

CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

NDA 20-829/S-023

NDA 20-830/S-026

NDA 21-409/S-005

Trade Name: Singulair Tablets; Singulair Chewable Tablets;
Singulair Oral Granules

Generic Name: montelukast sodium

Sponsor: Merck Research Laboratories

Approval Date: October 3, 2003

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APPROVAL LETTER



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 20-829/S-023, 20-830/S-026 and 21-409/S-005

Merck Research Laboratories
P.O. Box 2000, RY 33-720
Rahway NJ 07065-0900

Attention: William A Hanlon, Ph.D.
Associate Director, Regulatory Affairs

Dear Dr. Hanlon:

Please refer to your supplemental new drug applications dated April 2, 2003, received April 3, 2003, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Singular (montelukast sodium) Tablets, Singulaire (montelukast sodium) Chewable Tablets, and Singulair (montelukast sodium) Oral Granules.

These "Changes Being Effected" supplemental new drug applications provide for the addition of paresthesia/hypoesthesia to the Post-Marketing subsection of the ADVERSE REACTIONS section of the package insert and pin and needles/numbness to the "What are the possible side effects of SINGULAIR?" Section of the patient product information.

We completed our review of these supplemental new drug applications, they are approved, effective on the date of this letter, for use as recommended in the final printed labeling (FPL) submitted on April 2, 2003.

We remind you that you must submit patent information on form FDA 3542, *Patent Information Submitted Upon and After Approval of an NDA or Supplement*, within 30 days of the date of this letter as required by 21 CFR 314.53(c)(2)(ii) and 314.53(d)(2) at the address provided by 21 CFR 314.53(d)(4). The form may be obtained at <http://www.fda.gov/opacom/morechoices/fdaforms/cder.html>. To expedite review of this patent declaration form, we request you submit an additional copy of the form to this/these application(s) and to the Center for Drug Evaluation and Research "Orange Book" staff at

Food and Drug Administration
Office of Generic Drugs, HFD-610
Orange Book Staff
7500 Standish Place
Metro Park North II
Rockville, MD 20855-2773

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

MEDWATCH, HFD-410
FDA
5600 Fishers Lane
Rockville, MD 20857

We remind you that you must comply with the requirements for an approved NDA set forth under 21 CFR 314.80 and 314.81.

If you have any questions, call Akilah Green, Regulatory Project Manager, at (301) 827-5580.

Sincerely,

{See appended electronic signature page}

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

Enclosure

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

/s/

Badrul Chowdhury
10/2/03 05:31:57 PM

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 20-829/S-023

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APPROVED LABELING



9094215

Patient Information

SINGULAIR® (SING-u-lair) Tablets, Chewable Tablets, and Oral Granules

Generic name: montelukast (mon-te-LOO-kast) sodium

Read this information before you start taking SINGULAIR®. Also, read the leaflet you get each time you refill SINGULAIR, since there may be new information in the leaflet since the last time you saw it. This leaflet does not take the place of talking with your doctor about your medical condition and/or your treatment.

What is SINGULAIR®?

- SINGULAIR is a medicine called a leukotriene receptor antagonist. It works by blocking substances in the body called leukotrienes. Blocking leukotrienes improves asthma and seasonal allergic rhinitis (also known as hay fever). SINGULAIR is not a steroid.

SINGULAIR is prescribed for the treatment of asthma and seasonal allergic rhinitis:

1. Asthma.

SINGULAIR should be used for the long-term management of asthma in adults and children ages 12 months and older.

Do not take SINGULAIR for the immediate relief of an asthma attack. If you get an asthma attack, you should follow the instructions your doctor gave you for treating asthma attacks. (See the end of this leaflet for more information about asthma.)

2. Seasonal Allergic Rhinitis.

SINGULAIR is used to help control the symptoms of seasonal allergic rhinitis (sneezing, stuffy nose, runny nose, itching of the nose) in adults and children ages 2 years and older. (See the end of this leaflet for more information about seasonal allergic rhinitis.)

Who should not take SINGULAIR?

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

The active ingredient in SINGULAIR is montelukast sodium.

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

What should I tell my doctor before I start taking SINGULAIR?

Tell your doctor about:

- **Pregnancy:** If you are pregnant or plan to become pregnant. SINGULAIR may not be right for you.
- **Breast-feeding:** If you are breast-feeding, SINGULAIR may be passed in your milk to your baby. You should consult your doctor before taking SINGULAIR if you are breast-feeding or intend to breast-feed.
- **Medical Problems or Allergies:** Talk about any medical problems or allergies you have now or had in the past.
- **Other Medicines:** Tell your doctor about all the medicines you take, including prescription and non-prescription medicines, 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 adults and children 12 months of age and older with asthma:

- Take SINGULAIR once a day in the evening.
- Take SINGULAIR every day for as long as your doctor prescribes it, even if you have no asthma symptoms.

- You may take SINGULAIR with food or without food.
- If your asthma symptoms get worse, or if you need to increase the use of your inhaled rescue medicine for asthma attacks, call your doctor right away.
- **Do not take SINGULAIR for the immediate relief of an asthma attack.** If you get an asthma attack, you should follow the instructions your doctor gave you for treating asthma attacks.
- Always have your inhaled rescue medicine for asthma attacks with you.
- Do not stop taking or lower the dose of your other asthma medicines unless your doctor tells you to.
- If your doctor has prescribed a medicine for you to use before exercise, keep using that medicine unless your doctor tells you not to.

For adults and children 2 years of age and older with seasonal allergic rhinitis:

- Take SINGULAIR once a day, at about the same time each day.
- Take SINGULAIR every day for as long as your doctor prescribes it.
- You may take SINGULAIR with food or without food.

How should I give SINGULAIR oral granules to my child?

Do not open the packet until ready to use.

SINGULAIR 4-mg oral granules can be given either:

- directly in the mouth;

OR

- mixed with a spoonful of one of the following soft foods at cold or room temperature: applesauce, mashed carrots, rice, or ice cream. Be sure that the entire dose is mixed with the food and that the child is given the entire spoonful of the mixture right away (within 15 minutes).

IMPORTANT: Never store any oral granule/food mixture for use at a later time. Throw away any unused portion.

Do not put SINGULAIR oral granules in liquid drink. However, your child may drink liquids after swallowing the SINGULAIR oral granules.

What is the daily dose of SINGULAIR for asthma or seasonal allergic rhinitis?

For Asthma (Take in the evening):

- One 10-mg tablet for adults and adolescents 15 years of age and older,
- One 5-mg chewable tablet for children 6 to 14 years of age,
- One 4-mg chewable tablet or one packet of 4-mg oral granules for children 2 to 5 years of age, or
- One packet of 4-mg oral granules for children 12 to 23 months of age.

For Seasonal Allergic Rhinitis (Take at about the same time each day):

- One 10-mg tablet for adults and adolescents 15 years of age and older,
- One 5-mg chewable tablet for children 6 to 14 years of age, or
- One 4-mg chewable tablet or one packet of 4-mg oral granules for children 2 to 5 years of age.

What should I avoid while taking SINGULAIR?

If you have asthma and if your asthma is made worse by aspirin, continue to avoid aspirin or other medicines called non-steroidal anti-inflammatory drugs while taking SINGULAIR.

SINGULAIR®
(Montelukast Sodium)
Tablets, Chewable Tablets, and
Oral Granules

9094215



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SINGULAIR® (Montelukast Sodium)
Tablets, Chewable Tablets, and Oral Granules

What are the possible side effects of SINGULAIR?

The side effects of SINGULAIR are usually mild, and generally did not cause patients to stop taking their medicine. The side effects in patients treated with SINGULAIR were similar in type and frequency to side effects in patients who were given a placebo (a pill containing no medicine).

The most common side effects with SINGULAIR include:

- stomach pain
- stomach or intestinal upset
- heartburn
- tiredness
- fever
- stuffy nose
- cough
- flu
- upper respiratory infection
- dizziness
- headache
- rash

Less common side effects that have happened with SINGULAIR include (listed alphabetically):

agitation including aggressive behavior, allergic reactions (including swelling of the face, lips, tongue, and/or throat, which may cause trouble breathing or swallowing), hives, and itching, bad/vivid dreams, increased bleeding tendency, bruising, diarrhea, hallucinations (seeing things that are not there), indigestion, inflammation of the pancreas, irritability, joint pain, muscle aches and muscle cramps, nausea, palpitations, pins and needles/numbness, restlessness, seizures (convulsions or fits), swelling, trouble sleeping, and vomiting.

Rarely, asthmatic patients taking SINGULAIR have experienced a condition that includes certain symptoms that do not go away or that get worse. These occur usually, but not always, in patients who were taking steroid pills by mouth for asthma and those steroids were being slowly lowered or stopped. Although SINGULAIR has not been shown to cause this condition, **you must tell your doctor 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)

These are not all the possible side effects of SINGULAIR. For more information ask your doctor or pharmacist.

Talk to your doctor if you think you have side effects from taking SINGULAIR.

General Information about the safe and effective use of SINGULAIR

Medicines are sometimes prescribed for conditions that are not mentioned in patient information leaflets. Do not use SINGULAIR for a condition for which it was not prescribed. Do not give SINGULAIR to other people even if they have the same symptoms you have. It may harm them. **Keep SINGULAIR and all medicines out of the reach of children.**

SINGULAIR® (Montelukast Sodium)
Tablets, Chewable Tablets, and Oral Granules

Store SINGULAIR at 25°C (77°F). Protect from moisture and light. Store in original package.

This leaflet summarizes information about SINGULAIR. If you would like more information, talk to your doctor. You can ask your pharmacist or doctor for information about SINGULAIR that is written for health professionals.

What are the ingredients in SINGULAIR?

Active Ingredient: montelukast sodium

SINGULAIR chewable tablets contain aspartame, a source of phenylalanine.

Phenylketonurics: SINGULAIR 4-mg and 5-mg chewable tablets contain 0.674 and 0.842 mg phenylalanine, respectively.

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.
- **10-mg tablet:** microcrystalline cellulose, lactose monohydrate, croscarmellose sodium, hydroxypropyl cellulose, magnesium stearate, hydroxypropyl methylcellulose, titanium dioxide, red ferric oxide, yellow ferric oxide, and carnauba wax.

What is asthma?

Asthma is a continuing (chronic) inflammation of the bronchial passageways which are the tubes that carry air from outside the body to the lungs.

Symptoms of asthma include:

- coughing
- wheezing
- chest tightness
- shortness of breath

What is seasonal allergic rhinitis?

- Seasonal allergic rhinitis, also known as hay fever, is an allergic response caused by pollens from trees, grasses and weeds.
- Symptoms of seasonal allergic rhinitis may include:
 - stuffy, runny, and/or itchy nose
 - sneezing

Rx only



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NDA 21-409/S-005

ADMINISTRATIVE DOCUMENTS **AND** **CORRESPONDENCE**

Project Manager Labeling Review

NDA 20-829/S-023/ Singulair (montelukast sodium) Tablets
20-830/S-026/ Singulair (montelukast sodium) Chewable Tablets
21-409/S-005/Singulair (montelukast sodium) Oral Granules

SPONSOR: Merck

SUBMISSIONS DATED: April 2, 2003

RECEIVED: April 3, 2003

These changes being effected supplements provide for the addition of paresthesia/hypoesthesia to the Post-Marketing subsection of the ADVERSE REACTIONS section of the package insert and pin and needles/numbness to the "What are the possible side effects of SINGULAIR? Section of the patient product information.

I compared the labeling dated April 2, 2003, to the last approved labeling for each of these applications and there are no changes other than those requested by these supplements, therefore these supplements should be approved.

Sandy Barnes
Chief, Project Management Staff
Division of Pulmonary and Allergy Drug Products

**This is a representation of an electronic record that was signed electronically and
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/s/

Sandra Barnes
10/2/03 05:30:48 PM
CSO

Badrul Chowdhury
10/2/03 05:34:12 PM
MEDICAL OFFICER