemfibrozil (an inhibitor of both CYP 2C8 and 2C9) demonstrated that gemfibrozil, at a therapeutic dose, increased the systemic exposure of montelukast by 4.4-fold. Co-administration of itraconazole, gemfibrozil, and montelukast did not further increase the systemic exposure of montelukast. Based on available clinical experience, no dosage adjustment of montelukast is required upon co-administration with gemfibrozil *[see Overdosage (10)]*.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

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

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

In fertility studies in female rats, montelukast produced reductions in fertility and fecundity indices at an oral dose of 200 mg/kg (estimated exposure was approximately 70 times the AUC for adults at the maximum recommended daily oral dose). No effects on 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).

14 CLINICAL STUDIES

14.1 Asthma

Adults and Adolescents 15 Years of Age and Older with Asthma

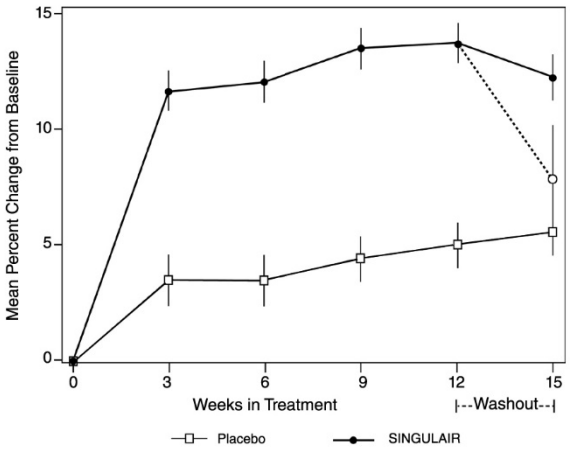
Clinical trials in adults and adolescents 15 years of age and older demonstrated there is no additional clinical benefit to montelukast doses above 10 mg once daily.

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 ($p \leq 0.05$). It is not known whether the results of this study can be generalized to patients with asthma who require higher doses of inhaled corticosteroids or systemic corticosteroids.

In another randomized, placebo-controlled, parallel-group trial (n=642) in a similar population of adult patients 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 (5.4)].*

14.2 Exercise-Induced Bronchoconstriction (EIB)

Exercise-Induced Bronchoconstriction (Adults, Adolescents, and Pediatric Patients 6 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

The efficacy of SINGULAIR 5-mg chewable tablets, when given as a single dose 2 hours before exercise for the prevention of EIB, was investigated in one multinational, randomized, double-blind, placebo-controlled crossover study that included a total of 64 pediatric patients 6 to 14 years of age with EIB. Exercise challenge testing was conducted at 2 hours and 24 hours following administration of a single dose of study drug (SINGULAIR 5 mg or placebo). The primary endpoint was the mean maximum percent fall in FEV_1 following the 2 hours post-dose exercise challenge. A single dose of SINGULAIR 5 mg demonstrated a statistically significant protective benefit against EIB when taken 2 hours prior to exercise (TABLE 4).

Similar results were shown at 24 hours post-dose (a secondary endpoint). Some patients were protected from EIB at 24 hours after administration; however, some patients were not. No timepoints were assessed between 2 and 24 hours post-dose.

Table 4: Mean Maximum Percent Fall in FEV_1 Following Exercise Challenge in Pediatric Patients (N=64) 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	15	20	-5 (-9, -1)
24 hours	13	17	-4 (-7, -1)

*Least squares-mean

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

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

In a 12-week, randomized, double-blind, parallel group study of 110 adult and adolescent asthmatics 15 years of age and older, with a mean baseline 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., $\geq$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 5. The remaining three trials that demonstrated efficacy showed similar results.

Table 5: 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.
† Statistically different from placebo ($p \leq 0.001$).
‡ The study was not designed for statistical comparison between SINGULAIR and the active control (loratadine).

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 6); 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 6: 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. 6628 — SINGULAIR Tablets, 4 mg, are pink, oval, bi-convex-shaped chewable tablets, with code MSD 711 on one side and SINGULAIR on the other. They are supplied as follows:

NDC 0006-1711-31 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.

No. 6543 — SINGULAIR Tablets, 5 mg, are pink, round, bi-convex-shaped chewable tablets, with code MSD 275 on one side and SINGULAIR on the other. They are supplied as follows:

NDC 0006-9275-31 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.

No. 6558 — SINGULAIR Tablets, 10 mg, are beige, rounded square-shaped, film-coated tablets, with code MSD 117 on one side and SINGULAIR on the other. They are supplied as follows:

NDC 0006-9117-31 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 0006-9117-54 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.

Storage

Store SINGULAIR 4-mg oral granules, 4-mg chewable tablets, 5-mg chewable tablets and 10-mg film-coated tablets at 20°C to 25°C (68°F to 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.

17 PATIENT COUNSELING INFORMATION

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

- Advise patients about the potential risk for serious neuropsychiatric symptoms and behavioral changes with SINGULAIR use.
- Discuss the benefits and risks of SINGULAIR with patients when prescribing or continuing treatment with SINGULAIR.
- Advise patients to monitor for changes in behavior or neuropsychiatric symptoms in patients taking SINGULAIR.
- Instruct patients to discontinue SINGULAIR and contact a healthcare provider immediately if changes in behavior or thinking that are not typical for the patient occur, or if the patient develops suicidal ideation or suicidal behavior.
- Advise patients 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.
- Advise patients 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.
- Advise patients to seek medical attention if short-acting inhaled bronchodilators are needed more often than usual, or if more than the maximum number of inhalations of short-acting bronchodilator treatment prescribed for a 24-hour period are needed.
- Instruct patients to continue other anti-asthma medications as prescribed unless instructed by a physician.
- Instruct patients with known aspirin sensitivity to continue avoidance of aspirin or non-steroidal anti-inflammatory agents while taking SINGULAIR.
- Inform phenylketonuric patients that the 4-mg and 5-mg chewable tablets contain phenylalanine (a component of aspartame).

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For patent information: www.merck.com/product/patent/home.html

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MEDICATION GUIDE

SINGULAIR® (SING-u-lair)

(montelukast sodium)

tablets **chewable tablets** **oral granules**

What is the most important information I should know about SINGULAIR?

Serious mental health problems have happened in people taking SINGULAIR or even after treatment has stopped. This can happen in people with or without a history of mental health problems. Stop taking SINGULAIR and tell your healthcare provider right away if you or your child have any unusual changes in behavior or thinking, including any of these symptoms:

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

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 inflammation of the lining of the nose (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 have an asthma attack, you should follow the instructions your healthcare provider gave you for treating asthma attacks.
2. Prevent exercise-induced asthma in people 6 years of age and older.
3. Help control the symptoms of allergic rhinitis such as sneezing, stuffy nose, runny nose, and itching of the nose. SINGULAIR is used to treat the following in people who have already taken other medicines that did not work well enough or in people who could not tolerate other medicines:
   - 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.

Do not take SINGULAIR if you are allergic to any of its ingredients. See the end of this Medication Guide for a complete list of the ingredients in SINGULAIR.

Before taking SINGULAIR, tell your healthcare provider about all your medical conditions, including if you:

- are allergic to aspirin.
- have phenylketonuria. SINGULAIR chewable tablets contain aspartame, a source of phenylalanine.
- have or have had mental health problems.
- are pregnant or plan to become pregnant. Talk to your healthcare provider if you are pregnant or plan to become pregnant, SINGULAIR may not be right for you.
- are breastfeeding or plan to breastfeed. 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 over the counter 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:

- Read the detailed **Instructions for Use** that comes with SINGULAIR oral granules.
- 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.**
- Stop taking SINGULAIR and tell your healthcare provider right away if you or your child have any unusual changes in behavior or thinking.
- You can take SINGULAIR with food or without food. See the section "**How can I give SINGULAIR oral granules to my child?**" in the **Instructions for Use** 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 healthcare provider right away.

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.
- Always have your rescue inhaler medicine with you for asthma attacks.
- Continue to take your other asthma medicines as prescribed unless your healthcare provider tells you to change how you take these medicines.

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

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

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, including:

- See **"What is the most important information I should know about SINGULAIR?"**
- **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 sometimes 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 of SINGULAIR include:

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

These are not all the possible side effects of SINGULAIR. Call your doctor 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 room temperature between 68°F to 77°F (20°C to 25°C).
- Keep SINGULAIR in the package it comes in.
- Keep SINGULAIR in a dry place and keep it away from light.
- **Keep SINGULAIR and all medicines out of reach of children.**

General information about the safe and effective use of SINGULAIR.

Medicines are sometimes prescribed for purposes other than those listed in a Medication Guide. 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.

You can ask your pharmacist or healthcare provider for information about SINGULAIR that is written for health professionals.

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.

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This Medication Guide has been approved by the U.S. Food and Drug Administration Revised: 04/2020

INSTRUCTIONS FOR USE
SINGULAIR® (SING-u-lair)
(montelukast sodium)
oral granules

This Instructions for Use contains information on how to use SINGULAIR oral granules.

Important Information:

- Before giving a dose of SINGULAIR oral granules, read this Instructions for Use to be sure you prepare and give the oral granules correctly.
- Give SINGULAIR oral granules to your child exactly as instructed by your healthcare provider.
- Stop giving SINGULAIR and tell your healthcare provider right away if your child has any unusual changes in behavior or thinking.
- Continue to give your child their asthma medicines as prescribed, unless your healthcare provider tells you to change how you give these medicines.
- You can give SINGULAIR oral granules with food or without food.

How can I give SINGULAIR oral granules to my child?

- **Do not** open the packet until ready to use.
- There are different ways you can give SINGULAIR 4-mg oral granules. You should choose the best method for your child:
  - right into the mouth
  - dissolved in 1 teaspoonful (5 mL) of cold or room temperature baby formula or breast milk
  - 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 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.

How should I store SINGULAIR?

- Store SINGULAIR at room temperature between 68°F to 77°F (20°C to 25°C).
- Keep SINGULAIR in the package it comes in.
- Keep SINGULAIR in a dry place and keep it away from light.
- **Keep SINGULAIR and all medicines out of the reach of children.**

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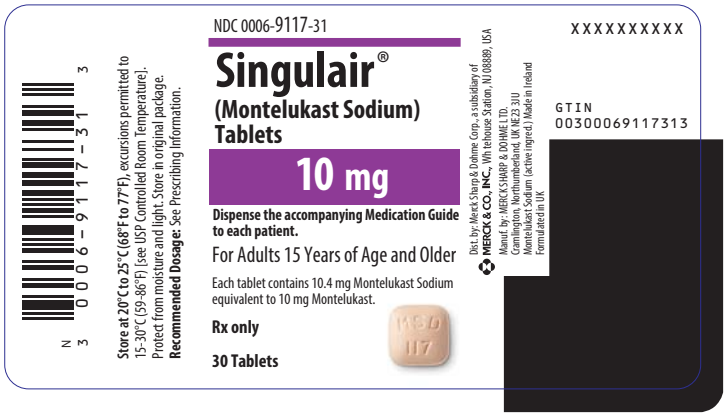
For more information, call the Merck National Service Center at 1-800-NSC-Merck (1-800-672-6372)

This Instructions for Use has been approved by the U.S. Food and Drug Administration Approved: April 2020



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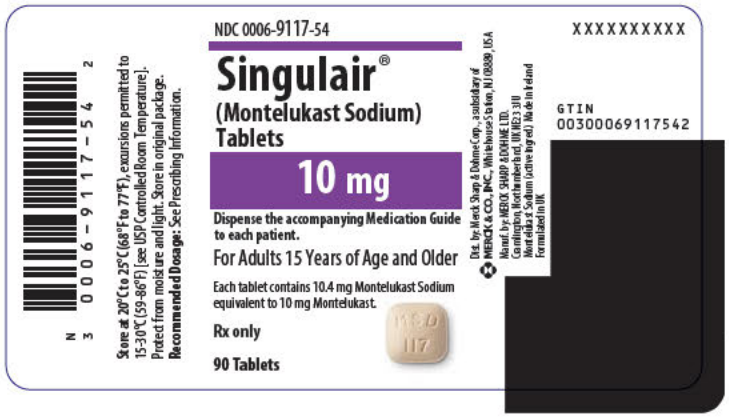

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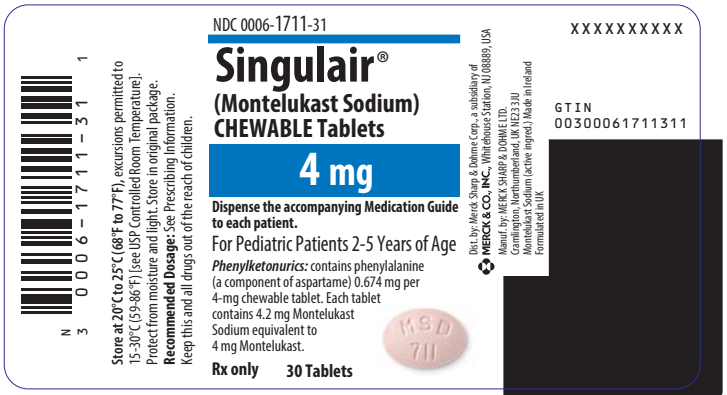

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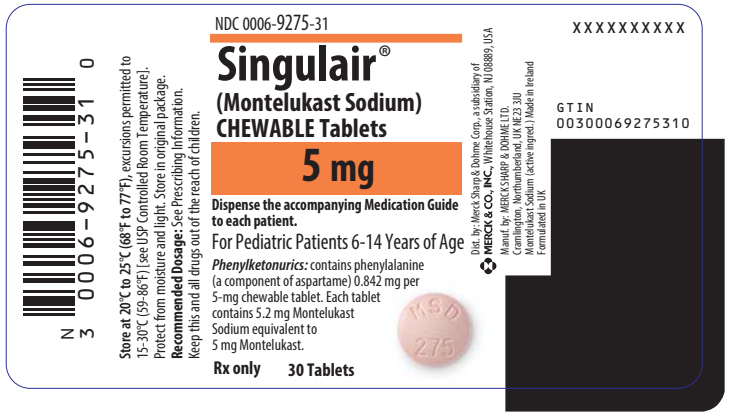

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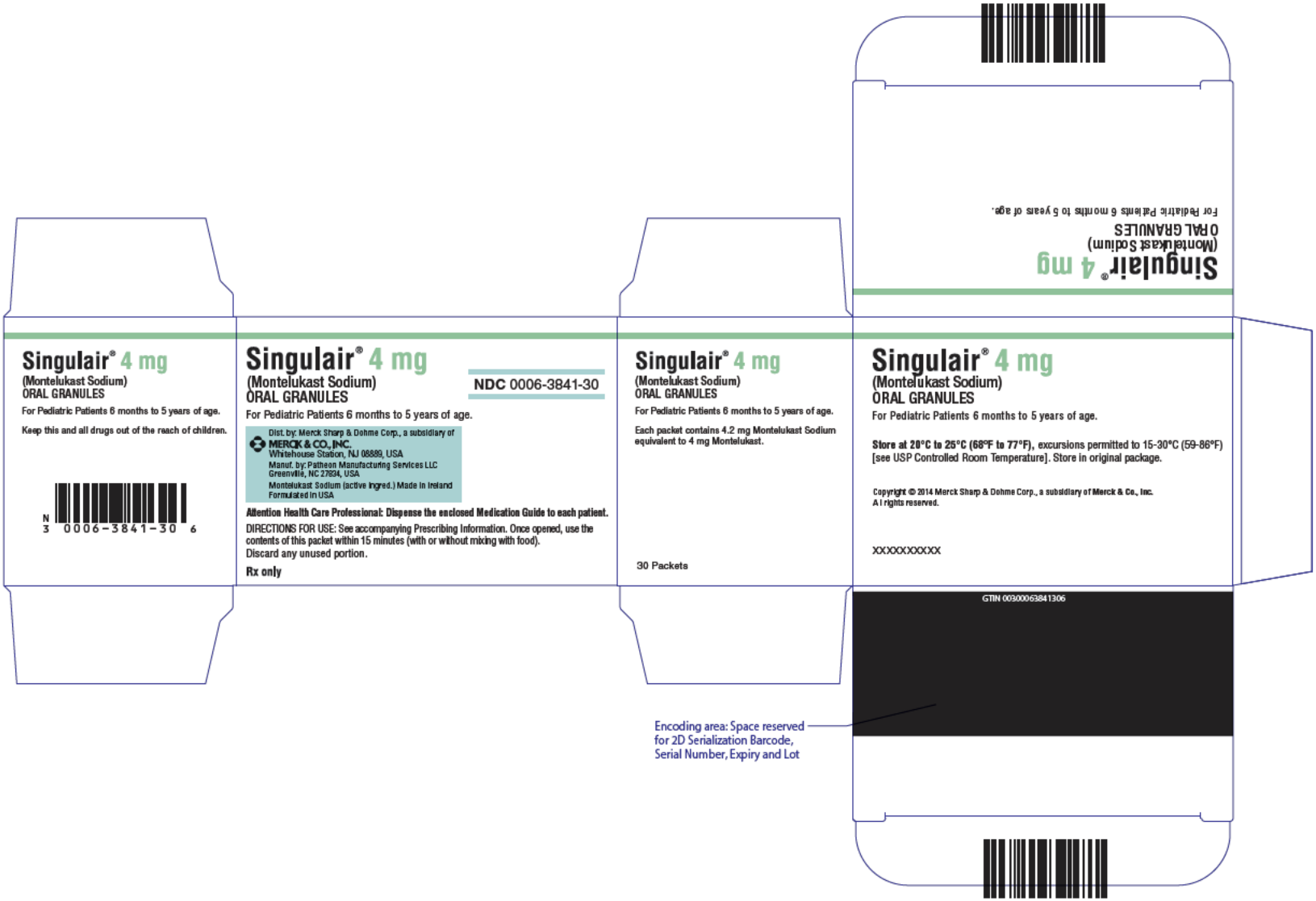

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/s/

SALLY M SEYMOUR
04/29/2020 02:59:11 PM

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

020829Orig1s073

CLINICAL REVIEW(S)

MEDICAL OFFICER REVIEW
Division Of Pulmonary, Allergy, and Rheumatology Products (HFD-570)

APPLICATION:	NDA 20-829 S-073 20-830 S-075 21-409 S-051	**TRADE NAME:**	Singulair
APPLICANT/SPONSOR:	Merck	**GENERIC NAME:**	Montelukast sodium tablets, chewable tablets, and oral granules
MEDICAL OFFICER:	Katherine Clarridge, M.D.		
TEAM LEADER:	Stacy Chin, M.D.	**CATEGORY:**	Leukotriene Receptor Antagonist
REVIEW DATE:	4/22/2020	**ROUTE:**	Oral

SUBMISSIONS REVIEWED IN THIS DOCUMENT

Document Date	CDER Stamp Date	Submission	Comments
4/3/2020	4/3/2020	NDA 20-829 S-073 20-830 S-075 21-409 S-051	Changes Being Effected (CBE)-0 Safety Labeling Changes Supplement

REVIEW SUMMARY:

This is a brief medical officer review of a Changes Being Effected (CBE)-0, safety labeling changes supplement for Singulair (Montelukast sodium) 10-mg tablets, 5-mg and 4-mg chewable tablets, and 4-mg oral granules. Singulair is a leukotriene receptor antagonist indicated for prophylaxis and chronic treatment of asthma in patients ≥ 12 months of age, acute prevention of exercise-induced bronchoconstriction (EIB) in patients ≥ 6 years of age, and relief of symptoms of allergic rhinitis (AR), seasonal allergic rhinitis (SAR) in patients ≥ 2 years of age, and perennial allergic rhinitis (PAR) in patients ≥ 6 months of age.

The FDA determined that the benefit-risk assessment for allergic rhinitis had changed since the initial approval and therefore decided to issue a boxed warning (BW) and medication guide (MG) to better communicate the potential risk of neuropsychiatric events with montelukast use. Additionally, the FDA issued a Drug Safety Communication (DSC) and press release (PR) to alert the public to the change in labeling and potential risk of NP events with use of montelukast. For additional details, refer to my previous review memo dated March 4, 2020.

The Division issued a Safety Labeling Change letter outlining the new safety information and proposed changes on March 4, 2020. The Sponsor has incorporated the Agency's labeling revisions with minor editorial edits. The new Medication Guide and Instructions for Use were reviewed by the Patient Labeling Team and found to be acceptable with revisions. Therefore, the recommended action on the safety labeling changes supplements for NDAs 21-409, 20-829, and 20-830 is approval.

OUTSTANDING ISSUES: None

RECOMMENDED REGULATORY ACTION		
IND/NEW STUDIES:	**SAFE TO PROCEED**	**CLINICAL HOLD**
NDA: APPROVAL X		

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/s/

KATHERINE E CLARRIDGE
04/22/2020 05:40:22 PM

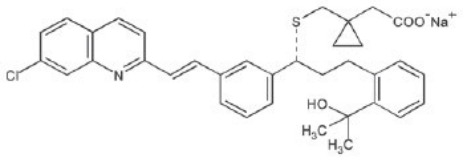
STACY J CHIN
04/23/2020 07:25:33 AM

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

020829Orig1s073

PRODUCT QUALITY REVIEW(S)

CHEMIST'S REVIEW *Review #1*	1. ORGANIZATION BRANCH 1/DPMA1/OLDP/OPQ	2. NDA NUMBER **20-829**
3. NAME AND ADDRESS OF APPLICANT *(City and State)* Merck Sharp & Dohme Corp., a Subsidiary of Merck & Co., Inc. 1 Merck Drive, P.O. Box 100 Whitehouse Station, NJ 08889-0100 Tel: (908) 423-1000 Name and Title of Applicant's Responsible Official Eleftheria Tsatsos, Sr. Scientist, Regulatory Liaison, Global Regulatory Affairs 126 E. Lincoln Avenue, P.O. Box 2000 RY34-B295 Rahway, NJ 07065 Tel: (732) 594-2129 Fax: (732) 594-6601 E-mail: eleftheria.tsatsos@merck.com		4. AF NUMBER 5. SUPPLEMENT (S) NUMBER(S) DATES(S) **S-73; CBE-30; SDN 1953; SN 0214** **S-73; CBE-30; SDN 1952; SN 0215** Letter Date: 04/03/2020 Stamp Date: 04/03/2020 **Due Date: 10/03/2020**
6. NAME OF DRUG SINGULAIR Tablets	7. NONPROPRIETARY NAME Montelukast Sodium	
8. SUPPLEMENT PROVIDES FOR: Safety Labeling Changes Under 505(o)(4) – Revision of USPI including addition of black box warning and limitation of allergic rhinitis indication; preparation of new Medication Guide and Instructions for Use.		
9. PROPOSED INDICATION FOR USE asthma, seasonal and perennial allergic rhinitis, exercise-induced bronchoconstriction	10. HOW DISPENSED RX x OTC ___	11. RELATED IND/NDA/DMF
12. DOSAGE FORM(S) Tablets	13. POTENCY 10 mg	
14. CHEMICAL NAME AND STRUCTURE **Montelukast sodium**: [R-(E)]-1-[[[1-[3-[2-(7-chloro-2quinolinyl)ethenyl]phenyl]-3-[2-(1-hydroxy-1-methylethyl)phenyl]-propyl]thio]methyl]cyclopropaneacetic acid, monosodium salt  Molecular Formula: $C_{35}H_{35}ClNNaO_3S$; Molecular Weight: 608.18		15. RECORDS AND REPORTS CURRENT YES__NO REVIEWED YES__NO
16. COMMENTS: The draft labeling text is adequate from CMC standpoint. Proposed carton and container labels for SINGULAIR NDA 20-829, NDA 20-830, and NDA 21-409 are also adequate.		
17. CONCLUSIONS AND RECOMMENDATIONS Proposed labeling changes are adequate from CMC standpoint.		
18. REVIEWER NAME Chong-Ho Kim, Ph.D.	SIGNATURE	DATE COMPLETED April 16, 2020

Background:

Merck Sharp & Dohme Corp. (Merck), a subsidiary of Merck & Co. Inc., submits the following Changes Being Effected Supplement to SINGULAIR® NDA 20-829, NDA 20-830, and NDA 21-409.

Reference is made to the FDA's March 4, 2020 Safety Labeling Change Notification, which requested several labeling changes, including the addition of a Boxed Warning, the creation of a Medication Guide, and a limitation of use statement for the allergic rhinitis indication. Reference is also made to the FDA's March 31, 2020 email communication, which noted the Agency's concurrence that a Changes Being Effected Supplement would be the appropriate submission type for these changes.

This supplemental application provides for changes in the labeling section of the approved SINGULAIR NDAs, in response to the FDA's Safety Labeling Change Notification. Merck agrees to include the FDA-proposed revisions in the product labeling, as requested by the Agency. As noted in the emails from Merck to the FDA on March 20, 2020 and March 23, 2020, Merck has accepted the majority of the FDA recommended changes, verbatim, but has also proposed additional revisions for accuracy, consistency, completeness, and/or clarity. These additional changes, which are not verbatim to the FDA proposed language, still support the FDA's message.

Merck is submitting an updated United States Prescribing Information label (NDA 20-829, 20-830, and 21-409), a new Medication Guide (NDA 20-829, 20-830, and 21-409), and a new Instructions for Use (NDA 21-409).

The proposed labeling text is supplied within Section 1.14.1.3 Draft labeling text.

Review:

1.12.14 Environmental Analysis

Merck is requesting a categorical exclusion from the requirements to prepare an Environmental Assessment under 21 CFR §25.31(a). The supplement meets the requirements of a categorical exclusion under 21 CFR §25.31(a) because it will not increase the use of the drug. To the best of the firm's knowledge, no extraordinary circumstances exist in regards to this action.

Evaluation: *Adequate*

1.14 Labeling
1.14.1 Draft Labeling
1.14.1.3 Draft Labeling Text

Evaluation: *Adequate*
There are no changes in Sections 11(DESCRIPTION) and 16 (HOW SUPPLIED/STORAGE AND HANDLING).

S-73; SDN 1952; SN 0215

This submission provides carton and container labeling for SINGULAIR NDA 20-829, NDA 20-830, and NDA 21-409, as requested in the FDA Safety Labeling Change Notification. Each NDA referenced in this letter will contain only the representative labels associated with that NDA.

NDA 20-829: SINGULAIR® Tablets (montelukast sodium)
NDA 20-830: SINGULAIR® Chewable Tablets (montelukast sodium)
NDA 21-409: SINGULAIR® Oral Granules (montelukast sodium)
MARKED UP CARTON AND CONTAINER LABELING

Review:

1.14 Labeling
1.14.1 Draft Labeling
1.14.1.1 Draft Carton and Container Labels

MK0476-10 mg – 90 tablets

(b) (4)

1.14.1.2 Annotated Draft Labeling Text

(b) (4)

Evaluation: *Adequate*
Revised container and carton labels are adequate.

CONCLUSION AND RECOMMENDATION:

The draft labeling text is adequate from CMC standpoint.
Proposed carton and container labels for SINGULAIR NDA 20-829, NDA 20-830, and NDA 21-409 are also adequate.

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/s/

CHONG HO KIM
04/22/2020 09:58:47 PM

RAMESH RAGHAVACHARI
04/23/2020 12:23:27 AM

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

020829Orig1s073

NON-CLINICAL REVIEW(S)

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

PHARMACOLOGY/TOXICOLOGY NDA REVIEW AND EVALUATION

Application number:	NDAs 20829/Supplement-73, 20830/Supplement-75, and 21409/Supplement-51
Supporting document/s:	NDA 20829 SDN 1952 NDA 20830 SDN 841 NDA 21409 SDN 506
Applicant's letter date:	April 3, 2020
CDER stamp date:	April 3, 2020
Product:	SINGULAIR® (montelukast sodium) Tablets, Chewable Tablets, and Oral Granules
Indication:	SINGULAIR is a leukotriene receptor antagonist indicated for: - Prophylaxis and chronic treatment of asthma in patients 12 months of age and older - Acute prevention of exercise-induced bronchoconstriction (EIB) in patients 6 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
Applicant:	Merck
Review Division:	Division of Pulmonary, Allergy, and Critical Care
Reviewer:	Matthew Whittaker, Ph.D. (TWR prepared this review with materials obtained/developed by

	MW)
Team Leader:	Timothy W. Robison, Ph.D., D.A.B.T.
Division Director:	Sally Seymour, M.D.
Project Manager:	Jessica Lee, Pharm.D.

Template Version: September 1, 2010

Disclaimer

Except as specifically identified, all data and information discussed below and necessary for approval of NDAs 20829/S-73, 21409/S-51, and 20830/S-75 are owned by Merck or are data for which Merck has obtained a written right of reference. Any information or data necessary for approval of NDAs 20829/S-73, 21409/S-51, and 20830/S-75 that Merck does not own or have a written right to reference constitutes one of the following: (1) published literature, or (2) a prior FDA finding of safety or effectiveness for a listed drug, as reflected in the drug's approved labeling. Any data or information described or referenced below from reviews or publicly available summaries of a previously approved application is for descriptive purposes only and is not relied upon for approval of NDAs 20829/S-73, 21409/S-51, and 20830/S-75.

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1 Executive Summary

1.1 Introduction

The Sponsor submitted a Changes Being Effected (CBE), safety labeling changes Supplement to SINGULAIR® NDAs 20-829, NDA 20-830, and NDA 21-409. The Supplement was submitted in response to the Division's March 4, 2020 Safety Labeling Change Notification, which requested several labeling changes that included the addition of a Boxed Warning, creation of a Medication Guide, and a limitation of use statement for the allergic rhinitis indication.

1.2 Brief Discussion of Nonclinical Findings

The biologic mechanisms underlying the neuropsychiatric events associated with montelukast treatment are currently not well understood. However, nonclinical studies clearly demonstrate that montelukast can distribute into the brain and possesses pharmacologic activity with brain cells that express CysLT1R, CysLT2R, and GPR17.

It became clear that product labeling for montelukast in Section 12.3 (Pharmacokinetics) with respect to its distribution into the rat brain was not clear. The labeling has been revised to clearly report that montelukast distributes into the brain in rats.

1.3 Recommendations

Changes to Section 12.3 (Pharmacokinetics) were recommended to describe that montelukast can cross the blood-brain barrier.

1.3.1 Approvability

The CBE supplement is recommended for approval.

1.3.3 Labeling

Section 12.3 (Pharmacokinetics) was revised as shown below. Additions are shown as underlined text. Deletions are shown in strikeout text. The Sponsor accepted these labeling changes.

12.3 Pharmacokinetics

Distribution

Montelukast is more than 99% bound to plasma proteins. The steady state volume of distribution of montelukast averages 8 to 11 liters. Orally administered montelukast distributes into the brain in rats. ~~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.~~

2 Drug Information

2.1 Drug

CAS Registry Number: 151767-02-1

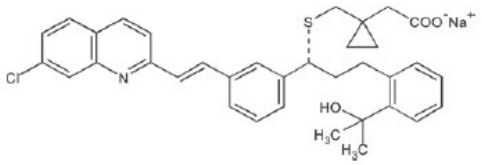
Tradename: SINGULAIR®

Generic Name: Montelukast

Chemical Name: [R-(E)]-1-[[[1-[3-[2-(7-chloro-2quinolinyl)ethenyl]phenyl]-3-[2-(1-hydroxy-1-methylethyl)phenyl]propyl]thio]methyl]cyclopropaneacetic acid, monosodium salt

Molecular Formula/Molecular Weight: $C_{35}H_{35}ClNNaO_3S$ / 608.18 g/mole

Structure:



Pharmacologic Class: Leukotriene receptor antagonist

2.3 Drug Formulation

SINGULAIR® (montelukast sodium) is available as tablets, chewable tablets, and oral granules.

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.

2.6 Proposed Clinical Population and Dosing Regimen

SINGULAIR® is a leukotriene receptor antagonist indicated for:

- Prophylaxis and chronic treatment of asthma in patients 12 months of age and older
- Acute prevention of exercise-induced bronchoconstriction (EIB) in patients 6 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

Administration (by indications):

- Asthma: Once daily in the evening for patients 12 months and older
- Acute prevention of EIB: One tablet at least 2 hours before exercise for patients 6 years of age and older
- Seasonal allergic rhinitis: Once daily for patients 2 years and older
- Perennial allergic rhinitis: 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. For oral granules: Must administer within 15 minutes after opening the packet (with or without mixing with food).

2.7 Regulatory Background

Singulair (montelukast sodium) tablets and chewable tablets were approved on February 20, 1998 and Singulair (montelukast sodium) oral granules was approved on July 26, 2002.

Since the approval of these products, the Agency has become aware of a serious risk of neuropsychiatric adverse reactions with Singulair (montelukast sodium). This information was based upon review of reports of neuropsychiatric adverse reactions, including agitation, aggression, depression, sleep disturbances, suicidal thoughts, and behavior (including suicide) in the FDA Adverse Event Reporting System (FAERS). We have also become aware of published literature regarding montelukast activity in the central nervous system in animal models (Marschallinger J, Schäffner I, Klein B, Gelfert R, Rivera FJ, Illes S, *et al.* Structural and functional rejuvenation of the aged brain by an approved anti-asthmatic drug. Nat Commun 2015; 6: 8466). We note that animal studies show that montelukast distributes into the brain in rats (see below). Available data regarding the risk of neuropsychiatric events with Singulair (montelukast sodium) were discussed at a September 27, 2019, joint meeting of the Pediatric Advisory Committee and the Drug Safety and Risk Management Advisory Committee.

The Division on March 4, 2020 issued a Safety Labeling Change Notification, which requested several labeling changes that included the addition of a Boxed Warning, creation of a Medication Guide, and a limitation of use statement for the allergic rhinitis indication.

The present supplement was submitted by the Sponsor in response to the Safety Labeling Change Notification.

3 Studies Submitted

3.3 Previous Reviews Referenced

Pharmacology and Toxicology Reviews of NDA 20829 (1998).

11 Integrated Summary and Safety Evaluation

The biologic mechanisms underlying the neuropsychiatric events associated with montelukast treatment are currently not well understood. However, evidence from animal studies suggests that montelukast can distribute into the brain and possesses pharmacological activity in cells of the brain.

Rats received a single oral dose of 10 mg/kg [^{14}C]-montelukast. A C_{max} for brain concentrations of radioactivity occurred at 6-hours postdose, which was approximately 1.7-fold higher than plasma radioactivity concentrations (see Table 1)[1]. By 24-hours postdose, significant systemic elimination of radioactivity was evident. Concentrations of radioactivity in the brain were also declining. In a separate tissue distribution study, rats received montelukast by the oral route at a dose of 10 mg/kg/day for 7 days[2]. Montelukast was detectable in brain tissue and cerebrospinal fluid (CSF) in rats, which provided evidence for its ability to cross the blood-brain barrier (see Figure 1). This evidence was consistent with experimental data obtained in rats during the nonclinical development of montelukast by Merck that montelukast distributes into the brain.

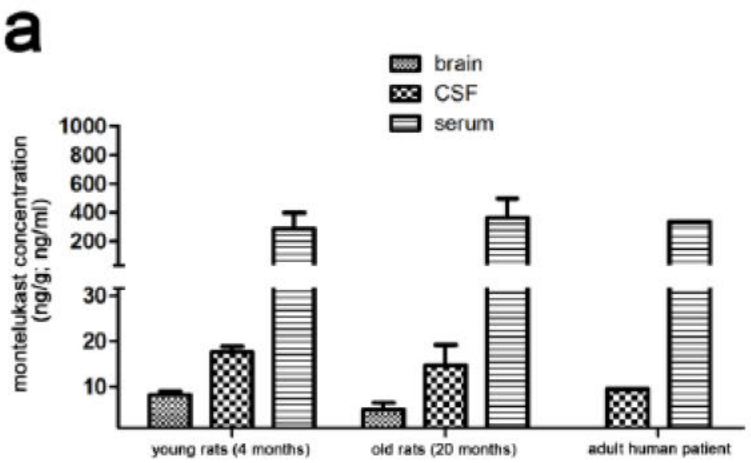
Table 1 [^{14}C]-montelukast distribution in rats (Data submitted by the Sponsor in NDA 20829)

	1 h			6 h			24 h	
Tissue	µg/g or µg/ml	% total		µg/g or µg/ml	% total		µg/g or µg/ml	% total
Small Intestine	85.9	48.5%		27.20	18.0%		1.68	13.2%
Stomach	29.53	16.7%		8.27	5.5%		1.14	9.0%
Liver	20.3	11.5%		6.65	4.4%		0.77	6.1%
Large Intestine	15.4	8.7%		24.90	16.5%		1.31	10.3%
Cecum	4.02	2.3%		67.70	44.9%		3.95	31.1%
Kidney	2.56	1.4%		1.95	1.3%		0.21	1.7%

[1] FDA Pharmacology Review of Singulair®. NDA 20829 (1998)
[2] Marschallinger *et al.* (2015). Structural and functional rejuvenation of the aged brain by an approved anti-asthmatic drug. *Nature Communications*. 6: 8466.

Mesenteric LN	5.42	3.1%		4.00	2.7%		0.24	1.9%
Pancreas	4.18	2.4%		2.84	1.9%		0.19	1.5%
Fat	1.2	0.7%		0.86	0.6%		0.16	1.3%
Heart	1.44	0.8%		0.88	0.6%		1.08	8.5%
Adrenals	1.81	1.0%		0.54	0.4%		0.33	2.6%
Plasma	1.23	0.7%		0.49	0.3%		0.07	0.6%
Lung	1.62	0.9%		1.51	1.0%		0.39	3.1%
Bladder	0.49	0.3%		0.45	0.3%		0.1	0.8%
Skin	0.41	0.2%		0.30	0.2%		0.1	0.8%
Muscle	0.4	0.2%		0.34	0.2%		0.05	0.4%
Spleen	0.61	0.3%		0.52	0.3%		0.16	1.3%
Testes	0.38	0.2%		0.39	0.3%		0.05	0.4%
Red Blood Cells	0.19	0.1%		0.15	0.1%		0.06	0.5%
Brain	**0.12**	**0.1%**		**0.84**	**0.6%**		**0.68**	**5.3%**
Total	177.21	100.0%		150.78	100.0%		12.72	100.0%

Figure 1 Blood-brain barrier penetrance of systemically administered montelukast (From Marschallinger *et al*. (2015). Structural and functional rejuvenation of the aged brain by an approved anti-asthmatic drug. Nature Communications. 6: 8466)



Montelukast is a potent competitive antagonist (IC_{50} = 2.3 nM) at its target, the CysLT1 receptor[3]. However, expression of the CysLT1R in the normal human brain is very low/non-existent. Montelukast is also a competitive antagonist of (IC_{50} = ~60 nM) of GPR17, a G-protein coupled receptor which is expressed on neurons and glial cells in

[3] Sarau et al. (1999). Identification, molecular cloning, expression, and characterization of a cysteinyl leukotriene receptor. *Molecular Pharmacology*. 56: 657-663.

the human brain[4,5]. GPR17 is recognized as a regulator of oligodendrocyte development and remyelinating function. Montelukast inhibition of GPR17 function on neurons and/or glial cells may contribute to the biologic processes underlying the observed neuropsychiatric events associated with montelukast treatment.

Table 2 Binding of montelukast to CysLT1R, CysLT2R, and GPR17

Receptor	Receptor expression in human brain[f]	Ligand	Ligand binding (nM)	Montelukast binding (nM)	Reference
CysLT1R	None	LTC4	24[a]	2.3[b]	Sarau et al. (1999). *Mol Pharm.* 56, 657-663.
		LTD4	2.5[a]		
		LTE4	240[a]		
CysLT2R	Yes – moderate	LTC4	3.35[c]	>10,000[c]	Heise et al. (2000) *JBC.* 275, 30531-30536
		LTD4	3.48[c]		
		LTE4	693[c]		
GPR17	Yes – moderate	LTC4	0.3[d]	60[e]	Ciana et al. (2006). *The EMBO Journal*. 25, 4615-4627.
		LTD4	7.2[d]		

[a] EC_{50} for Ca^{2+}mobilization in HEK-293 cells expressing human CysLT1R
[b] IC_{50} for inhibition of 33 nM LTD4 induced Ca^{2+} mobilization in HEK-293 cells expressing human CysLT1R
[c] IC_{50} value in equilibrium competition assay with [^{3}H]LTD4 in COS-7 cell membranes expressing human CysLT2R
[d] EC_{50} for induction of [^{35}S]GTPγS binding to human GPR17 expressed in 1321N1 cells (human astrocytoma cell line)
[e] IC_{50} for inhibition of 100 nM LTD_4-induced [^{35}S]GTPγS binding in 1321N1 cells expressing human GPR17
[f] The Human Protein Atlas (proteinatlas.org)

The role of leukotrienes in the brain, in particular their contribution to degeneration and regeneration, is unclear and controversial in some cases[6,7]. Elevated levels of leukotrienes have been reported in acute as well as chronic CNS lesions[8,9] and also in the aged brain[10], where they might mediate neuroinflammatory responses including microglia activation. Microglia express the cysteinyl leukotriene receptor CysLTR1, which mediates proinflammatory effects of leukotrienes, and microglia induce the expression of CysLTR2 and of the leukotriene related GPR17 receptor after

[4] Ciana *et al*. (2006) The orphan receptor GPR17 identified as a dual uracil nucleotides/cysteinyl-leukotrienes receptor. The EMBO Journal. 25: 4615 – 4627.
[5] The Human Protein Atlas. Proteinatlas.org.
[6] Kyritsis, N. *et al.* (2012). Acute inflammation initiates the regenerative response in the adult zebrafish brain. Science 338, 1353–1356.
[7] Phillis, J. W., Horrocks, L. A. and Farooqui, A. A. (2006). Cyclooxygenases, lipoxygenases, and epoxygenases in CNS: their role and involvement in neurological disorders. Brain Res. Rev. 52, 201–243.
[8] Farias, S., Frey, L. C., Murphy, R. C. & Heidenreich, K. A. (2009). Injury-related production of cysteinyl leukotrienes contributes to brain damage following experimental traumatic brain injury. J Neurotrauma 26, 1977–1986.
[9] Tang, S. S. *et al.* (2013). Leukotriene D4 induces cognitive impairment through enhancement of CysLT(1) R-mediated amyloid-beta generation in mice. Neuropharmacology 65, 182–192.
[10] Chinnici, C. M., Yao, Y. and Pratico, D. (2007). The 5-lipoxygenase enzymatic pathway in the mouse brain: young versus old. Neurobiol. Aging 28, 1457–1462.

ischemia[11,12]. Antagonizing CysLTR1 and GPR17 with the specific inhibitor, montelukast, reduced the levels of inflammatory cytokine expression[11,12,13]. CysLTRs are also expressed on endothelial cells, where they mediate blood-brain barrier leakage, and montelukast restored blood-brain barrier integrity[14]25. Expression of the leukotriene receptor, GPR17, in adult neurospheres detected a montelukast-induced dose-dependent increase in progenitor proliferation[15]26. Montelukast is positioned to target at least three of the age-related cellular changes in the brain, that is, microglia activation, blood-brain barrier integrity, and neurogenesis. The clinical significance of these findings is unclear.

GPR17 is a purinergic receptor (P2Y-like receptor) and G protein coupled receptor. It is expressed on oligodendrocyte precursors, but not astrocytes. GPR17 is a key regulator of oligodendrocyte progenitor differentiation. GPR17 activation causes progression of immature oligodendrocyte progenitors towards mature myelinating oligodendrocytes. Oligodendrocytes myelinate neurons in the brain and spinal cord. Myelinated tracts coordinate communication between different brain regions. GPR17 is a sensor of brain damage as it is up regulated in response to the release of nucleotides and cysteinyl leukotrienes in a focal ischemia model[11]. Further, GPR17 participates in lesion repair in the rodent brain and in patients with traumatic brain injury. Mature oligodendrocytes no longer express GPR17. The clinical significance of these findings is unclear.

Montelukast has been shown to be protective in several animal models of acute CNS injury and stroke; the clinical significance of this data is not known. However, Eriksson et al.[16] recently showed that montelukast inhibited cellular proliferation and maturation in the hippocampus of the intact juvenile mouse brain. In this study, juvenile mice (postnatal day 19) were treated with montelukast (10 mg/kg/day, intraperitoneal injection) for 14 days. The total number of dividing cells (Ki-67$^+$) was decreased by approximately 50% in the granule cell layer (GCL) of the dentate gyrus of the hippocampus. Total neurons and microglia (Iba1$^+$) in the GCL were also decreased in montelukast treated animals relative to vehicle controls. The clinical significance of these findings is unclear.

These studies clearly demonstrate that montelukast can distribute into the brain and has pharmacologic activity with brain cells that express CysLT1R, CysLT2R, and GPR17. It became clear that product labeling for montelukast in Section 12.3 (Pharmacokinetics) with respect to its distribution into the brain was not clear. The labeling has been revised to clearly report that montelukast distributes into the brain.

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[11] Lecca, D. *et al.* (2008). The recently identified P2Y-like receptor GPR17 is a sensor of brain damage and a new target for brain repair. PLoS ONE 3, e3579.

[12] Zhang, X. Y. *et al.* (2013). HAMI 3379, a CysLT2 receptor antagonist, attenuates ischemia-like neuronal injury by inhibiting microglial activation. J. Pharmacol. Exp. Ther. 346, 328–341.

[13] Saad, M. A., Abdelsalam, R. M., Kenawy, S. A. and Attia, A. S. (2015). Montelukast, a cysteinyl leukotriene receptor-1 antagonist protects against hippocampal injury induced by transient global cerebral ischemia and reperfusion in rats. Neurochem. Res. 40, 139–150.

[14] Lenz, Q. F. *et al.* (2014). Cysteinyl leukotriene receptor (CysLT) antagonists decrease pentylenetetrazol-induced seizures and blood-brain barrier dysfunction. Neuroscience 277, 859–871.

[15] Huber, C. *et al.* (2011). Inhibition of leukotriene receptors boosts neural progenitor proliferation. Cell Physiol. Biochem. 28, 793–804.

[16] Eriksson *et al.* (2018). The anti-asthmatic drug, montelukast, modifies the neurogenic potential in the young healthy and irradiated brain. *Cell Death and Disease*. 9: 775.

Section 12.3 Pharmacokinetics

Original Labeling (1998):

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.

Revised Labeling (2020):

Distribution

Montelukast is more than 99% bound to plasma proteins. The steady state volume of distribution of montelukast averages 8 to 11 liters. **Orally administered montelukast distributes into the brain in rats.**

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/s/

TIMOTHY W ROBISON
04/27/2020 12:54:56 PM
Timothy Robison for Matthew Whittaker

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

020829Orig1s073

OTHER REVIEW(S)

LABEL AND LABELING REVIEW
Division of Medication Error Prevention and Analysis (DMEPA)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

*** This document contains proprietary information that cannot be released to the public***

Date of This Review:	April 15, 2020
Requesting Office or Division:	Division of Pulmonology, Allergy, and Critical Care (DPACC)
Application Type and Number:	NDA 20829/S-073 NDA 20830/S-075 NDA 21409/S-051
Product Name, Dosage Form, and Strength:	Singulair (montelukast sodium) Tablets, 10 mg Singulair (montelukast sodium) Chewable Tablets, 4 mg and 5 mg Singulair (montelukast sodium) Oral Granules, 4 mg
Product Type:	Single Ingredient Product
Rx or OTC:	Prescription (Rx)
Applicant Name:	Merck Sharp & Dohme Corp (Merck)
FDA Received Date:	April 3, 2020
OSE RCM #:	2020-698
DMEPA Safety Evaluator:	Sarah K. Vee, PharmD
DMEPA Team Leader (Acting):	Ashleigh Lowery, PharmD, BCCCP

1 REASON FOR REVIEW

Merck submitted safety labeling changes for Singulair for Agency review on April 3, 2020. The supplement is in response to Safety Labeling Change (SLC) notification. We evaluated the proposed labels and labeling for areas of vulnerability that could lead to medication errors.

2 MATERIALS REVIEWED

We considered the materials listed in Table 1 for this review. The Appendices provide the methods and results for each material reviewed.

Table 1. Materials Considered for this Review	
Material Reviewed	Appendix Section (for Methods and Results)
Product Information/Prescribing Information	A
Previous DMEPA Reviews	B
Human Factors Study	C – N/A
ISMP Newsletters*	D – N/A
FDA Adverse Event Reporting System (FAERS)*	E – N/A
Other	F – N/A
Labels and Labeling	G

N/A=not applicable for this review
*We do not typically search FAERS or ISMP Newsletters for our label and labeling reviews unless we are aware of medication errors through our routine postmarket safety surveillance

3 OVERALL ASSESSMENT OF THE MATERIALS REVIEWED

Merck submitted labeling supplements for Singulair in response to a March 4, 2020 SLC notification from the Agency. The proposed labeling changes include the addition of a Boxed Warning to the prescribing information and a new Medication Guide. The proposed changes to the container label and carton labeling include the addition of instructions to provide a Medication Guide (see Appendix G). DMEPA performed a risk assessment of the proposed revisions to the prescribing information, container label, and carton labeling. We find the proposed labeling revisions to be acceptable from a medication error perspective.

4 CONCLUSION & RECOMMENDATIONS

Our evaluation of the proposed prescribing information, container label, and carton labeling did not identify areas of vulnerability that may lead to medication errors. We find the proposed changes acceptable and do not have any recommendations at this time.

APPENDICES: METHODS & RESULTS FOR EACH MATERIALS REVIEWED

APPENDIX A. PRODUCT INFORMATION/PRESCRIBING INFORMATION

Table 2 presents relevant product information for Singulair received on April 3, 2020 from Merck Sharp & Dohme Corp (Merck).

Table 2. Relevant Product Information for Singulair	
Initial Approval Date	February 20, 1998 (tablets and chewable tablets) and July 26, 2002 (oral granules)
Active Ingredient	montelukast sodium
Indication	• Prophylaxis and chronic treatment of asthma in patients 12 months of age and older • Acute prevention of exercise-induced bronchoconstriction (EIB) in patients 6 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. Reserve use for patients who have an inadequate response or intolerance to alternative therapies
Route of Administration	oral
Dosage Form	tablets, chewable tablets, granules
Strength	10 mg, 4 mg, 5 mg, 4 mg
Dose and Frequency	Administration (by indications): • Asthma: Once daily in the evening for patients 12 months and older. • Acute prevention of EIB: One tablet at least 2 hours before exercise for patients 6 years of age and older. • Seasonal allergic rhinitis: Once daily for patients 2 years and older. • Perennial allergic rhinitis: 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.
How Supplied	Oral Granules: 30 unit of use carton with 30 packets. Tablets: bottles of 30

	10 mg tablets: bottles of 30 and 90
Storage	Store SINGULAIR 4-mg oral granules, 4-mg chewable tablets, 5-mg chewable tablets and 10-mg filmcoated tablets at 20°C to 25°C (68°F to 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.

APPENDIX B. PREVIOUS DMEPA REVIEWS

On April 13, 2020, we searched for previous DMEPA reviews relevant to this current review using the term "singulair". Our search identified two previous reviews[a,b], and we confirmed that our previous recommendations were implemented.

APPENDIX G. LABELS AND LABELING

G.1 List of Labels and Labeling Reviewed

Using the principles of human factors and Failure Mode and Effects Analysis,[c] along with postmarket medication error data, we reviewed the following Singulair labels and labeling submitted by Merck Sharp & Dohme Corp (Merck).

- Container label received on April 3, 2020
- Carton labeling received on April 3, 2020
- Prescribing Information (Image not shown) received on April 3, 2020, available from \\CDSESUB1\evsprod\NDA020829\020829.enx, \\CDSESUB1\evsprod\NDA021409\021409.enx, \\CDSESUB1\evsprod\NDA020830\020830.enx
- Medication Guide received on April 3, 2020, available from \\CDSESUB1\evsprod\NDA020829\020829.enx, \\CDSESUB1\evsprod\NDA021409\021409.enx, \\CDSESUB1\evsprod\NDA020830\020830.enx

[a] Owens, L. Label and Labeling Review for Singulair (NDA 020829/S-068, NDA 020830/S-070, NDA 021409/S-045). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2014 AUG 26. RCM No.: 2014-1342.

[b] Barlow, M. Label and Labeling Review for Singulair (NDA 20829/S-069; NDA 20830/S-071; NDA 21409/S-047). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2016 OCT 14. RCM No.: 2016-1854.

[c] Institute for Healthcare Improvement (IHI). Failure Modes and Effects Analysis. Boston. IHI:2004.

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Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Medical Policy Initiatives
Division of Medical Policy Programs

PATIENT LABELING REVIEW

Date:	April 9, 2020
To:	Jessica Lee, PharmD Senior Regulatory Project Manager **Division of Pulmonary, Allergy, and Rheumatology Products (DPARP)**
Through:	LaShawn Griffiths, MSHS-PH, BSN, RN Associate Director for Patient Labeling **Division of Medical Policy Programs (DMPP)** Marcia Williams, PhD Team Leader, Patient Labeling **Division of Medical Policy Programs (DMPP)**
From:	Nyedra Booker, PharmD, MPH Patient Labeling Reviewer **Division of Medical Policy Programs (DMPP)**
Subject:	Review of Patient Labeling: Medication Guide (MG) and Instructions for Use (IFU) Safety Labeling Change(s)
Drug Name (established name):	SINGULAIR (montelukast sodium)
Dosage Form and Route:	tablets, chewable tablets, and oral granules
Application Type/Number and Supplement Number:	NDA 20829/S-073 NDA 20830/S-075 NDA 21409/S-51
Applicant:	Merck & Co., Inc.

1 INTRODUCTION

On April 3, 2020, Merck & Co., Inc. submitted for the Agency's review a Safety Labeling Changes (SLC) Under 505(o)(4)-Changes Being Effected (CBE) for SINGULAIR (montelukast sodium) tablets, for oral (NDA 20829/S-073), SINGULAIR (montelukast sodium) chewable tablets, for oral use (NDA 20830/S-075) and SINGULAIR (montelukast sodium) oral granules (NDA 21409/S-051). The purpose of this SLC is to submit labeling changes including the addition of a Boxed Warning, a limitation of use statement for the allergic rhinitis indication and the creation of a Medication Guide (MG) and new Instructions for Use (IFU) for SINGULAIR (montelukast sodium) as requested by the Agency.

This review is written by the Division of Medical Policy Programs (DMPP) in response to a request by the Division of Pulmonary, Allergy, and Rheumatology Products (DPARP) on April 3, 2020 for DMPP to review the Applicant's proposed MG and IFU for SINGULAIR (montelukast sodium).

2 MATERIAL REVIEWED

- Draft SINGULAIR (montelukast sodium) tablets, chewable tablets, and oral granules MG received on April 3, 2020, and received by DMPP on April 7, 2020.
- Draft SINGULAIR (montelukast sodium) oral granules IFU received on April 3, 2020 and received by DMPP on April 8, 2020.
- Draft SINGULAIR (montelukast sodium) Prescribing Information (PI) received on April 3, 2020, revised by the Review Division throughout the review cycle, and received by DMPP on April 7, 2020.

3 REVIEW METHODS

In our safety labeling change review of the MG and IFU we:

- simplified wording and clarified concepts where possible
- ensured that the MG and IFU are consistent with the Prescribing Information (PI)

4 CONCLUSIONS

The MG and IFU are acceptable with our recommended changes.

5 RECOMMENDATIONS

- Please send these comments to the Applicant and copy DMPP on the correspondence.
- Consult DMPP during the next review cycle for a comprehensive review of the Patient Labeling to bring it up to Patient Labeling standards.

- Our review of the MG and IFU are appended to this memorandum. Consult DMPP regarding any additional revisions made to the PI to determine if corresponding revisions need to be made to the MG and IFU.

Please let us know if you have any questions.

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/s/

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04/09/2020 08:48:33 AM

LASHAWN M GRIFFITHS
04/09/2020 09:40:50 AM

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

020829Orig1s073

ADMINISTRATIVE AND CORRESPONDENCE DOCUMENTS

Taylor, Renee

From: Green, Dionna
Sent: Monday, September 10, 2018 2:40 PM
To: Marie Kalm; Brill, Marieann
Subject: RE: Montelukast and the developing brain

Hello Dr. Kalm,

Thank you for sharing this publication with us. We have passed it along to other colleagues at FDA as well.

Best regards,
Dionna

Dionna Green, MD | Deputy Director, Office of Pediatric Therapeutics
Office of the Commissioner | US Food and Drug Administration
10903 New Hampshire Avenue, White Oak Building 32 Room 5152
Silver Spring, MD 20993
Tel: (301) 796-1543 | Fax: (301) 847-8720
Email: Dionna.Green@fda.hhs.gov

From: Marie Kalm [mailto:marie.kalm@neuro.gu.se]
Sent: Friday, August 31, 2018 6:04 AM
To: Brill, Marieann <Marieann.Brill@fda.hhs.gov>; Green, Dionna <Dionna.Green@fda.hhs.gov>
Subject: Montelukast and the developing brain

Dear Marieann and Dionna,
I was contacted by (b) (6) regarding our latest publication about montelukast and its effects on the developing brain. She wanted me to share this publication with you. In general, we saw some negative effects in hippocampus from administering montelukast i.p. to young mice. I have attached the article if you are interested. Please let me know if you have any questions!
Have a nice weekend!
Marie

****
Marie Kalm, PhD, Assistant Professor
Department of Pharmacology
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Medicinaregatan 13, 4th floor
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Phone +46 31 786 34 25

Mobile (b) (6)
Marie.Kalm@neuro.gu.se
****

Taylor, Renee

From: Green, Dionna
Sent: Friday, August 31, 2018 1:48 PM
To: Seymour, Sally; Patanavanich, Saharat
Cc: McCune, Susan; Brill, Marieann; Cope, Judith Ulett
Subject: FW: Montelukast and the developing brain
Attachments: s41419-018-0783-7.pdf

Hello Sally and Sarahat,
We (in OPT) received the email below from Marie Kalm from the University of Gothenburg notifying us about her recent publication on montelukast and its effects on the developing brain. We wanted to send it along to you in case you were not already aware of her findings.
Thank you,
Dionna Green

Dionna Green, MD | Deputy Director, Office of Pediatric Therapeutics
Office of the Commissioner | US Food and Drug Administration
10903 New Hampshire Avenue, White Oak Building 32 Room 5152
Silver Spring, MD 20993
Tel: (301) 796-1543 | Fax: (301) 847-8720
Email: Dionna.Green@fda.hhs.gov

From: Marie Kalm [mailto:marie.kalm@neuro.gu.se]
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To: Brill, Marieann <Marieann.Brill@fda.hhs.gov>; Green, Dionna <Dionna.Green@fda.hhs.gov>
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Have a nice weekend!
Marie

****
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Eriksson et al. *Cell Death and Disease* (2018)9:775
DOI 10.1038/s41419 018 0783 7

Cell Death & Disease

ARTICLE Open Access

The anti-asthmatic drug, montelukast, modifies the neurogenic potential in the young healthy and irradiated brain

Yohanna Eriksson[1], Martina Boström[1,2], Åsa Sandelius[3], Kaj Blennow[3,4], Henrik Zetterberg[3,4,5,6], Georg Kuhn[7,8] and Marie Kalm[1]

Abstract

Brain tumors are the most common form of solid tumors in children. Due to the increasing number of survivors, it is of importance to prevent long term treatment induced side effects. Montelukast, a leukotriene receptor antagonist, may have the desired neuroprotective properties. The aim of the study was to determine whether montelukast could reduce adverse effects of cranial irradiation (CIR) to the young brain. Daily injections of montelukast or vehicle was given to young mice for 4 or 14 days in combination with CIR or under normal conditions. Montelukast treatment for 4 days protected against cell death with 90% more cell death in the vehicle group compared to the montelukast group 24 h after CIR. It also resulted in less microglia activation 6 h after CIR, where montelukast lowered the levels of CD68 compared to the vehicle groups. Interestingly, the animals that received montelukast for 14 days had 50% less proliferating cells in the hippocampus irrespective of receiving CIR or not. Further, the total number of neurons in the granule cell layer was altered during the sub acute phase. The number of neurons was decreased by montelukast treatment in control animals (15%), but the opposite was seen after CIR, where montelukast treatment increased the number of neurons (15%). The results show beneficial effects by montelukast treatment after CIR in some investigated parameters during both the acute phase and with longer drug treatment. However, it also resulted in lower proliferation in the hippocampus under normal conditions, indicating that the effects of montelukast can be either beneficial or unfavorable, depending on the circumstances.

Introduction

Children with asthma receive daily treatment and according to international guidelines the first choice of treatment is inhaled corticosteroids. The treatment is often combined with adrenergic β_2 receptor agonists. The second choice for treatment is leukotriene receptor antagonists, for example, montelukast (Singulair®), which is approved for use in children (<12 years)[1]. It is not unusual that the first and second choices are combined. Montelukast has been considered well tolerated in children due to mild and transient side effects[2]. However, current reports show that montelukast treatment can cause psychiatric adverse drug reactions in children, such as sleep disorder, anxiety, aggressiveness, and hyperactivity with an incidence higher than 10%[3–5]. The underlying reasons for these side effects remain unknown.

Leukotrienes are normally present at low levels in the brain but increase during pathological conditions[6]. Montelukast has been described to be neuroprotective, for example, in the aging brain and after focal cerebral ischemia[7,8]. In the aging brain, increased activation of microglia is accompanied with decreased hippocampal neurogenesis and cognitive decline[7]. Daily, oral

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Full list of author information is available at the end of the article.
Edited by B. Joseph

SPRINGER NATURE CDDpress

administration of montelukast to rats for 6 weeks improved these negative changes in the aging brain[7], effects that could also be beneficial in radiotherapy-induced injury in children.

Brain tumors are the most common form of solid tumors in children[9], with surgery, chemotherapy, and radiotherapy as the main treatment strategies[10]. All of these treatments cause late side effects, with radiotherapy having the highest severity when graded[11]. Side effects range from sleep disturbance to cognitive impairment[12]. The mechanisms of chronic radiation-induced damage involve, for example, long-term toxicity to neural cell types, including stem and progenitor cells, loss of oligodendrocytes, and inflammatory responses[13]. Cranial radiotherapy also changes the chemical milieu and affects supporting cells such as microglia[14,15]. The subgranular zone (SGZ) in the hippocampus, an area in the brain that harbor stem cells, is very sensitive to radiotherapy in both the young and adult brain, and loss of these cells may contribute to cognitive deficits[16–18]. Finding means to ameliorate radiation-induced injury is of great interest for the increasing number of long-term childhood cancer survivors.

Targeting the irradiation-induced inflammatory response is of interest to prevent negative effects on cognition and neurogenesis. Inhibiting microglia with MW-151, a selective inhibitor of proinflammatory microglial cytokine production, restored hippocampal-dependent learning, improved synaptic function, and partially protected neurogenesis after cranial irradiation (CIR) to the adult rat brain[19]. Further, it has been shown that indomethacin, a common nonsteroidal anti-inflammatory drug, has the potential to partly increase neurogenesis after CIR in adults[20]. Blocking chemokine (C C motif) receptor 2 (Ccr2) has also prevented neuronal dysfunction and hippocampal-dependent memory dysfunction induced by irradiation toward the adult mouse brain[21]. We have previously shown that the juvenile and adult brain have different radiation-induced inflammatory responses[22], which is of importance if using an anti-inflammatory approach to protect the brain from CIR-induced injury. In the developing brain, it has been shown that blocking the complement cascade can improve reversal learning after CIR, but without effects on neurogenesis[23]. As mentioned earlier, montelukast is a leukotriene receptor antagonist. Leukotrienes are lipid mediators of inflammation and are metabolized from arachidonic acid through the 5-lipoxygenase (5-LOX) pathway. It has been shown that minocycline, a tetracycline antibiotic that blocks the activation of 5-LOX, had positive effects on cognitive impairment and decreased apoptosis in newborn neurons (DCX^+) following a single dose of 20 Gy irradiation to the brain of 1 month old rats[24]. Inhibiting the 5-LOX pathway to target the inflammatory response could therefore be an interesting strategy to investigate when trying to protect the normal tissue during radiotherapy. The purpose of this study was to investigate the effect of montelukast in combination with CIR to the young brain.

Results

The study outline is presented in Fig. 1a. Weight gain was carefully monitored for all mice injected daily for 14 days and an interaction between treatment, drug, and time was observed ($P = 0.036$, Fig. 1b c). CIR resulted in a significantly delayed weight gain compared to control animals and stayed below the other groups throughout the experiment. Interestingly, the montelukast group did not show the same delayed weight gain following CIR.

Acute phase following CIR

To investigate the acute CIR-induced injury, caspase activity in brain homogenate and neurofilament light chain (NFL) in serum was measured. Cell death (caspase-3/7-activity) increased to similar levels in both the vehicle and the montelukast group at 6 h after CIR ($P = 0.0004$, Fig. 2a). The relative increase after CIR was 125% in the vehicle groups (post hoc, $P = 0.0121$) and 141% in the montelukast groups (post hoc, $P = 0.0116$). Interestingly, the levels of caspase activity had decreased back to normal levels at 24 h after CIR. However, there was a drug effect at this time ($P = 0.0078$, Fig. 2a) with 90% more cell death in the CIR vehicle group compared to the CIR montelukast group (post hoc, $P = 0.0357$). The level of NFL, reflecting neuronal injury, increased in serum 6 h after CIR ($P = 0.0055$, Fig. 2b). This trend was seen in both the vehicle (post hoc, 58%, $P = 0.1136$) and the montelukast groups (post hoc, 77%, $P = 0.0565$). However, no difference was observed between the different groups at 24 h after CIR.

Cluster of differentiation 68 (CD68) and chemokine (C C motif) ligand 2 (CCL2) were measured in brain homogenate to evaluate the inflammatory response following CIR. The level of CD68 was significantly altered 6 h after CIR ($P = 0.0128$, Fig. 2c). At this time point montelukast lowered the levels of CD68 compared to both vehicle groups (post hoc, n.s.). The levels of CCL2 increased significantly after CIR in both vehicle and montelukast groups at both time points ($P < 0.0001$, Fig. 2d). The vehicle group showed a CIR-induced increase of 298% (post hoc, $P < 0.0001$) and the montelukast group a CIR-induced increase of 254% (post hoc, $P < 0.0001$) 6 h after the injury.

Sub-acute phase following CIR

Twelve days after CIR, the volumes of corpus callosum, thalamus, and dentate gyrus were measured (Fig. 3a b). The volume of corpus callosum was smaller following CIR for both vehicle and montelukast groups ($P = 0.0115$,

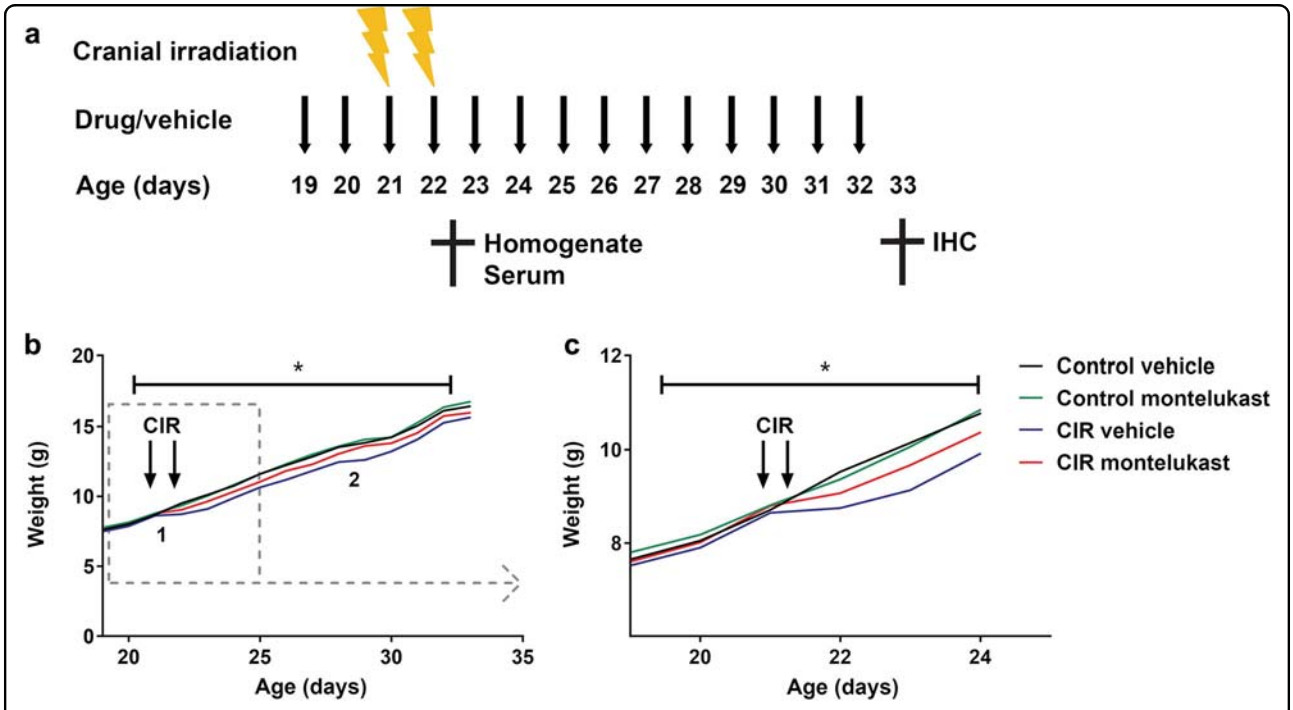

Fig. 1 Study outline and weight gain. a Study outline. The weight was measured daily throughout the experiment. The entire period is shown in (**b**). A lag in weight gain was observed in the groups that received CIR (1). The montelukast groups weaned 1 day later than the vehicle groups (2). The days before and after CIR are zoomed in (**c**). CIR cranial irradiation, IHC immunohistochemistry. † sacrifice. $n_{\text{control vehicle}}$ 10, $n_{\text{control montelukast}}$ 9, $n_{\text{CIR vehicle}}$ 6, $n_{\text{CIR montelukast}}$ 7. Statistical results from three way ANOVA are presented in the figures, * interaction between treatment, drug, and time. *P 0.036

Fig. 3c). For vehicle animals, it was 25% smaller (post hoc, $P = 0.0334$) and for the montelukast group the decrease was 13.4% (post hoc, n.s). No difference was observed in the thalamic region or the dentate gyrus (Fig. 3d e). However, an analysis of the subregions in the dentate gyrus revealed that the volumes of the granule cell layer (GCL, $P = 0.0228$, Fig. 3f) and hilus ($P = 0.0243$, Fig. 3h) changed following CIR. The CIR vehicle group had a smaller volume compared to the control vehicle group in the GCL (9.8%, post hoc, n.s.) and the hilus (16.6%, post hoc, n.s.). The CIR montelukast group also had a smaller volume compared to the non-irradiated montelukast group in the GCL (17.4%, post hoc, n.s., $P = 0.0827$) and the hilus (16.0%, post hoc, n.s.). There was no difference in the molecular layer (ML) (Fig. 3h).

Cellular effects in the GCL were assessed by determining the total numbers of neurons (Neurotrace^{TM}), proliferating cells (Ki-67^{+}) and newborn neurons (doublecortin, DCX^{+}). Analysis of the total number of neurons revealed a significant interaction between treatment and drug ($P = 0.0364$, Fig. 4a b). The vehicle CIR group had 23% less neurons in the GCL compared to vehicle controls. This was not observed in the montelukast group, where CIR did not alter the levels of neurons. Interestingly, montelukast treatment decreased the number of neurons with 15% when comparing vehicle controls and montelukast controls. Proliferation was assessed by quantifying the number of Ki-67^{+} cells (Fig. 4c d). Montelukast decreased proliferation during normal conditions with 50% (post hoc, $P = 0.0291$), while CIR did not significantly alter the proliferation levels. The total number of newborn neurons (DCX^{+}) was decreased in the GCL after CIR but not altered by montelukast ($P < 0.0001$, Fig. 4e f). CIR treatment decreased the level of newborn neurons with 63% in the vehicle CIR group compared to vehicle controls (post hoc, $P < 0.0001$) and 55% in the montelukast CIR group compared to montelukast controls (post hoc, $P < 0.0001$).

To investigate effects on non-neuronal cells in the dentate gyrus, microglia (Iba^{+}), oligodendrocytes (Olig2^{+}), and astrocytes (S100^{+}, possibly including a subpopulation of neurons) were quantified. The number of microglia was affected by both montelukast treatment ($P = 0.0233$) and CIR ($P = 0.015$, Fig. 5a b). However, the post hoc test only revealed a difference between the vehicle control group and the montelukast CIR group in GCL (post hoc, $P = 0.0066$). Similar trends were observed in the hilus and ML. Further, the number of oligodendrocytes decreased following CIR in GCL ($P < 0.0001$), hilus ($P = 0.00005$), and ML ($P = 0.000243$, Fig. 5c d). No effect was observed following montelukast treatment. In the GCL, the vehicle CIR group had 23% less

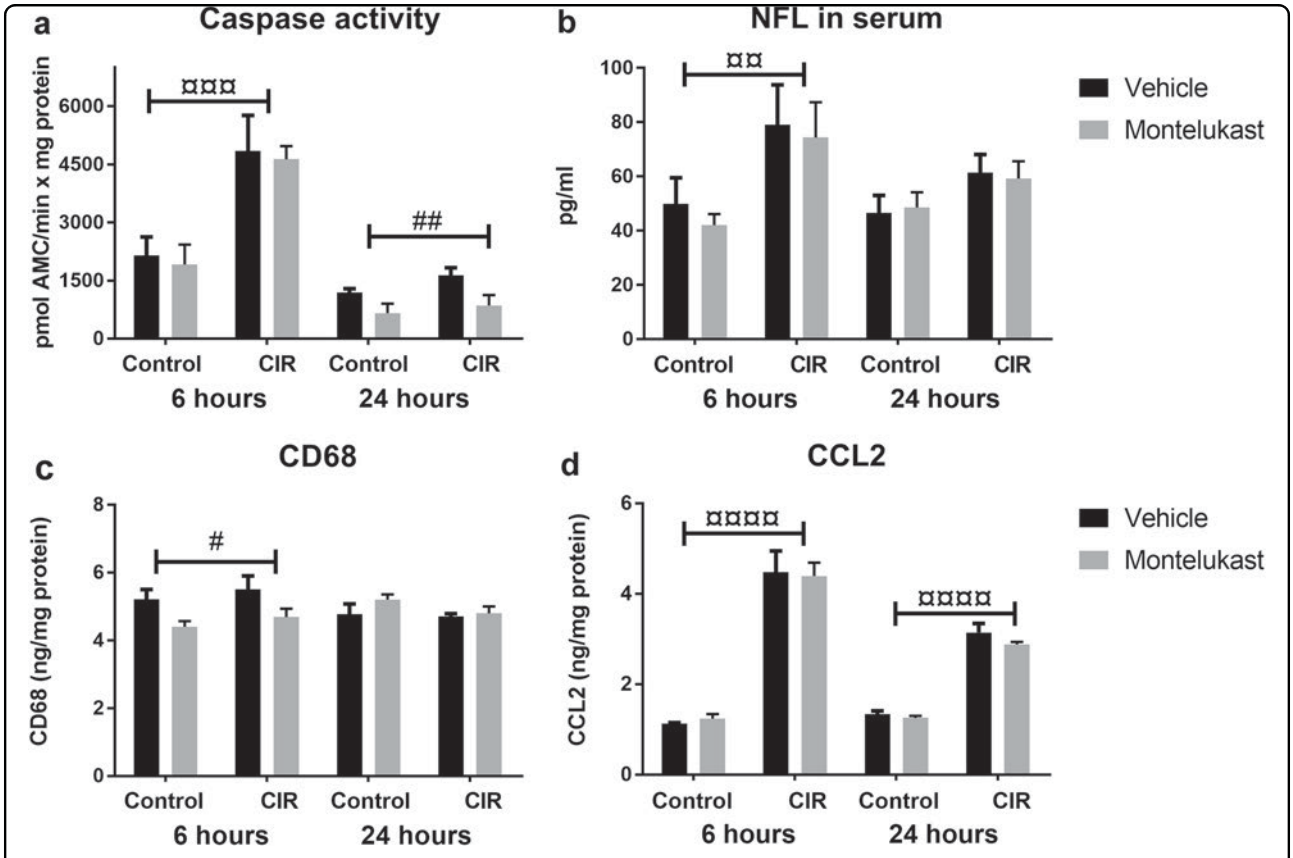

Fig. 2 Markers of neuronal injury and inflammation were measured following CIR and montelukast treatment. a Levels of caspase 3/7 activity, reflecting cell death. **b** NFL in serum, reflecting neuronal injury. **c** Levels of CD68, reflecting microglial activation. **d** Levels of CCL2, reflecting the proinflammatory response. CCL2 chemokine (C C motif) ligand 2, CD68 cluster of differentiation 68, CIR cranial irradiation, NFL neurofilament light chain. **a** $n_{\text{control vehicle 6 h}}$ 5, $n_{\text{control montelukast 6 h}}$ 5, $n_{\text{CIR vehicle 6 h}}$ 5, $n_{\text{CIR montelukast 6 h}}$ 5, $n_{\text{control vehicle 24 h}}$ 5, $n_{\text{control montelukast 24 h}}$ 4, $n_{\text{CIR vehicle 24 h}}$ 5, $n_{\text{CIR montelukast 24 h}}$ 5. **b** $n_{\text{control vehicle 6 h}}$ 9, $n_{\text{control montelukast 6 h}}$ 9, $n_{\text{CIR vehicle 6 h}}$ 5, $n_{\text{CIR montelukast 6 h}}$ 6, $n_{\text{control vehicle 24 h}}$ 7, $n_{\text{control montelukast 24 h}}$ 7, $n_{\text{CIR vehicle 24 h}}$ 5, $n_{\text{CIR montelukast 24 h}}$ 5. **c**, **d** n 5 for all groups. Error bars indicate ± SEM. Statistical results from two way ANOVA are presented in the figures. ¤ treatment (control/CIR), # drug (vehicle/montelukast), $^{\#}P < 0.05$, $^{¤¤}P < 0.01$, $^{¤¤¤}P < 0.001$, $^{¤¤¤¤}P < 0.0001$

oligodendrocytes compared to the vehicle controls (post hoc, $P = 0.039$). For the montelukast CIR group, the relative reduction of oligodendrocytes in the GCL was 38% compared to the montelukast control group (post hoc, $P = 0.0007$). Similar changes were observed in the hilus and the ML for both vehicle and montelukast groups. The number of $S100^{+}$ cells was not affected by montelukast or CIR treatment (Fig. 5e f).

Discussion

Radiotherapy is an effective treatment for brain tumors but unfortunately causes long-lasting side effects in the brain. In this study, parameters that are known to be affected by CIR were investigated to evaluate the effect of montelukast on radiation-induced injury in the developing brain. The major findings were the following: (1) Montelukast treatment resulted in reduced cell death during the acute phase after CIR. (2) The number of neurons was altered by montelukast treatment with a positive effect after CIR, but with a negative effect during normal conditions. (3) Proliferation in the hippocampal neurogenic zone decreased by montelukast treatment. These data indicate that the effects of montelukast can be either beneficial or unfavorable, depending on the physiological conditions.

Delayed weight gain has previously been observed after CIR to the developing brain[25], but the underlying mechanism is not clear. Two possibilities, which are often seen in patients, are alterations in the hormonal balance or injury to the mucous membrane. A CIR-induced injury in the mucosa in the mouth and throat would make it painful for the mice to eat. Regarding the hormonal levels, the thyroid hormones FT3 and FT4 have been shown to be unaffected 4 months after CIR in a similar mouse model[26]. Presumably, the delayed weight gain is an effect of both hypothalamic pituitary axis dysfunction

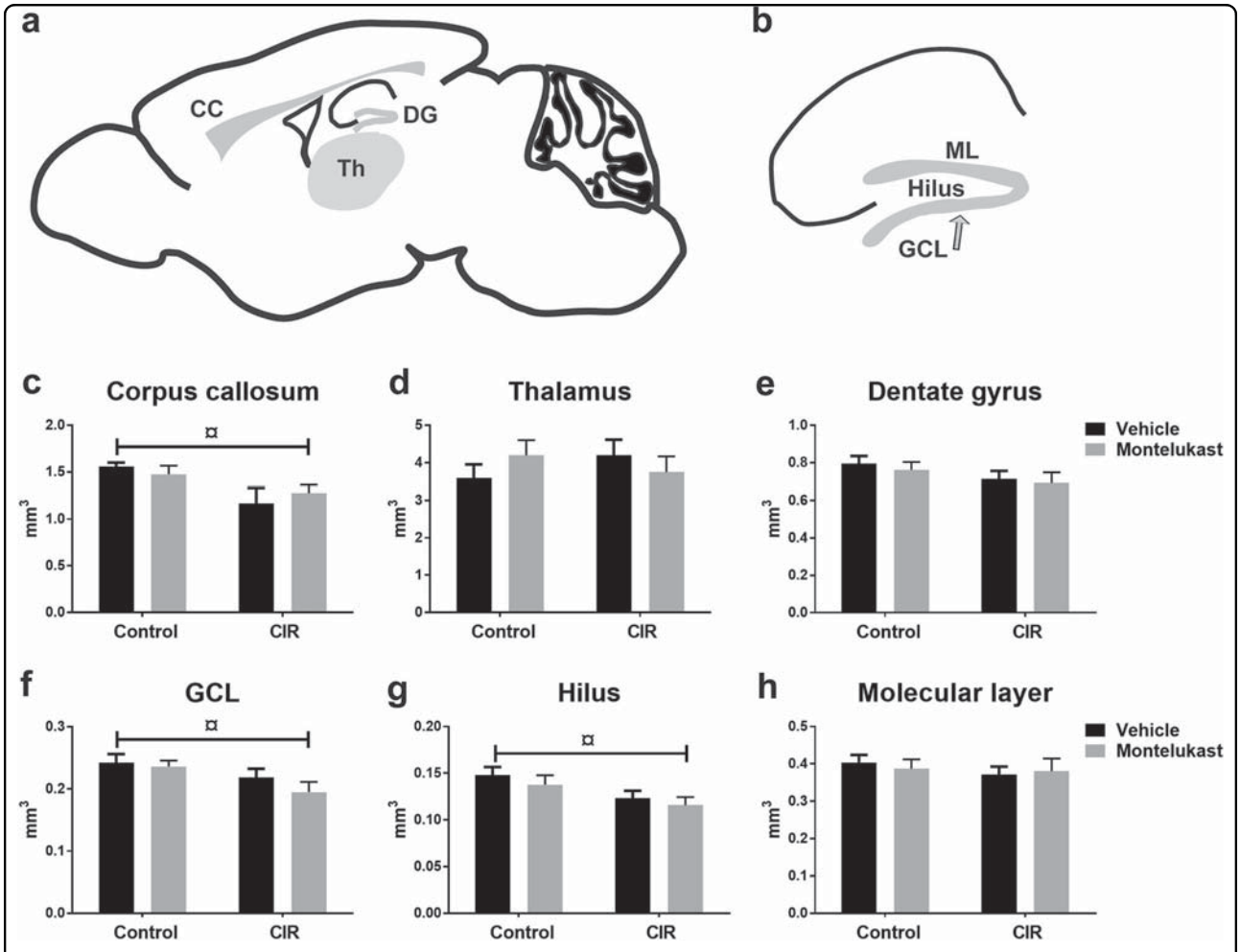

Fig. 3 Volumetric alterations following CIR and montelukast treatment. a Investigated areas are highlighted in the schematic overview. The hippocampal regions are illustrated in **b**. The volumes were measured in the corpus callosum (**c**), thalamus (**d**), and hippocampal dentate gyrus (**e**). The subregions of the dentate gyrus; GCL (**f**), hilus (**g**), and molecular layer (**h**) are also presented. CC corpus callosum, CIR cranial irradiation, DG dentate gyrus, GCL granule cell layer, ML molecular layer, Th thalamus. **c** $n_{\text{control vehicle}}$ 7, $n_{\text{control montelukast}}$ 9, $n_{\text{CIR vehicle}}$ 6, $n_{\text{CIR montelukast}}$ 5. **d** $n_{\text{control vehicle}}$ 9, $n_{\text{control montelukast}}$ 9, $n_{\text{CIR vehicle}}$ 6, $n_{\text{CIR montelukast}}$ 7, **e**, **f**, **g**, **h** $n_{\text{control vehicle}}$ 8, $n_{\text{control montelukast}}$ 9, $n_{\text{CIR vehicle}}$ 6, $n_{\text{CIR montelukast}}$ 5. Error bars indicate ± SEM. Statistical results from two way ANOVA are presented in the figures, ¤ treatment (control/CIR), $^{¤}P < 0.05$

and injury in the mucous membrane. Here, CIR caused a significantly delayed weight gain in the vehicle group but not in the montelukast group. The different reactions after CIR suggest that montelukast may have a protective effect on the physiological response to CIR, possibly due to its anti-inflammatory effects.

Acute cell death and increased levels of the neuronal injury marker, NFL, in serum are two expected findings following CIR, especially in a still developing brain[27,28]. In this study, the vehicle group exhibited more cell death compared to the montelukast group acutely following CIR. It has been demonstrated that montelukast could increase the proliferation of neuronal precursor cells in vitro through the receptors CysLT1R and GPR17[29]. However, there was no effect on cell fate or differentiation in that study. In this in vivo study, we observed the opposite. Montelukast rather had a negative effect on both proliferation and maturation under control conditions. It is possible that montelukast administration immediately negatively affected the cell proliferation, resulting in less proliferating cells at the time of CIR. This would then be reflected by less cell death. Further, it has been shown that microglia express, for example, GPR17[30,31], and it is therefore possible that montelukast have a direct impact on microglia which would affect both the levels of CD68 and Iba1. Also, microglia themselves could affect the injury since they are known producers of reactive oxygen species and proinflammatory factors[32], and excess of these factors can worsen brain injury. Interestingly, montelukast had a positive effect on the

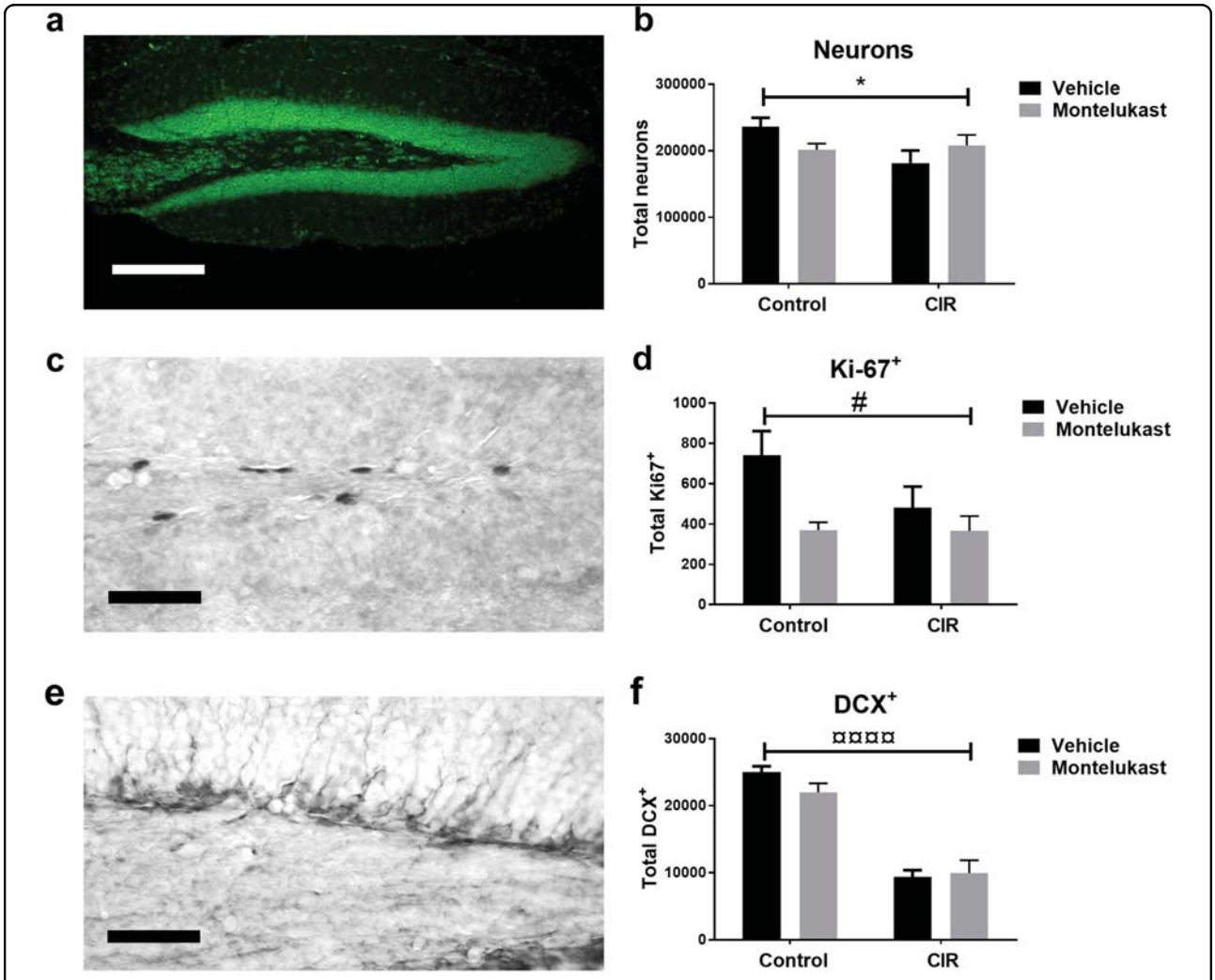

Fig. 4 Cellular effects in the GCL following CIR and montelukast treatment. a A microphotograph of Neurotrace™ in the dentate gyrus. **b** Neurons were quantified in the GCL where a significant interaction was observed. **c** Proliferating cells, assessed by Ki 67$^+$ staining. **d** Ki 67$^+$ quantification in the hippocampal neurogenic SGZ. **e** Newborn cells, measured as total numbers of DCX$^+$ cells. **f** DCX$^+$ quantification in the SGZ. **a** Scale bar 20 µm. **b** $n_{\text{control vehicle}}$ 8, $n_{\text{control montelukast}}$ 9, $n_{\text{CIR vehicle}}$ 6, $n_{\text{CIR montelukast}}$ 6. **c** Scale bar 50 µm. **d** $n_{\text{control vehicle}}$ 9, $n_{\text{control montelukast}}$ 8, $n_{\text{CIR vehicle}}$ 5, $n_{\text{CIR montelukast}}$ 4. **e** Scale bar 50 µm. **f** $n_{\text{control vehicle}}$ 8, $n_{\text{control montelukast}}$ 9, $n_{\text{CIR vehicle}}$ 6, $n_{\text{CIR montelukast}}$ 5. CIR cranial irradiation, DCX doublecortin, GCL granule cell layer, SGZ subgranular zone. Error bars indicate ± SEM. Statistical results from two way ANOVA are presented in the figures, ¤ treatment (control/CIR), # drug (vehicle/montelukast), * interaction between treatment and drug. *$P < 0.05$, #$P < 0.05$, ¤¤¤¤$P < 0.0001$

number of mature neurons after CIR, but not on the number of proliferating cells or newborn neurons. Hence, the survival of newborn neurons was positively affected in this scenario.

Montelukast has been tested in neurological conditions where inflammation and cognitive dysfunction is of interest. For example, montelukast acutely protects cerebral tissue in neonatal rats following ischemic brain damage[33]. These findings are in line with our results with lower levels of cell death in the montelukast group following CIR. Another study has shown beneficial effects on spatial memory and cognition in the aging brain after montelukast treatment[7]. An in vitro study showed an increased proliferation of neuronal progenitors after montelukast administration, but using higher doses it decreased proliferation[29]. This support our finding that montelukast could have a negative effect on neuronal proliferation in the intact juvenile brain.

Whether montelukast is beneficial or not seems to depend on the absence or presence of injury in the young brain. Positive results from montelukast treatment have been seen in the aging brains of rats after a dose of 10 mg/kg body weight[7]. The dose to treat asthma in children (2 5 years old) is however 4 mg/day regardless of body weight. In this study, we have examined the effects of montelukast in the young brain after CIR at

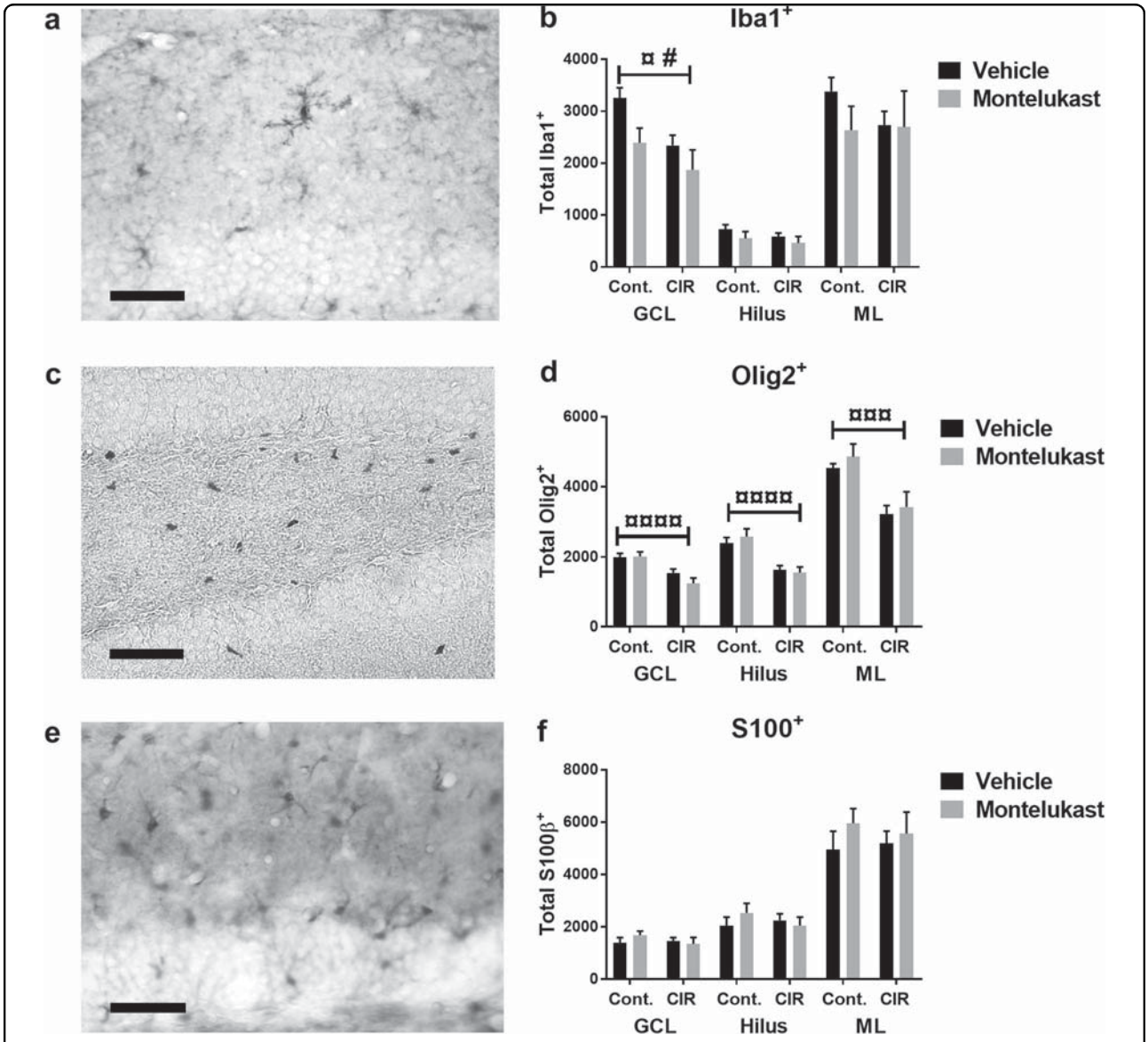

Fig. 5 Effects on non neuronal cells in the dentate gyrus following CIR and montelukast treatment. A microphotograph (**a**) and quantifications (**b**) of microglia (Iba1$^+$) in subregions of the dentate gyrus (GCL, hilus, and ML). A microphotograph (**c**) of oligodendrocytes (Olig2$^+$), and subsequent quantifications in subregions of the dentate gyrus (**d**). A microphotograph (**e**) and quantifications (**f**) of astrocytes (S100$^+$) in subregions of the dentate gyrus. CIR cranial irradiation, GCL granule cell layer, Iba1 ionized calcium binding adapter molecule 1, ML molecular layer, Olig2 oligodendrocyte transcription factor 2, S100 S100 calcium binding protein. **a**, **c**, **e** Scale bar 50 µm. **b** $n_{\text{control vehicle}}$ 8, $n_{\text{control montelukast}}$ 9, $n_{\text{CIR vehicle}}$ 6, $n_{\text{CIR montelukast}}$ 5. **d** $n_{\text{control vehicle}}$ 7, $n_{\text{control montelukast}}$ 8, $n_{\text{CIR vehicle}}$ 6, $n_{\text{CIR montelukast}}$ 5. **f** $n_{\text{control vehicle}}$ 10, $n_{\text{control montelukast}}$ 9, $n_{\text{CIR vehicle}}$ 6, $n_{\text{CIR montelukast}}$ 7. Statistical results from two way ANOVA are presented in the figures, ¤ treatment (control/CIR), # drug (vehicle/montelukast), $^{¤\#}P < 0.05$, $^{¤¤¤}P < 0.001$, $^{¤¤¤¤}P < 0.0001$

the same dose as in the aging study, 10 mg/kg, but during a shorter time course compared to the clinical situation. Our aim was to investigate if this dose of montelukast could have similar protective effects after CIR, as the damage resembles the aging brain with elevated inflammation and less proliferation. Nevertheless, our findings could also contribute to explaining some alterations that montelukast induce in the young healthy brain as we have seen negative effects both acutely and after 2 weeks of daily administration of montelukast. However, more studies are needed to explore the therapeutic window for montelukast in pediatric patients. It should be emphasized that asthma itself can induce hypoxia in the brain, leading to, for example, cognitive dysfunction[34]. A future perspective could be to investigate if montelukast is a good treatment in such cases to control asthma and

at the same time minimize injuries from the hypoxia for this group of children.

In summary, montelukast has negative effects on the maturation of the GCL during normal conditions, whereas during a pathological condition, such as following CIR, the effects can be protective. These findings, with the affected proliferation during normal conditions, in combination with the new profile for psychiatric adverse drug reactions, suggests that prescribing montelukast to young children should be a well thought through decision. However, more studies are needed to investigate if the negative effects are occurring also at lower dose spans and if the effect is chronic if ending the treatment with montelukast.

Material and methods

Animals

C57BL/6J mice with six female pups per mother were ordered from Charles River Laboratories, Germany. Animals were housed according to normal procedures at the Experimental Biomedicine animal facility (University of Gothenburg, Gothenburg, Sweden). The mice were kept on a 12-h light cycle with food and water provided *ad libitum*. The room temperature was 19 21 °C with 40 70% relative humidity. Animal experiments were approved by the Gothenburg committee of the Swedish Animal Welfare Agency (2015 72).

Montelukast treatment

Montelukast sodium powder (Sigma, USA) was dissolved in 99.5% ethanol, diluted 1:10 with 0.9% saline (NaCl), and administered by intraperitoneal injections at a dose of 10 mg/kg. Animals ($n = 6$ 10) received daily injections of montelukast or vehicle (0.9% NaCl with 10% ethanol) starting 2 days before CIR, resulting in four doses for the acute study and 14 doses for the sub-acute study (Fig. 1a).

Cranial irradiation procedure

A linear accelerator True Beam STX (600 MU/min, 5.6 Gy/min; Radiation Oncology Systems, USA) with 6 MV nominal photon energy was used for CIR as described earlier[28]. Briefly, all animals were anesthetized on postnatal day 21 with a mixture of oxygen and isoflurane (Attane Vet, VM Pharma AB, Sweden) to immobilize the animals during the procedure. The whole brain was irradiated with a clinically relevant dose of 2 × 4 Gy with 12-h interval, using a radiation field of 2 × 2 cm, a source to skin distance of 99.5 cm, and a dose variation of ±5%. After CIR, animals were returned to their dams. Control animals were anesthetized but did not receive CIR. Typically, pediatric patients with brain tumors are treated with radiotherapy, once a day, 5 days per week, for several weeks. The treatment protocol varies depending on tumor type and other relevant factors, but often it is 50 59.4 Gy in 28 33 fractions of 1.8 Gy. This study was designed to investigate the radiation-induced injury in the normal tissue (8 Gy given in two fractions), hence a much lower dose than the tumor bed receive.

Acute tissue preparation

Brains were quickly removed after sacrifice, put in liquid nitrogen and stored at −80 °C. Brains were homogenized by sonication in phosphate-buffered saline containing Triton X-100 (Merck KGaA, Germany), ethylenediaminetetraacetic acid (EDTA, Sigma-Aldrich, USA), and protease inhibitor cocktail (cOmplete, EDTA-free, Roche, Switzerland). Samples were then centrifuged and supernatant stored at −80 °C. Protein concentration was measured using the Pierce BCA protein Assay Kit (Thermo Scientific, USA) according to the protocol provided by the manufacturer.

Sub-acute tissue preparation

Animals were anesthetized with sodium pentobarbital (Pentothal, Electra-box Pharma, Sweden) and transcardially perfused with 0.1 M phosphate buffer (pH 7.5) to rinse the vascular system, followed by 6% formaldehyde (pH 7.4; Histofix; Histolab Products AB, Sweden). Brains were gently removed, immersion-fixed in Histofix for 24 h and stored in a sucrose solution (30% sucrose in 0.1 M phosphate buffer, pH 7.5). The right hemisphere was cut sagittally into 25 µm sections in a series of 12, using a sliding microtome (SM2010R, Leica Microsystems, Germany), and stored at 4 °C in a cryoprotectant solution (25% ethylene glycol and 25% glycerol).

Blood collection

Mice were anesthetized with a mixture of oxygen and isoflurane, blood was drawn from the heart with a 1 mL syringe (Omnifix®, BRAUN, Germany) and centrifuged for 5 min. Serum was collected and stored at −80 °C.

Fluorometric assay of caspase-3-like activity

Caspase-dependent cell death was measured using a caspase activity assay. An aliquot of 20 µl tissue homogenate was added to a microplate and mixed with 80 µl extraction buffer ($n = 5$, duplicate samples) and analyzed as described earlier[35]. Cleavage of Ac-DEVD-AMC (for caspase-3/7-activity, Peptide Institute, Japan, cat. no.3171-v) was measured and expressed as pmol AMC released per mg protein and minute.

Enzyme-linked immunosorbent assay

Enzyme-linked immunosorbent assays (ELISA) were used to investigate chemokine (C C motif) ligand 2 (CCL2, MJE00, R&D Systems, USA) and cluster of differentiation 68 (mouse CD68, EKM1518, Nordic BioSite,

Sweden) expression. Analyses were performed according to instructions of the manufacturers and the amount of investigated proteins measured using a SpectraMax i3x (Molecular Devices, USA).

Serum NFL

Serum sample neurofilament light chain (NFL) concentration was determined using an in-house NFL assay on the single molecule array (Simoa) platform, which has been described in detail previously[36]. Briefly, paramagnetic carboxylated beads (Quanterix Corp, USA) were coated with a mouse anti-NFL antibody (UD1, Uman-Diagnostics, Sweden) and incubated with sample and a biotinylated mouse anti-NFL antibody (UD2, Uman-Diagnostics, Sweden) in a Simoa HD-1 instrument (Quanterix).

Immunohistochemistry

Sections were treated as follows: rinsed (always in Tris-buffered saline [TBS], 50 mM Tris-HCl in 150 mM NaCl), incubated in 0.6% H_2O_2 in TBS for 30 min, rinsed and incubated for 30 min in a TBS block solution with 3% donkey serum (Jackson ImmunoResearch Laboratories Inc, USA), and 0.1% Triton X-100 (Merck KGaA, Germany). Sections were incubated overnight at 4 °C in block solution using the following primary antibodies: oligodendrocyte transcription factor 2 (1:500, rabbit anti-Olig2, ab109186, Abcam, UK), marker of proliferation Ki-67 (1:1000, rabbit anti-Ki-67, ab15580, Abcam, UK), S100 calcium-binding protein (1:2000, mouse anti-S100, MA5-12969, ThermoFisher Scientific, USA), rabbit anti-ionized calcium-binding adapter molecule 1 (1:1000, rabbit anti-Iba1, 019-19741, WAKO Pure Chemical Industries ltd, Japan), and doublecortin (1:500, polyclonal goat anti-DCX, Santa Cruz Biotechnology, USA). Sections were rinsed, incubated for 1 h with block solution and biotinylated secondary antibodies (1:1000, Jackson ImmunoResearch Laboratories Inc, USA), rinsed and incubated with avidin-biotin-peroxidase (10 µL/mL TBS of A and B, Vectastain Elite ABC Kit, Vector Laboratories, USA) for 1 h. Sections were rinsed and developed in 3,3′-diaminobenzidine (DAB, Saveen Werner AB, Sweden) diluted in TBS with H_2O_2 and $NiCl_2$, until sufficient color was noted. After rinsing in tap water, sections were mounted using 0.1 M phosphate buffer, pH 7.5, and dried overnight, then cover slipped with X-Tra-Kitt (Medite GmbH, Germany).

NeuroTrace Fluorescent Nissl stain

Sections were rinsed in TBS and then washed in TBS with 0.1% Triton X-100 for 10 min. After further washing, sections were incubated with NeuroTrace™ 500/525 Green Fluorescent Nissl stain for 20 min (N21480, ThermoFisher Scientific, USA). Following several rinsing steps in TBS, the sections were mounted and cover slipped with ProLong® Gold Antifade Reagent (ThermoFisher Scientific, USA).

Stereological procedures

Cells were counted in every 12th section using systematic-random sampling (Stereoinvestigator, MicroBrightField, USA) and a Leica DM6000 B microscope (Leica Microsystems, Germany). Counting started on sections containing a clearly divided dorsal and ventral hippocampus (only the dorsal granule cell layer [GCL] was measured). Total volumes were calculated according to the Cavalieri principle ($V = \mathrm{SA} \times P \times T$, where V is the total volume, SA is the sum of area measurements, P is the inverse of the sampling fraction, and T is the section thickness). The total number of cells was obtained by dividing the number of counted cells with the sampling fraction. Volumes for corpus callosum and thalamus were also measured in sections eligible for hippocampal quantifications.

NeuroTrace was used to quantify neurons in GCL (×40 objective). A 275 × 75-µm grid was randomly placed over the traced area and counting frames (25 × 25 µm) were placed within the grid. The total number of GCL neurons per animal was calculated by dividing the number of counted cells with the sampling fractions, i.e., fraction of sampling area/total traced area × series fraction (1/12) × optical dissector height/physical section thickness.

Statistics

For statistical analyses, two-way ANOVA was used (drug and treatment as main effects), followed by a post hoc test (Sidak, corrected for multiple testing using GraphPad Prism 7.02). Weight was analyzed using three-way ANOVA (Stata). Statistical significance was considered if $P < 0.05$.

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Conflict of interest

Authors K.B. and H.Z. are co founders of Brain Biomarker Solutions in Gothenburg AB, a GU Ventures based platform company at the University of Gothenburg. H.Z. has served at advisory boards of Eli Lilly and Roche Diagnostics and has received travel support from Teva. The remaining authors declare that they have no conflict of interest.

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