CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: 20-830/S008

CORRESPONDENCE

Merck & Co., Inc.
West Point, PA 19486

DESK COPY

March 3, 2000

MERCK
Research Laboratories

Robert J. Meyer, M.D.
Division of Pulmonary and Allergy Drug Products
HFD-570, Room 10B-45
Office of Drug Evaluation II (CDER)
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857

Dear Dr. Meyer:

NDA 20-830/S-008: SINGULAIR™ Chewable Tablets
(montelukast sodium)

Response to Pending Supplemental New Drug Application

Reference is made to the supplemental New Drug Application cited above for SINGULAIR™ Chewable Tablets (montelukast sodium) submitted on May 6, 1999 for the chronic treatment of asthma in pediatric patients aged 2 - 5 years old. Reference is also made to a telephone conversation on March 2, 2000 between Ms. Sandy Barnes and Dr. Steven Caffé, in which Ms. Barnes requested the submission of the clean running text of the final Package Circular and Patient Package Insert

With this submission, we are providing the requested information.

We consider the filing of this submission to be a confidential matter, and request the Food and Drug Administration not make its content, nor any future communications in regard to it, public without first obtaining the written permission of Merck & Co., Inc.

Questions concerning this response should be directed to Steven E. Caffé, M.D. (732-594-2182) or, in my absence, to Bonnie J. Goldmann, M.D. (610-397-2383).

Sincerely,

Steven E. Caffé, MD
Senior Director, Regulatory Affairs

Attachments: Clean running text of:
Package Circular
Patient Package Insert

Hand Delivered

Desk copy: Mr. David Hilfiker, HFD-570, Room 10B-45 (w/attachments and diskette)

Q:CAT\AS\NDA20-830

DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION

APPLICATION TO MARKET A NEW DRUG, BIOLOGIC, OR AN ANTIBIOTIC DRUG FOR HUMAN USE

(Title 21, Code Of Federal Regulations, 314)

Form Approved OMB No. 0910-0338.
Expiration Date: April 30, 2000
See OMB Statement on last page.

FOR FDA USE ONLY

APPLICATION NUMBER

APPLICANT INFORMATION

NAME OF APPLICANT
Merck Research Laboratories, a Division of Merck & Co., Inc.

DATE OF SUBMISSION
March 3, 2000

TELEPHONE NO. *(Include Area Code)*
732-594-2182

FACSIMILE (FAX) Number *(Include Area Code)*
732-594-1030

APPLICANT ADDRESS *(Number, Street, City, State, Country, Zip Code or Mail Code, and U.S. License number if previously issued)*:
Sumneytown Pike, P.O. Box 4
RY 33-720
West Point, PA 19486

AUTHORIZED U.S. AGENT NAME & ADDRESS *(Number, Street, City, State, ZIP Code, telephone & FAX number)* IF APPLICABLE
—

PRODUCT DESCRIPTION

NEW DRUG OR ANTIBIOTIC APPLICATION NUMBER, OR BIOLOGICS LICENSE APPLICATION NUMBER (If previously issued) **NDA 20-830**

ESTABLISHED NAME *(e.g., Proper name, USP/USAN name)*
Montelukast Sodium

PROPRIETARY NAME *(trade name)* IF ANY
SINGULAIR®

CHEMICAL/ BIOCHEMICAL/BLOOD PRODUCT NAME *(If any)* **[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**

CODE NAME *(If any)*

DOSAGE FORM
Chewable Tablets

STRENGTHS
—

ROUTE OF ADMINISTRATION
Oral

(PROPOSED) INDICATION(S) FOR USE:
Treatment of asthma

APPLICATION INFORMATION

APPLICATION TYPE *(Check one)*
☑ NEW DRUG APPLICATION (21 CFR 314.50) ☐ ABBREVIATED APPLICATION (ANDA, AADA, 21 CFR 314.94)
☐ BIOLOGICS LICENSE APPLICATION (21 CFR part 601)

IF AN NDA, IDENTIFY THE APPROPRIATE TYPE ☑ 505 (b) (1) ☐ 505 (b) (2) ☐ 507

IF AN ANDA, OR AADA, IDENTIFY THE REFERENCED LISTED DRUG PRODUCT THAT IS THE BASIS FOR THE SUBMISSION
Name of Drug — Holder of Approved Application

TYPE OF SUBMISSION (check one)
☐ ORIGINAL APPLICATION ☑ AMENDMENT TO A PENDING APPLICATION ☐ RESUBMISSION
☐ PRESUBMISSION ☐ ANNUAL REPORT ☐ ESTABLISHMENT DESCRIPTION SUPPLEMENT ☐ SUPAC SUPPLEMENT
☐ EFFICACY SUPPLEMENT ☐ LABELING SUPPLEMENT ☐ CHEMISTRY MANUFACTURING AND CONTROLS SUPPLEMENT ☑ OTHER

REASON FOR SUBMISSION Response to Pending Supplemental New Drug Application

PROPOSED MARKETING STATUS (check one) ☑ PRESCRIPTION PRODUCT (Rx) ☐ OVER THE COUNTER PRODUCT (OTC)

NUMBER OF VOLUMES SUBMITTED 1 THIS APPLICATION IS ☑ PAPER ☐ PAPER AND ELECTRONIC ☐ ELECTRONIC

ESTABLISHMENT INFORMATION

Provide locations of all manufacturing, packaging and control sites for the drug substance and drug product (continuation sheets may be used if necessary). Include name, address, contact, telephone number, registration number (CFN), DMF number, and manufacturing steps and/or type of testing (e.g. Final dosage form, Stability testing) conducted at the site. Please indicate whether the site is ready for inspection or, if not, when it will be ready.

Cross References (list related License Applications, INDs, NDAs, PMAs, 510(k)s, IDEs, BMFs, and DMFs referenced in the current application)

This application contains the following items: *(Check all that apply)*	
	1. Index
X	2. Labeling (check one) ☒ Draft Labeling ☐ Final Printed Labeling
	3. Summary (21 CFR 314.50 (c))
	4. Chemistry Section
	A. Chemistry, manufacturing, and controls information (e.g. 21 CFR 314.50 (d) (1), 21 CFR 601.2)
	B. Samples (21 CFR 314.50 (e) (1), 21 CFR 601.2 (a)) (Submit only upon FDA's request)
	C. Methods validation package (e.g. 21 CFR 314.50 (e) (2) (I), 21 CFR 601.2)
	5. Nonclinical pharmacology and toxicology section (21 CFR 314.50 (d) (2), 21 CFR 601.2)
	6. Human pharmacokinetics and bioavailability section (21 CFR 314.50 (d) (3), 21 CFR 601.2)
	7. Microbiology section (21 CFR 314.50 (d) (4))
	8. Clinical data section (21 CFR 314.50 (d) (5), 21 CFR 601.2)
	9. Safety update report (21 CFR 314.50 (d) (5) (vi) (b), 21 CFR 601.2)
	10. Statistical section (21 CFR 314.50 (d) (6), 21 CFR 601.2)
	11. Case report tabulations (21 CFR 314.50 (f) (1), 21 CFR 601.2)
	12. Case reports forms (21 CFR 314.50 (f) (1), 21 CFR 601.2)
	13. Patent information on any patent which claims the drug (21 U.S.C. 355 (b) or (c))
	14. A patent certification with respect to any patent which claims the drug (21 U.S.C. 355 (b) (2) or (j) (2) (A))
	15. Establishment description (21 CFR Part 600, if applicable)
	16. Debarment certification (FD&C Act 306 (k) (1))
	17. Field copy certification (21 CFR 314.5 (k) (3))
	18. User Fee Cover Sheet (Form FDA 3397)
	19. OTHER (Specify)

CERTIFICATION

I agree to update this application with new safety information about the product that may reasonably affect the statement of contraindications, warnings, precautions, or adverse reactions in the draft labeling. I agree to submit safety update reports as provided for by regulation or as requested by FDA. If this application is approved, I agree to comply with all laws and regulations that apply to approved applications, including, but not limited to the following:

1. Good manufacturing practice regulations in 21 CFR 210 and 211, 606, and/or 820.
2. Biological establishment standards in 21 CFR Part 600.
3. Labeling regulations in 21 CFR 201, 606, 610, 660 and/or 809.
4. In case of a prescription drug product or biological product, prescription drug advertising regulations in 21 CFR 202.
5. Regulations on making changes in application in 21 CFR 314.70, 314.71, 314.72, 314.97, 314.99, and 601.12.
6. Regulations on reports in 21 CFR 314.80, 314.81, 600.80 and 600.81.
7. Local, State and Federal environmental impact laws.

If this application applies to a drug product that FDA has proposed for scheduling under the Controlled Substances Act, I agree not to market the product until the Drug Enforcement Administration makes a final scheduling decision.

The data and information in this submission have been reviewed and, to the best of my knowledge are certified to be true and accurate.

Warning: a willfully false statement is a criminal offense, U.S. Code, title 18, section 1001.

SIGNATURE OF RESPONSIBLE OFFICIAL OR AGENT	TYPED NAME AND TITLE	DATE
	Steven E. Caffé, M.D. **Senior Director, Regulatory Affairs**	03|03|00

ADDRESS (Street, City, State, and ZIP Code)	Telephone Number
Merck Research Laboratories (RY 33-720) **Sumneytown Pike, PO Box 4** **West Point, PA 19486**	**732-594-2182**

Public reporting burden for this collection of information is estimated to average 40 hours per response, including the time for reviewing instructions, searching existing data sources, gathering and maintaining the data needed, and completing and reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information, including suggestions for reducing this burden to:

DHHS, Reports Clearance Officer
Paperwork Reduction Project (0910-0338)
Hubert H. Humphrey Building, Room 531-H
200 Independence Avenue, S.W.
Washington, DC 20201

An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB control number.

Please DO NOT RETURN this form to this address.

WITHHOLD 16 pages

Draft

Labeling

Hilfiker

Memorandum of Telephone Facsimile Correspondence

Date: January 21, 2000

To: Steve Caffé, M.D.
Senior Director, Merck U.S. Regulatory Affairs

Fax No.: 732-594-1030

From: David Hilfiker
Project Manager

Through: Albert Chen, Ph.D. OCPB Reviewer /S/
Ramana Uppoor, Ph.D. OCPB Team Leader /S/

Subject: Additional Information Requested for 2-5 Year Old Supplement

# of Pages: 4

We are providing the attached information via telephone facsimile for your convenience, to expedite the progress of your drug development program. This material should be viewed as unofficial correspondence. Please feel free to contact me if you have any questions regarding the contents of this transmission.

Thank you.

cc: Orig NDA 20-830/S-008
HFD-570/Div File
HFD-570/Hilfiker
HFD-570/Uppoor
HFD-570/Chen

/S/

David Hilfiker
Project Manager
Division of Pulmonary Drug Products

c/

Steve:

Per our telephone conversation today, one additional piece of information is needed to complete the Clinical Pharmacology & Biopharmaceutics review of your supplemental application for the Singulair 4 mg chewable tablet in 2-5 year old children.

We refer to your original supplemental application, submitted May 6, 1999. Under the CMC section, item C.5.c.3. provides dissolution results. On page C-92 (attached), you provide Table C-41, which includes the dissolution results for Batch EXP9701.

Provide dissolution data generated on biobatch MR-3393 in a tabular presentation similar to Table C-41. Currently, the only information that has been provided on this batch are mean % dissolved in 10, 20, and 30 minutes (see Table C-51, page C-100 of C.5.c.3., attached).

For comparison, provide similar dissolution data in a similar presentation for a commercial-scale batch of the 5 mg chewable tablets manufactured at the commercial manufacturing facility in Wilson, North Carolina.

Thank you.

Dave Hilfiker

Attachments: pages C-92 and C-100
Section C.5.c.3., May 6, 1999, submission to 20-830/S-008
(HARD COPY ONLY)

WITHHOLD 2 pages

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

AUG - 6 1999

Merck and Co., Inc.
Attention: Bonnie J. Goldman, M.D.
Vice President, Regulatory Affairs
BLA-30
P.O. Box 4
West Point, PA 19486

RE: Pediatric Refund Request for Singular (Montelukast Sodium) Chewable Tablets, NDA 20-830, Supplement 008

Dear Dr. Goldman:

This responds to your July 29, 1999, letter requesting a refund of the Fiscal Year 1999 application fee paid under the Prescription Drug User Fee Act of 1992 (PDUFA) as amended by the Food and Drug Administration Modernization Act of 1997 (Modernization Act) for Singular (montelukast sodium) Chewable Tablets, New Drug Application (NDA) 20-830, Supplement 008 (S-008). According to your request Mr. Steven Caffé of Merck and Co., Inc. (Merck) was notified in a telephone conversation by Mr. David Hilfiker of the Center For Drug Evaluation and Research's Pulmonary Division that Merck could request a refund of the user fee paid for this supplement because it is for a pediatric indication.

The PDUFA, as amended by the Modernization Act, exempts a supplement to an original new drug application from application fees if the supplement is for a new indication for use in pediatric populations (section 736(a)(1)(F), 21U.S.C. 379h(a)(1)(F)).

Our records show that FDA received NDA 20-830, S-008 on May 7, 1999, and that FDA was notified of the user fee payment of [redacted] (user fee ID # 3707) on April 23, 1999. Our review of the proposed labeling submitted in the supplement confirms that the proposed indication is for use in pediatric populations only. Consequently, because S-008 to NDA 20-830 for Singular Chewable Tablets is a supplement for a new indication for use in pediatric populations, it is not subject to an application fee under the PDUFA as amended by the Modernization Act.

We have asked the Office of Financial Management to refund the [redacted] application fee paid by Merck. If Merck does not receive the refund by August 31, 1999, please contact Mr. Michael Roosevelt, Chief, Systems Accounting Branch, at (301) 827-5088.

If you have any further questions concerning this matter or other user fee questions, please contact Mr. Michael Jones or Ms. Beverly Friedman at (301)-594-2041.

Sincerely,

/S/

Jane A. Axelrad
Associate Director for Policy
Center for Drug Evaluation and Research

CC: Dr. Steven Caffé,
Senior Director, Regulatory Affairs
Merck and Co., Inc.

APPEARS THIS WAY
ON ORIGINAL

Hilfiker

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

NDA 20-830/S-008

JUN 13 1999

Merck & Co.
Sumneytown Pike
West Point, PA 19486

Attention: Larry P. Bell, M.D.
Senior Director, Regulatory Affairs

Dear Dr. Bell:

We acknowledge receipt of your supplemental application for the following:

Name of Drug: SINGULAIR® (montelukast sodium) Chewable Tablets, 4mg

NDA Number: 20-830

Supplement Number: S-008

Date of Supplement: May 6, 1999

Date of Receipt: May 7, 1999

Unless we find the application not acceptable for filing, this application will be filed under Section 505(b)(1) of the Act on July 6, 1999, in accordance with 21 CFR 314.101(a).

All communications concerning this NDA should be addressed as follows:

Center for Drug Evaluation and Research
Division of Pulmonary Drug Products, HFD-570
Office of Drug Evaluation II
Attention: Document Control Room 10B-03
5600 Fishers Lane
Rockville, MD 20857

Sincerely,

/S/

/FOR

Cathie Schumaker
Chief, Project Management Staff
Division of Pulmonary Drug Products, HFD-570
Office of Drug Evaluation II
Center for Drug Evaluation and Research

Hilfiker

RECORD OF TELEPHONE CONVERSATION

Date:	June 18, 1999
Project Manager:	Hilfiker
Subject:	Information Required for Filing of the Application
NDA:	20-830/S-008
Sponsor:	Merck
Product Name:	Singulair 4-mg Chewable Tablets

I contacted Merck to inform them primarily of the filing issues for supplement 20-830/S-008. Specifically, the following information is needed in order to file this application on July 6, 1999.

1. Two paper copies of study protocols for Studies 066 and 072.
2. Two paper copies of the complete study reports for Study 066 and Study 072 (submitted as an interim safety analysis of the ongoing Chronic Asthma Study).

Other information that is needed but not required prior to the filing date of the application will be discussed at a later date. Merck agreed to return my call and inform me of their ability to respond to these information requests on or before July 5, 1999.

David Hilfiker /S/ 6-18-99
Project Manager

Cc: Original NDA 20-830/S-008
HFD-570/Division file
HFD-570/Hilfiker
HFD-570/Schumaker

APPEARS THIS WAY
ON ORIGINAL