



Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation ODE II

FACSIMILE TRANSMITTAL SHEET

DATE: July 12, 2002

To: David Altarac, M.D., M.P.A. Director, Regulatory Affairs	From: Christine Yu, R.Ph. <i>YSL</i> Regulatory Project Manager
Company: Merck Research Laboratories	Division of Pulmonary & Allergy Drug Products
Fax number: 732-594-1030	Fax number: 301-827-1271
Phone number: 732-594-0135	Phone number: 301-827-1051

Subject: NDA 21-409 Singulair Oral Granules Carton & Package labeling comments

Total no. of pages including cover: 3

Comments: For Labeling teleconference, July 15, 2002, 10:30 – 11:30 am.

Document to be mailed: YES NO

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The following are the comments for the proposed Container (packet) Label

1. The proprietary name, established name, and product description are presented in a confusing manner. To avoid confusion, remove the word _____ from all labels and package inserts.
2. The name Oral Granules should be relocated to appear in conjunction with the proprietary name with a size commensurate to the proprietary name.
3. Print the word Singulair on the container in one color.
4. Increase the prominence of the abbreviation "mg" after the product strength.
5. Revise the "Each packet contains:" statement to read 4.2 mg of montelukast sodium equivalent to 4 mg montelukast. This applies to all labels and package insert as well.
6. Revise the labeling to state "For Pediatric Patients 12 months to 5 Years of age" on all container, cartons, and package inserts.
7. The "Opening Instructions" illustrations on the front panel show the packet being opened along a horizontal direction. The front panel has a vertical dotted line along the left side of the packet along with a horizontal notch. The back panel has a horizontal dotted line along the top of the packet. The "Opening Instructions" illustration and the dotted line markings are difficult to interpret. Please revise the "Opening Instructions" and or dotted line markings accordingly to eliminate confusion.
8. The storage statement "Store at 25°C (77°F)" should be in bold font.
9. Add the following instructions after the dosage statement: "Once opened, use the contents of this packet within 15 minutes. Discard any unused portion".

The following comments are for the Carton (Trade and Complimentary).

10. All comments for the Container Label (except 7) apply to the carton.
11. Delete the children's pictures on the carton panel. The product name and strength should be the most prominent information on the labels and labeling.
12. Delete the blue box that states _____ At first glance the image looks like the product strength. This information appears in print following the blue box, and is therefore unnecessary.

13. All the information printed in white lettering on a blue background above the trade name is blurry and difficult to read. Please correct for readability.

In the next printing modify all the approved labels, cartons, PIs and PPIs to be consistent with the above stated comments.

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/s/

Christine Yu
7/12/02 04:17:44 PM
CSO

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U.S. Food and Drug Administration
 Center for Drug Evaluation and Research
 Office of Drug Evaluation II

**Division of Pulmonary and Allergy
 Drug Products**

Parklawn Building, Room 10B-45
 5600 Fishers Lane HFD - 570
 Rockville, MD 20857

To:

Name: A. David Altman

Organization Name/Dept: Air, Regulatory Affairs

CC: _____

Phone number: 732-594-0135

Fax number: 732-594-1030

From: [S]

FAX: 301 - 827 - 1271

Phone: 301 - 827 - 1050

- Urgent
- For Review
- Please Comment
- Please Reply
- OTHER: _____

Date sent: July 12, 02

Number of pages including cover page: 21

Message: Changes tracked version of draft FDA Labelling (PI, PPI)

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20 pages redacted from this section of
the approval package consisted of draft labeling

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/s/

Christine Yu

7/22/02 02:23:13 PM

CSO

Division's proposal for PI & PPI (changes tracked), faxed
to Merck 7/12/02.

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Yu, Christine

From: Poochikian, Guiragos K
Sent: Friday, July 12, 2002 2:58 PM
To: Peri, Prasad; Yu, Christine; Mann, Marianne C; Starke, Peter; Chowdhury, Badrul A
Subject: FW: [DRUG] Oral Granules - Nomenclature

FYI.
GP

-----Original Message-----

From: Charles Barnstein [mailto:CHBarnstein@email.msn.com]
Sent: Friday, July 12, 2002 1:48 PM
To: Guiragos K. Poochikian, Ph.D.
Cc: Yana R. Mille; Thomas S. Foster, Pharm. D.; Thomas P. Reinders, Pharm. D.; Stephanie Y. Crawford, Ph.D.; R. David Lauper, Pharm. D.; Philip D. Walson, M.D.; Michael J. Groves, Ph.D.; Loyd V. Allen, Jr., Ph.D.; Jerry Phillips, B.S.; Jan Towers, Ph.D.; Herbert S. Carlin, D.Sc.; Edward M. Cohen, Ph.D.; Douglas D. Glover, M.D.; Dawn M. Boothe, DVM, Ph.D.; Joseph M. Betz, Ph.D.; Keith Marshall, Ph.D.; Daniel L. Boring, Ph.D.; William M. Heller, Ph.D.; W. Larry Paul, Ph.D.
Subject: [DRUG] Oral Granules - Nomenclature

Dear Dr. Poochikian:

For the record, this reports on the decision of the USP Expert Committee on Nomenclature and Labeling (EC NL) for nomenclature of the product described as _____

As I relayed to you by my voicemail telephone message this morning, balloting of EC NL members was conducted by email, and the EC NL voted to approve nomenclature for the article in the form **[DRUG] Oral Granules**.

Kind regards,

Charles H. Barnstein, Ph.D.

**APPEARS THIS WAY
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Yu, Christine

From: Mann, Marianne C
Sent: Tuesday, July 09, 2002 3:09 PM
To: Yu, Christine
Cc: Chowdhury, Badrul A
Subject: FW: URGENT Dosage Form Question

chris---if we make this an issue, we will likely need such emails in the review package to support our position---so I'm forwarding this your way!

-Marianne

-----Original Message-----

From: Poochikian, Guiragos K
Sent: Tuesday, July 09, 2002 2:56 PM
To: Chowdhury, Badrul A; Mann, Marianne C; Peri, Prasad; Starke, Peter
Subject: FW: URGENT Dosage Form Question

After several e-mails it seems Oral Granules is in and _____ is out.

See below.

GP

-----Original Message-----

From: Hess, William A
Sent: Tuesday, July 09, 2002 2:44 PM
To: Mille, Yana R
Cc: Poochikian, Guiragos K; Boring, Daniel L; Golson, Lillie D
Subject: RE: URGENT Dosage Form Question

Yana,

The CDER NSC recommended that 'granules' be used as the dosage form rather than _____. Neither CDER or USP liked the term _____ for many reasons, including 1) it does not describe the dosage form at all, 2) it does describe an action, which may or may not occur, 3) it is similar to the term used for some candy _____ which if used in an OTC context, could result in drug safety issues.

My personal notes from a USP EC N&L from several years ago state the following: "The word _____ has been used on the labeling of many capsule products to denote that the capsule can be pulled apart and the contents sprinkled on food. Although there are currently no approved drug products being currently marketed with the word _____ as a part of the established name, the term continues to appear elsewhere near the established name as a part of the proprietary name in the labeling. The USP NC decided that this was not a new dosage form, and they recommended that the word _____ be removed from labeling."

Hope that this helps some,
Bill

> -----Original Message-----

> From: Mille, Yana R
> Sent: Tuesday, July 09, 2002 1:38 PM
> To: Boring, Daniel L; Hess, William A; Golson, Lillie D
> Cc: Poochikian, Guiragos K

> Subject: URGENT Dosage Form Question

>

> Hello,

>

Charles Barnstein, USP, just called me to say that Guirag Poochikian called USP to find out the acceptable nomenclature for a packet of granules intended to be sprinkled on food. (Guirag, please speak up if I have any of the story wrong.) Guirag, Charles, Herb Carlin, and Bill Heller are all in favor of referring to the product as "Oral Granules." However, before USP sends this name out to their committee for a vote, they wanted to make sure CDER was in agreement. Thus, I am contacting y'all.

>

> I believe granules _____ were discussed at a Nomenclature Standards meeting. Unfortunately, I am not 100% certain about the outcome. Since only _____ do not appear in the CDER Data Standards Manual but Granules do, I suspect that we would agree with the term Oral Granules. Is that the case? I have no indication that these are delayed or extended release so a modifier would not be needed.

>

> As I understand it, an answer is needed immediately!!!!!! Please respond by 10 AM tomorrow morning so USP has time to get this out for a vote and get back to Guirag within his specified time frame.

>

> Thank you,

> Yana

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Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation ODE II

FACSIMILE TRANSMITTAL SHEET

DATE: June 28, 2002

To: David Altarac, M.D., M.P.A. Director, Regulatory Affairs	From: Christine Yu, R.Ph. Regulatory Project Manager
Company: Merck Research Laboratories	Division of Pulmonary & Allergy Drug Products
Fax number: 732-594-1030	Fax number: 301-827-1271
Phone number: 732-594-0135	Phone number: 301-827-1051
Subject: NDA 21-409 Singulair — CMC comments and request for additional information.	

Total no. of pages including cover: 3

Comments: Please provide response as soon as possible.

Document to be mailed: YES NO

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Please submit the requested information as soon as possible:

1. Provide clarification []
s identified impurities
2. Provide confirmation that []]
3. Tighten the acceptance criteria for [] to reflect the levels of observed data from the commercial batches used to manufacture the drug product. Submit adequate data to support your proposal.
4. Provide justification and explanation for the out of specification results obtained for assay [] in the drug product by July 15, 2002, as committed to in the June 7, 2002, submission.
5. As stated earlier in the Agency's letter dated May 7, 2002, to ensure reproducible products in terms of dissolution and degradation profiles, provide adequate validation data []
1 on the drug product. Once established, these attributes along with their respective optimized process conditions should be reflected in the master batch record.
6. You have stated in your correspondence dated June 7, 2002, that the three NDA stability batches were tested for microbial content at release and at [] time point and that they met the requirements. Provide these results and the appropriate acceptance criteria for microbial testing of the drug product.
7. Submit tightened dissolution acceptance criterion for the drug product to reflect the observed data.
8. Provide comparative changes in the manufacturing process for the *validation batches* (2089088, 2089090, and 2089249), [] *batches* used for stability (MR-4218, 1005-46, and 1005-42), *Clinical Trial batches* used also in pharmacokinetic studies (MR-4284, MR-4491 and MR-3808), and the [] *batch* (1040795) that led to significant change in the dissolution values obtained for the [] time point. The mean dissolution values obtained at the [] time point for the validation batches

are reduced by approximately — % compared with the other batches at the same time point.

9. The Agency recommends that the shelf life acceptance criteria for — Total Degradants be tightened to reflect the data observed from the primary stability batches.
10. Provide updated specification sheets to reflect the modifications above.

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/s/

Christine Yu
6/28/02 11:01:27 AM
CSO



Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation ODE II

FACSIMILE TRANSMITTAL SHEET

DATE: May 31, 2002

To: David Altarac, M.D., M.P.A. Director, Regulatory Affairs	From: Christine Yu, R.Ph. <i>CS</i> Regulatory Project Manager
Company: Merck Research Laboratories	Division of Pulmonary & Allergy Drug Products
Fax number: 732-594-1030	Fax number: 301-827-1271
Phone number: 732-594-0135	Phone number: 301-827-1051
Subject: NDA 21-409 Singulair Request for additional information	
Total no. of pages including cover: 2	

Comments:

Document to be mailed: YES NO

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Handwritten notes and a circled mark in the top right corner.

Please provide the following information:

- The mean and standard deviation values as well as individual AUC, Cmax, and Tmax values obtained from individuals enrolled in Protocol 039. [Reference 50 contains Protocol 039 entitled, "A randomized, 2-period, multicenter study to evaluate the safety, tolerability and plasma concentration profile of MK-0476 administered as a chewable formulation in 6 to 8-year old children (Tanner Stage I) with asthma," submitted September 28, 2001.]
- The mean and individual pharmacokinetic parameters generated in children 9 to 16 years of age who received Singulair in study Protocols 021 and 036. [Protocol 021 is found in Reference 53, entitled, "Single-dose plasma concentration profile study of the MK-0476 tablet in adolescents with asthma." Protocol 036 is found in Reference 63, entitled, "An open, single oral dose, 1-period study to evaluate the plasma concentration profile of MK-0476 (Phase III tablet formulation) in adolescents in early puberty (Tanner stages II and III) with asthma."]
- If available, any individual pharmacokinetic parameters generated in children ages 9-14 years of age after receiving a single 5 mg dose of Singulair chewable tablets.

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Food and Drug Administration
 Center for Drug Evaluation and Research
 Office of Drug Evaluation ODE II

FACSIMILE TRANSMITTAL SHEET

DATE: May 10, 2002

To: David Altarac, M.D., M.P.A. Director, Regulatory Affairs	From: Christine Yu, R.Ph. Regulatory Project Manager <i>CS</i>
Company: Merck Research Laboratories	Division of Pulmonary & Allergy Drug Products
Fax number: 732-594-1030	Fax number: 301-827-1271
Phone number: 732-594-0135	Phone number: 301-827-1051
Subject: NDA 21-409 Request for additional information- Clinical Pharmacology & Biopharmaceutics	
Total no. of pages including cover: 2	

Comments:

Document to be mailed: YES NO

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1. Please submit the following information regarding Protocol 066 (population pharmacokinetics in children with asthma 2 to 5 years old, Reference 54 of the September 28, 2001, submission):
 - a. Data sets that include the following parameters.
 - Identification
 - Time
 - Dose
 - Concentration
 - Covariates (e.g., age, weight, body surface area)
 - b. Program code used for the population pharmacokinetic analysis.
 - c. Model building information.
 - d. Output of final model.

2. Please submit covariates (e.g., age, weight, race) for Protocol 034 (Reference 51, submitted September 28, 2001), a bioequivalence study using film-coated and chewable tablets in healthy male volunteers.

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5/7/02

NDA 21-409

DISCIPLINE REVIEW LETTER

Merck & Co., Inc.
RY 33-720
P.O. Box 2000
Rahway, NJ 07065-0900

Attention: David Altarac, M.D., M.P.A.
Director, Regulatory Affairs

Dear Dr. Altarac:

Please refer to your September 28, 2001, new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Singulair ~~_____~~ (montelukast sodium oral granules).

Our reviews of the Chemistry, Manufacturing and Controls (CMC) sections of your submission are complete, and we have identified the following deficiencies:

1. The following comments pertain to the drug substance



2. The following comments pertain to the excipients used in the drug product

- a. Provide adequate acceptance specifications for all excipients to ensure batch to batch consistency and performance of the drug product. Provide the source, origin, and certificates of analyses for the excipients used to manufacture the primary stability lots ~~_____~~ of montelukast sodium oral granules described in volume 1.3, Attachments 1-3 of the September 28, 2001, submission.

- b. Establish appropriate specifications for _____ impurities in each of the excipients used in the drug product. If _____ are not used in the preparation of each of the excipients, submit letters to this effect by each supplier of each excipient intended to be used in the drug product.
3. The following comments pertain to the manufacturing process of the drug product
- a. [_____]
_____ } These parameters should be reflected in the master batch record.
 - b. Provide adequate validation data pertaining to [_____]
_____ } The effect of these parameters should be reflected in the master batch record with appropriate operating parameters.
 - c. Justify [_____]
_____ } Clarify if the commercial batches will also be manufactured _____ }
 - d. Update the master batch record to specify a controlled room temperature and humidity during the manufacturing process as claimed in the NDA page C-12 (e.g., <25°C and <50°C RH) of the submission dated September 28, 2001.
4. The following comments pertain to the drug product, drug product specifications, methods, and container closure
- a. Provide assurance (e.g., results from microbial studies) on the capability of the formulation to sustain microbial growth. Establish appropriate specifications for _____ impurities in the drug product.
 - b. Revise the dissolution specifications to Q= _____ in _____ minutes to reflect the data observed.
 - c. Tighten the shelf life acceptance criteria for _____ Total impurities to reflect the observed data from stability batches.
 - d. Provide the stability of Montelukast sodium oral granules in various baby food products when exposed to light for _____ Provide the stability of montelukast sodium in additional baby foods that would potentially be used along with the drug product (e.g., chocolate syrup, milk-based formula, soy-based formula, hydrolyzed protein formula, milk, water).

e. Clarify the following comments/discrepancy pertaining to specifications for

(i) []

(ii) []

f. Tighten the Montelukast Sodium assay acceptance criterion to reflect the data.

g. Update the impurities seen in the drug product to include total unspecified impurities. List all impurities (including drug substance impurities) in the drug product specifications. Since the drug substance impurities are not included in the total impurities of the drug product, they should be clearly stated in the specifications as a footnote.

h. Provide details of the preparation of a reference standard for the drug product.

i. Provide the result of the USP <671> testing for the proposed container package laminates. Update the specification sheet to indicate zero number of pin holes (vol.1.3, page 46 of the September 28, 2001, submission). Provide appropriate of the packaging components used to form the pouches.

j. Provide updated shelf life data for the drug product placed on stability. Comments on the shelf life are being withheld pending the availability of this data.

k. Clarify how the incoming foil laminate sample is prepared for the IR acceptance test.

l. Following comments pertain to the test method for montelukast Assay, Degradates, and Identity (method Number 011410007M02).

(i) []

(ii) []

(iii) Provide the accuracy of the method to quantitate all the impurities at the levels normally seen in the drug product. Provide the method validation in terms of linearity for the degradants. Use of the active reference standard may not be appropriate surrogate for the impurities which do not have the same relative response factor as Montelukast Sodium.

We are providing these comments to you before we complete our review of the entire application to give you preliminary notice of issues that we have identified. In conformance with the prescription drug user fee reauthorization agreements, these comments do not reflect a final decision on the information reviewed and should not be construed to do so. These comments are preliminary and subject to change as we finalize our review of your application. In addition, we may identify other information that must be provided before we can approve this application. If you respond to these issues during this review cycle, depending on the timing of your response, and in conformance with the user fee reauthorization agreements, we may not be able to consider your response before we take an action on your application during this review cycle.

If you have any questions, call Christine Yu, Regulatory Project Manager, at 301-827-1051.

Sincerely,



Guirag Poochikian, Ph.D.
Chemistry Team Leader
Division of Pulmonary and Allergy Drug Products, HFD-570
DNDC 2, Office of New Drug Chemistry
Center for Drug Evaluation and Research

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/s/

Guiragos Poochikian
5/7/02 04:19:37 PM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION

REQUEST FOR CONSULTATION

TO: (Division/Office): Biometrics HFD-715

FROM: Prasad Peri/HFD-570

DATE 5/1/02	IND NO.	NDA NO. 21-409	TYPE OF DOCUMENT Original Application	DATE OF DOCUMENT 9/28/01
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NAME OF DRUG: Singulair®	PRIORITY CONSIDERATION 3	CLASSIFICATION OF DRUG S	DESIRED COMPLETION DATE 05/24/02
--------------------------	-----------------------------	-----------------------------	-------------------------------------

NAME OF FIRM: Merck Research Labs

REASON FOR REQUEST

I. GENERAL

- | | | |
|--|--|---|
| <input type="checkbox"/> NEW PROTOCOL | <input type="checkbox"/> PRE-NDA MEETING | <input type="checkbox"/> RESPONSE TO DEFICIENCY LETTER |
| <input type="checkbox"/> PROGRESS REPORT | <input type="checkbox"/> END OF PHASE II MEETING | <input type="checkbox"/> FINAL PRINTED LABELING |
| <input type="checkbox"/> NEW CORRESPONDENCE | <input type="checkbox"/> RESUBMISSION | <input type="checkbox"/> LABELING REVISION |
| <input type="checkbox"/> DRUG ADVERTISING | <input type="checkbox"/> SAFETY/EFFICACY | <input type="checkbox"/> ORIGINAL NEW CORRESPONDENCE |
| <input type="checkbox"/> ADVERSE REACTION REPORT | <input type="checkbox"/> PAPER NDA | <input type="checkbox"/> FORMULATIVE REVIEW |
| <input type="checkbox"/> MANUFACTURING CHANGE/ADDITION | <input type="checkbox"/> CONTROL SUPPLEMENT | <input checked="" type="checkbox"/> OTHER (Specify below) |
| <input type="checkbox"/> MEETING PLANNED BY _____ | | |

II. BIOMETRICS

STATISTICAL EVALUATION BRANCH	STATISTICAL APPLICATION BRANCH
<input type="checkbox"/> TYPE A OR B NDA REVIEW <input type="checkbox"/> END OF PHASE II MEETING <input type="checkbox"/> CONTROLLED STUDIES <input type="checkbox"/> PROTOCOL REVIEW <input type="checkbox"/> OTHER	<input type="checkbox"/> CHEMISTRY <input type="checkbox"/> PHARMACOLOGY <input type="checkbox"/> BIOPHARMACEUTICS <input type="checkbox"/> OTHER

III. BIOPHARMACEUTICS

- | | |
|--|---|
| <input type="checkbox"/> DISSOLUTION | <input type="checkbox"/> DEFICIENCY LETTER RESPONSE |
| <input type="checkbox"/> BIOAVAILABILITY STUDIES | <input type="checkbox"/> PROTOCOL-BIOPHARMACEUTICS |
| PHASE IV STUDIES | <input type="checkbox"/> IN-VIVO WAIVER REQUEST |

IV. DRUG EXPERIENCE

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

V. SCIENTIFIC INVESTIGATIONS

CLINICAL

PRECLINICAL

COMMENTS/SPECIAL INSTRUCTIONS (Attach additional sheets if necessary):

Please evaluate stability data for expiration dating period. Parameters for evaluation includes Assay, Impurities _____ and Total impurities. Stability and Statistical Analyses Data in the SAS transport format have been requested by the project manager. Only 25°C and 30°C data should be used for the calculations. A copy of the proposed shelf life specifications for the drug product is attached.

cc: Orig NDA 21409
HFD-570/Div File
HFD-570/PPeri/CYwJGibbert

SIGNATURE OF REQUESTER

/S/

METHOD OF DELIVERY (Check one)

MAIL HAND

SIGNATURE OF RECEIVER

SIGNATURE OF DELIVERER

Moisture (Release Only)	Max. / 1%	USP <921>; Test according to the KF method described in [C-2] [011410007M06]
<u>Release</u>		Assay by HPLC [C-2]
Montelukast Assay	/ of label claim (mg/packet)	[011410007M02]
/ Any other degradation product	Max Max /	
Total Degradates*	Max /	
<u>Shelf-life</u>		
Montelukast Assay	/ % of label claim (mg/packet)	
/ Any other degradation product	Max Max / Max %	
Any other degradation product	1%	
Total Degradates*	Max /	
* excluding montelukast sodium drug substance impurities		

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151 5/20/02

DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE FOOD AND DRUG ADMINISTRATION			REQUEST FOR CONSULTATION	
TO: (Division/Office) Luqi Pei Pharmacology			FROM: Prasad Peri/HFD-570	
DATE: 5/01/02	IND NO.:	NDA NO.: NDA21-409	TYPE OF DOCUMENT: Original NDA	DATE OF DOCUMENT: 9/28/01
NAME OF DRUG Singulair®		PRIORITY CONSIDERATION: 3	CLASSIFICATION OF DRUG: S	DESIRED COMPLETION DATE: 05/17/02
NAME OF APPLICANT: Merck Research Laboratories				
REASON FOR REQUEST				
I. GENERAL				
<input type="checkbox"/> NEW PROTOCOL <input type="checkbox"/> PROGRESS REPORT <input type="checkbox"/> NEW CORRESPONDENCE <input type="checkbox"/> DRUG ADVERTISING <input type="checkbox"/> ADVERSE REACTION REPORT <input type="checkbox"/> MANUFACTURING CHANGE/ADDITION <input type="checkbox"/> MEETING PLANNED BY _____		<input type="checkbox"/> PRE-NDA MEETING <input type="checkbox"/> END OF PHASE II MEETING <input type="checkbox"/> RESUBMISSION <input type="checkbox"/> SAFETY/EFFICACY <input type="checkbox"/> PAPER NDA <input type="checkbox"/> CONTROL SUPPLEMENT		<input type="checkbox"/> REPONSE TO DEFICIENCY LETTER <input type="checkbox"/> FINAL PRINTED LABELING <input type="checkbox"/> LABELING REVISION <input type="checkbox"/> ORIGINAL NEW CORRESPONDENCE <input type="checkbox"/> FORMULATIVE REVIEW <input checked="" type="checkbox"/> OTHER (Specify below)
II. BIOMETRICS				
STATISTICAL EVALUATION BRANCH			STATISTICAL APPLICATION BRANCH	
<input type="checkbox"/> TYPE A OR B NDA REVIEW <input type="checkbox"/> END OF PHASE II MEETING <input type="checkbox"/> CONTROLLED STUDIES <input type="checkbox"/> PROTOCOL REVIEW <input type="checkbox"/> OTHER			<input type="checkbox"/> CHEMISTRY <input type="checkbox"/> PHARMACOLOGY <input type="checkbox"/> BIOPHARMACEUTICS <input type="checkbox"/> OTHER	
III. BIOPHARMACEUTICS				
<input type="checkbox"/> DISSOLUTION <input type="checkbox"/> BIOAVAILABILITY STUDIES <input type="checkbox"/> PHASE IV STUDIES			<input type="checkbox"/> DEFICIENCY LETTER RESPONSE <input type="checkbox"/> PROTOCOL-BIOPHARMACEUTICS <input type="checkbox"/> IN-VIVO WAIVER REQUEST	
IV. DRUG EXPERIENCE				
<input checked="" type="checkbox"/> PHASE IV SURVEILLANCE/EPIDEMIOLOGY PROTOCOL DRUG USE e.g. POPULATION EXPOSURE, ASSOCIATED DIAGNOSES COMPARATIVE RISK ASSESSMENT ON GENERIC DRUG GROUP <input type="checkbox"/> REVIEW OF MARKETING EXPERIENCE, DRUG USE AND SAFETY			<input type="checkbox"/> SUMMARY OF ADVERSE EXPERIENCE <input type="checkbox"/> POISON RISK ANALYSIS <input type="checkbox"/> CASE REPORTS OF SPECIFIC REACTIONS (List below)	
V. SCIENTIFIC INVESTIGATIONS				
<input type="checkbox"/> CLINICAL			<input type="checkbox"/> PRECLINICAL	
COMMENTS/SPECIAL INSTRUCTIONS (Attach additional sheets if necessary): Please evaluate impurity levels permitted by the following specifications for excipients in the drug product: This pharm/tox consult is for evaluating the safety of the observed level of impurities _____ in Singulair _____ when mixed with food. In particular, the _____ level reaches almost _____ when mixed with Rice (see attached table) after 30 minutes. Impurity _____ was formed at _____ level in applesauce when stored for 30 minutes. Merck claims that the levels of up to _____ have been qualified in preclinical studies. Please evaluate effect of this instability observation in patient population younger than 2 years of age.				
SIGNATURE OF REQUESTER [/S/]			METHOD OF DELIVERY (Check one) <input type="checkbox"/> MAIL <input checked="" type="checkbox"/> HAND	
SIGNATURE OF RECEIVER			SIGNATURE OF DELIVERER	

cc: Orig. NDA21-409 HFD-570/Div. File/PPeri/YuC

Redacted /

page(s) of trade secret.

and/or confidential

commercial information

(b4)

MEMORANDUM

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

DATE: May 3, 2002
TO: File
FROM: Luqi Pei, Ph.D.
SUBJECT: _____
NDA 21-409, Singulair _____ (montelukast sodium) Oral
Granules

This memo documents my conclusion that a new preclinical safety evaluation of degradation products, _____ is no longer needed. The memo also closes a Chemistry Consultation request initiated by Dr. Prasad Peri on May 1, 2002. My conclusion is based on the finding that the detected levels of these compounds in the _____ are lower than those in Singulair 4 and 5 mg Chewable Tablets. Also, there is no new information suggesting additional risk or safety concerns associated with the degradation products.

The review team was discussing the safety of _____ in the Singulair _____ application in the past few days. The sponsor reported the detection of up to _____ when the Singulair _____ is mixed with baby food rice. A look at past reviews of Singulair reveals that the detected level of _____ in the _____ is lower than their approved specifications _____ in Singulair 4 and 5 mg Chewable Tablets. The approval of the compounds in the tablets was based on Dr. Shannon Williams review dated October 30, 1997 in NDAs 20-829 and 20-830 which indicates that a safety factor of 56 (based on _____ exists between the expected daily in take in children and animal NOAEL value in a 3-month toxicity study.

Also, the discussion in the past few days is based on irrelevant information. There is no evidence suggesting that _____ might be carcinogenic. The National Toxicology Program study shows that _____ is carcinogenic in male mice, but _____ and _____ are chemically different molecules. It is questionable to extrapolate or transfer the carcinogenic potential of _____ to _____. Thus, the reported levels of the _____ do not cause any new and additional safety concerns. Another safety evaluation of these degradation products is not warranted.

I have informed the review team of the above conclusion on 5/3/02

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this page is the manifestation of the electronic signature.**

/s/

Lugi Pei
5/3/02 03:47:38 PM
PHARMACOLOGIST

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ON ORIGINAL

4/19/02

CONSULTATION RESPONSE
Division of Medication Errors and Technical Support
Office of Drug Safety
(ODS; HFD-400)

DATE RECEIVED: February 21, 2002

DUE DATE: April 21, 2002

DMETS CONSULT #: 02-0030

TO: Robert Meyer, MD
Director, Division of Pulmonary and Allergy Drug Products
HFD-570

THROUGH: Christine Yu, R.Ph.
Regulatory Project Manager
HFD-570

PRODUCT NAME:
Singulair
(Montelukast Sodium)
Oral Granules
4 mg packets

NDA SPONSOR:
Merck & Co., Inc.

NDA # 21 - 409

SAFETY EVALUATOR: Scott Dallas, R.Ph.

SUMMARY: In response to a consult from the Division of Pulmonary and Allergy Drug Products (HFD-570), the Division of Medication Errors and Technical Support (DMETS) conducted a review of the proposed proprietary name, "Singulair" to determine the potential for confusion with approved proprietary and established names as well as pending names.

DMETS RECOMMENDATION: DMETS has no objection to the use of the proprietary name, "Singulair". This name must be re-evaluated approximately 90 days prior to the expected approval of the NDA. A re-review of the name prior to NDA approval will rule out any objections based upon approvals of other proprietary or established names from the signature date of this document. In addition, DMETS recommends implementation of the label revisions outlined in Section III of this review.

**APPEARS THIS WAY
ON ORIGINAL**

Carol Holquist, RPh
Deputy Director
Division of Medication Errors and Technical Support
Office of Drug Safety
Phone: (301) 827-3242 Fax (301) 443-5161

Jerry Phillips, RPh
Associate Director
Office of Drug Safety
Center for Drug Evaluation and Research
Food and Drug Administration

**Division of Medication Errors and Technical Support
Office of Drug Safety
HFD-400; Parklawn Building Room 15B32
Center for Drug Evaluation and Research**

PROPRIETARY NAME REVIEW

DATE OF REVIEW: April 17, 2002

NDA NUMBER: 21- 409

NAME OF DRUG: Singulair _____
(Montelukast Sodium)

IND SPONSOR: Merck & CO., Inc.

I. INTRODUCTION:

This consult was written in response to a request from the Division of Pulmonary and Allergy Drug Products (HFD-570) for an assessment of the proposed proprietary name, Singulair _____. This proposed tradename was submitted with NDA 21-409. DMETS also reviewed the container label, carton labeling, and insert labeling.

PRODUCT INFORMATION

Singulair contains the active ingredient montelukast sodium. Montelukast sodium is a selective leukotriene receptor antagonist that inhibits the cysteinyl leukotriene CysLT₁ receptor. Cysteinyl leukotrienes are products of arachidonic acid metabolism and are released from various cells, including mast cells and eosinophils. Cysteinyl leukotrienes and leukotriene receptor occupation have been correlated with the pathophysiology of asthma. Montelukast binds with high affinity and selectivity to the CysLT₁ receptor. Montelukast inhibits the physiologic actions of cysteinyl leukotriene (LTD₄) at the CysLT₁ receptor without any agonist activity. Singulair has been available in a 4 mg and 5 mg chewable tablet, and a 10 mg tablet. This review concerns the new dosage formulation of Singulair 4 mg _____ available in a packet. This new dosage formulation is for pediatric patients age _____. The dose is one packet of Singulair 4 mg _____ daily to be taken in the evening.

II. RISK ASSESSMENT:

The standard DMETS proprietary name review was not conducted for this consult because "Singulair" has been utilized in the U.S. marketplace since February 20, 1998.

A. AERS Search

The FDA Adverse Event Reporting System (AERS) database was searched for all postmarketing safety reports of medication errors associated with "Singulair". The search was conducted with the Meddra Preferred Term (PT) "Medication Error". The search identified 37 reports, of which 7 involved name confusion with Singulair. A brief summary of the 7 reports involved with the name confusion is provided in Attachment A. The reports revealed the name Singulair was confused with two proprietary names and two established

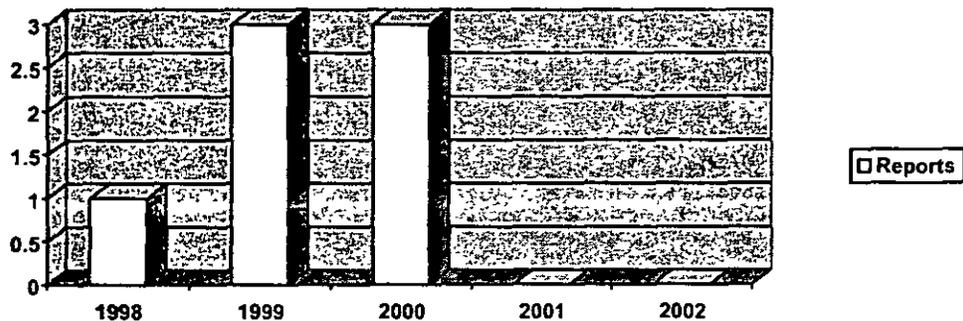
names. The proprietary names were Sinequan (3), and Sular (2) and the established names were Selegiline (1), and Simvastatin (1).

B. SAFETY EVALUATOR RISK ASSESSMENT

Singlair ——— was evaluated with respect to any Singlair name confusion identified in the Adverse Event Reporting System, and any potential name confusion with respect to the current Singlair product line and with the addition of the proposed product.

The FDA Adverse Event Reporting System (AERS) database search revealed seven postmarketing reports involving name confusion with the proprietary name, Singlair. The confused medication names were Sinequan, Sular, Selegiline, and Simvastatin. All these names are for medications approved prior to the February 20, 1998 approval of Singlair. These names contain some qualities to cause them to sound alike and/or look alike. Additionally, name confusion can be further reinforced when characteristics are common to both medications. All five medications have an overlapping dosage strength and dosing frequency. Six reports involved the 10 mg dosage strength, a shared strength to Singlair, Sinequan, Sular, and Simvastatin. One report involved the 5 mg dosage strength, a shared strength to Singlair, Selegiline and Simvastatin. The usual dosing frequency for Singlair, Sinequan, Sular and Simvastatin is once a day. Singlair, Sinequan, and Simvastatin are also generally dosed at bedtime. All of the dosing frequency directions included in the reports would have been acceptable for either medication involved with the name confusion. A bar graph is included below to illustrate the number of reports involved with name confusion for each calendar year. Since 2000, no more reports involving name confusion between Singlair and another medication have been reported. Medication errors are known to occur when a new medication is introduced into the market. This may explain the large number of errors reported in 1999 and 2000. Based on the fact no new reports have been reported since 2000, DMETS is not considering any action with the proprietary name, Singlair at this time. However, DMETS will continue to monitor post-marketing medication errors in association with these proprietary and established names.

Reports of Medication Errors due to Name Confusion
Versus Calendar Year



The Singlair product line already has a product manufactured in a 4 mg dosage strength. Singlair is available as a 4 mg chewable tablet. No reports involving name confusion were

detected during the AERS search with the 4 mg chewable tablet. If this formulation is approved, Singulair will be available in a 4 mg chewable tablet and a 4 mg oral granule packet. Since both 4 mg formulations contain the same quantity of active ingredient a dispensing mistake would not be a safety concern in regards to dosing, but could be a safety concern in regards to administration. Singulair _____ contains a new modifier _____, and formulation (oral granules in a packet) to the product line. The modifier, _____ is an established modifier to distinguish a pediatric dosage formulation. Two common pediatric products that share the modifier are Topamax _____ and Depakote _____. Topamax _____ is available as a 15 mg or 25 mg capsule, and Depakote _____ is available as a 125 mg capsule. Another product, Paser, shares both a similar formulation description and dosage numeral. Paser is only available in a packet containing 4 grams of delayed release granules. Since Topamax, Depakote, and Paser do not look alike or sound alike to Singulair, the potential risk of medication errors involving these products should be low. However, the labels and labeling for Singulair use the terminology, _____, and oral granules. This can lead to confusion for the health professionals and patients as to whether the product should be known as Singulair _____ or Singulair Granules. It is important for this formulation to be known and prescribed as "Singulair _____" to distinguish itself from the Singulair 4 mg chewable tablet, and Paser 4 gram granules.

III. LABELING, PACKAGING, AND SAFETY RELATED ISSUES:

DMETS has reviewed the proposed container label, complementary carton labeling and package insert. DMETS has attempted to focus on safety issues to prevent possible medication errors. Areas of possible improvement have been identified, in the interest of minimizing potential user error and patient safety.

DMETS recommends consulting Dan Boring of the USAN council and the Labeling and Nomenclature Committee for the proper designation of the established name. The following recommendations may have to be revised based on the outcome of the consult concerning the established name.

A. Container Label

1. The proprietary name, established name, and product description are presented in a confusing manner. Since "Oral Granules" has a greater prominence than _____ it is unclear if the product would be known as Singulair _____ or Singulair Oral Granules. The name _____ should be relocated away from the product strength to appear in conjunction with the proprietary name with a size commensurate to the proprietary name.
2. The product strength is based on the active moiety "montelukast" rather than the salt "montelukast sodium". Therefore, DMETS recommends expressing the proprietary name, established name and strength in one of the following three manners:

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ON ORIGINAL**

[]

or

[]

or

[]
[]

DMETS prefers the first example as an option because this nomenclature is consistent with the USP recommendations on "labeling of salts of drugs".

3. Increase the prominence of the abbreviation "mg" after the product strength.

4. []

5. The "Opening Instructions" illustrations on the front panel show the packet being opened along a horizontal direction. The front panel has a vertical dotted line along the left side of the packet along with a horizontal notch. The back panel has a horizontal dotted line along the top of the packet. The "Opening Instructions" illustration and the dotted line markings are difficult to interpret. Please revise the "Opening Instructions" and or dotted line markings accordingly to eliminate confusion.

B. Complementary Carton Labeling

1. See comments A 1-5 above.

2. Delete or reduce the size of the children's pictures on the carton panel. The product name and strength should be the most prominent information on the labels and labeling.

3. Delete the blue box that states _____ . At first glance the image looks

like the product strength. This information appears in print following the blue box, and is therefore unnecessary.

4. All the information printed in white lettering on a blue background above the tradename is blurry and difficult to read. Please correct for readability.

C. Insert Labeling

1. In the "Description" section, the montelukast molar equivalent is expressed as 4.0 mg of free acid. DMETS does not recommend the use of a terminal zero in conjunction with the expression of any strength. To prevent confusion and medication errors the strength should be revised to read 4 mg.
2. To be in accordance with 21 CFR 201.57(f)(2) the full text of information for the patients found in the "Precautions" section should be reprinted at the end of the labeling.

IV. RECOMMENDATIONS:

1. DMETS has no objection to the use of the proprietary name, "Singulair _____"
2. DMETS recommends consulting Dan Boring of the USAN council and the Labeling and Nomenclature Committee for the proper designation of the established name.
3. DMETS recommends the above labeling revisions to encourage the safest possible use of the product.

DMETS would appreciate feedback of the final outcome of this consult. We are willing to meet with the Division for further discussion as well. If you have any questions concerning this review, please contact Sammie Beam at 301-827-3242.



Scott Dallas, R.Ph.
Safety Evaluator
Office of Drug Safety (DMETS)

**APPEARS THIS WAY
ON ORIGINAL**

ATTACHMENT A

Table 1

Individual Safety Report Number	Month / Year and Practice Location	Prescribed Medication	Interpreted Medication	Abbreviated Narrative and Patient Outcome if Known
3309455-7-00-01	11/98 – Retail Pharmacy	Singulair 10 mg	Sinequan 10 mg	A prescription was filled and dispensed with Sinequan 10 mg capsules instead of Singulair 10 mg tablets. The patient administered the medication for 3 days before the medication error was detected. After the medication error was corrected report states the patient was "doing fine."
3209115-7-00-01	01/99 – Retail Pharmacy	Singulair 10 mg	Sinequan 10 mg	A prescription was filled with Sinequan 10 mg capsules instead of Singulair 10 mg tablets. The medication error was detected through patient counseling. The patient never received the wrong medication.
3301739-1-00-01	02/99 – Retail Pharmacy	Singulair 10 mg	Sular 10 mg	A prescription was filled with Sular 10 mg tablets instead of Singulair 10 mg tablets. The medication error was detected through patient counseling. The patient never received the wrong medication.
3254873-9-00-01	04/99 – Retail Pharmacy	Selegiline 5 mg	Singulair 5 mg	A unit dose Singulair 5 mg tablet was dispensed for a Selegiline 5 mg tablet. A nurse detected the medication error. The wrong medication was not administered to the patient.
3563850-x-00-01	04/00 – Retail Pharmacy	Singulair 10 mg	Sular 10 mg	A prescription was filled and dispensed with Sular 10 mg tablets instead of Singulair 10 mg tablets. The patient administered the medication for one week. The report states the patient experienced "low blood pressure and dizziness".
3563831-6-00-01	07/00 – Retail Pharmacy	Sinequan 10 mg	Singulair 10 mg	A prescription was filled for Singulair 10 mg tablets instead of Sinequan 10 mg capsules. The medication error was detected through patient counseling. The patient never received the wrong medication.
3652018-4-00-01	11/00 – Outpatient Pharmacy	Singulair 10 mg	Simvastatin 10mg	A prescription was filled with Simvastatin 10 mg tablets instead of Singulair 10 mg tablets. The error was detected during patient counseling when the patient questioned the tablet appearance. The patient was not dispensed the wrong medication.

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this page is the manifestation of the electronic signature.**

/s/

Scott Dallas
4/19/02 12:35:22 PM
PHARMACIST

Carol Holquist
4/19/02 12:48:54 PM
PHARMACIST

Jerry Phillips
4/19/02 02:22:49 PM
DIRECTOR

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ON ORIGINAL**

18/ 2/21/02

DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE FOOD AND DRUG ADMINISTRATION	REQUEST FOR CONSULTATION
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<i>Division/Office:</i> Office of Drug Safety, HFD-400	FROM: Christine Yu, R.Ph. Regulatory Project Manager, HFD-570
--	--

DATE February 20, 2002	IND NO.	NDA NO. 21-409	TYPE OF DOCUMENT Original NDA	DATE OF DOCUMENT September 28, 2001
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NAME OF DRUG Singulair	PRIORITY CONSIDERATION Standard	CLASSIFICATION OF DRUG 3S	DESIRED COMPLETION DATE June 14, 2002
---------------------------	------------------------------------	------------------------------	--

NAME OF FIRM: Merck & Co., Inc.

REASON FOR REQUEST

I. GENERAL

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

STATISTICAL EVALUATION BRANCH	STATISTICAL APPLICATION BRANCH
<input type="checkbox"/> TYPE A OR B NDA REVIEW <input type="checkbox"/> END OF PHASE II MEETING <input type="checkbox"/> CONTROLLED STUDIES <input type="checkbox"/> PROTOCOL REVIEW <input type="checkbox"/> OTHER (SPECIFY BELOW):	<input type="checkbox"/> CHEMISTRY REVIEW <input type="checkbox"/> PHARMACOLOGY <input type="checkbox"/> BIOPHARMACEUTICS <input type="checkbox"/> OTHER (SPECIFY BELOW):

III. BIOPHARMACEUTICS

<input type="checkbox"/> DISSOLUTION <input type="checkbox"/> BIOAVAILABILITY STUDIES <input type="checkbox"/> PHASE IV STUDIES	<input type="checkbox"/> DEFICIENCY LETTER RESPONSE <input type="checkbox"/> PROTOCOL-BIOPHARMACEUTICS <input type="checkbox"/> IN-VIVO WAIVER REQUEST
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IV. DRUG EXPERIENCE

<input type="checkbox"/> PHASE IV SURVEILLANCE/EPIDEMIOLOGY PROTOCOL <input type="checkbox"/> DRUG USE e.g. POPULATION EXPOSURE, ASSOCIATED DIAGNOSES <input type="checkbox"/> CASE REPORTS OF SPECIFIC REACTIONS (List below) <input type="checkbox"/> COMPARATIVE RISK ASSESSMENT ON GENERIC DRUG GROUP	<input type="checkbox"/> REVIEW OF MARKETING EXPERIENCE, DRUG USE AND SAFETY <input type="checkbox"/> SUMMARY OF ADVERSE EXPERIENCE <input type="checkbox"/> POISON RISK ANALYSIS
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V. SCIENTIFIC INVESTIGATIONS

<input type="checkbox"/> CLINICAL	<input type="checkbox"/> PRECLINICAL
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COMMENTS/SPECIAL INSTRUCTIONS:
 Please perform trade name review for "Singulair"

SIGNATURE OF REQUESTER	METHOD OF DELIVERY (Check one)
	<input type="checkbox"/> MAIL <input checked="" type="checkbox"/> HAND
SIGNATURE OF RECEIVER	SIGNATURE OF DELIVERER

Attached Hard copy: Container Label, Carton Label
 Attached to consult electronically: Approved PI and PPI, Proposed PI & PPI



Food and Drug Administration
 Center for Drug Evaluation and Research
 Office of Drug Evaluation ODE II

FACSIMILE TRANSMITTAL SHEET

DATE: April 17, 2002

To: David Altarac, M.D., M.P.A. Director, Regulatory Affairs	From: Christine Yu, R.Ph. Regulatory Project Manager
Company: Merck Research Laboratories	Division of Pulmonary & Allergy Drug Products
Fax number: 732-594-1030	Fax number: 301-827-1271
Phone number: 732-594-0135	Phone number: 301-827-1051

/S/

Subject: NDA 21-409 Request for additional information

Total no. of pages including cover: 3

Comments:

Document to be mailed: YES NO

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- Any toxic tests conducted?

We have the following additional requests.

- 1) The PDF files for proposed labeling do not show the proposed changes. Please provide annotated PDF files for the proposed labeling.

The following requests and questions relate to study P176:

- 2) In study P176, the secondary efficacy endpoint of oral corticosteroid use differed for the montelukast and placebo groups. In addition, that difference appeared to be largest for the 6-12 month groups and larger for boys than girls. To investigate this further, please provide information that relates the use of oral corticosteroids prior to, up to and during the study. Include demographic information regarding the subgroup of patients who required oral corticosteroid rescue during the study. Specifically, list how many of these patients required oral corticosteroids before being enrolled in the trial. List this information by both the number of days and total courses of oral corticosteroids over the previous year. Although our primary interest is the 6-12 month group, please provide this information for both age groups as well as broken down by sex, concomitant medication, and race.
- 3) Provide information on how the demographic information was obtained. Did the parent-complete the questionnaire or was the information completed by the primary physician or study coordinator?
- 4) For those patients who are listed in the demographics as having allergic rhinitis, please specify the person responsible for the diagnosis of allergic rhinitis. Likewise, please specify the person responsible for the diagnosis of all other diagnoses listed in the demographics.
- 5) The following question is in reference to the electronic submission dated September 28, 2001, following the "ndatoc.pdf" file, item 8 "Clinical" section, Reference P176, Category 4: Data, page 833 of 1239, Appendix 4.4, Table 4.4.2, under the subheading "Year when asthma first diagnosed." The patients in this table were all 6-12 months of age. Clarify the separation between the "same year" and "the first year (of life)." Likewise, for page 840 of 1239, Table 4.4.4, provide an explanation of the groupings for the 12-24 month old patients ("same year," "the first year," and "the second year").
- 6) For the same section referred to in comment five, Page 834 of 1239, Table 4.4.2, regarding the 6-12 month old patients, provide a definition of 'biological family member' as it was used to develop this table. Same question applies to page 840 of 1239, Table 4.4.4 for the 12-24 month old patients.
- 7) The following diagnostic evaluations for recurrent wheezing were not submitted in the study report. If these diagnostic evaluations were conducted and the results are available, please submit information on the numbers of patients who were evaluated and the results of the following tests:
 - chest x-rays,
 - sweat chlorides,
 - swallowing studies and
 - sinus radiography, including sinus CT.

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- 8) The study report provides no listing for the following diagnoses: prematurity, gastro-esophageal reflux disease (GERD), bronchiolitis, or respiratory syncytial virus (RSV) disease. Please provide this information, if available, as well as how the diagnosis was made (e.g., by laboratory confirmation of RSV disease versus clinical diagnosis alone).
- 9) The study report does not contain results of skin testing for the patients noted as having received it. Please provide this information, if available.
- 10) Eosinophil counts at baseline and treatment (Reference P176, page 95-6 of 1239 of the September 28, 2001, electronic submission) are not specified by age of the patient. Please provide this information, if available.
- 11) Please provide information to complete the table below.

The table below is a **suggested table** format to create a clinical index for asthma (i.e., the likelihood for patients enrolled in the study who will have a diagnosis of asthma at a later date). This table is similar in format to that in a recent publication (Castro-Rodriguez, Holberg et al. 2000) and includes the following categories:

- Parent with physician diagnosed (MD) asthma
- MD diagnosed eczema
- MD diagnosed AR
- Wheezing apart from colds
- Eosinophilia $\geq 4\%$

Study P176: Clinical index for asthma risk

Family History	≥ 6 months to <12 months		≥ 1 to <2 years	
	Montelukast n = 51	Placebo n = 33	Montelukast n = 124	Placebo n = 48
	n (%)	n (%)	n (%)	n (%)
Parent with MD asthma				
MD eczema				
MD allergic rhinitis				
Wheeze apart from URI				
Eosinophilia $\geq 4\%$				

Sources:

References:

Castro-Rodriguez, J. A., C. J. Holberg, et al. (2000). "A clinical index to define risk of asthma in young children with recurrent wheezing." Am J Respir Crit Care Med 162(4 Pt 1): 1403-6.

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/s/

Christine Yu
4/17/02 03:18:04 PM
CSO

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Food and Drug Administration
 Center for Drug Evaluation and Research
 Office of Drug Evaluation ODE II

FACSIMILE TRANSMITTAL SHEET

DATE: March 18, 2002

To: David Altarac, M.D., M.P.A. Director, Regulatory Affairs	From: Christine Yu, R.Ph. Regulatory Project Manager <i>1/ST</i>
Company: Merck Research Laboratories	Division of Pulmonary & Allergy Drug Products
Fax number: 732-594-1030	Fax number: 301-827-1271
Phone number: 732-594-0135	Phone number: 301-827-1051

Subject: NDA 21-409 Request for additional information

Total no. of pages including cover: 2

Comments:

Document to be mailed: YES NO

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We have the following requests for additional information.

1. Submit the following data regarding bioanalytical methods validation used in protocols 090, 183 and 136c1, in the original NDA submission dated September 28, 2001:
 - calibration curves used in analyzing samples,
 - intra-day accuracy and precision data, including equations and weighting factors, if any, and
 - the limit of quantitation.
2. Submit individual dissolution data for all the batches of Singulair _____ used in conducting pharmacokinetic studies.
3. Submit all dissolution data and dissolution profiles generated during the development of the dissolution method and specifications for Singulair_____
4. Provide a rationale for selecting the proposed dissolution media.

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Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation ODE II

FACSIMILE TRANSMITTAL SHEET

DATE: February 15, 2002

To: David Altarac, MD, MPA Director, Regulatory Affairs	From: Christine Yu, R.Ph. Regulatory Project Manager
Company: Merck & Co., Inc.	Division of Pulmonary & Allergy Drug Products
Fax number: 732-594-1030	Fax number: 301-827-1271
Phone number: 732-594-0135	Phone number: 301-827-1051

Subject: Request for information

Total no. of pages including cover: *22*

Comments: Please call me if you have any questions.

Document to be mailed: YES NO

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Please submit the following information for reference study P136C1 (Protocol 136/138):

1. Data sets including the following parameters.
 - Identification
 - Time
 - Dose
 - Concentration
 - Covariates (e.g., age, weight, body surface area)

Data should be submitted in SAS transferable version following the Guidance for industry for electronic submissions.

2. Program code from S-Plus and SAS for nonlinear-mixed effect PK analysis.
3. Model building information.
4. Output of final model from S-Plus and SAS.

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Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation ODE II

FACSIMILE TRANSMITTAL SHEET

DATE: December 7, 2001

To: David Altarac, M.D., M.P.A	From: Christine Yu, R.Ph.
Company: Director, Regulatory Affairs	Division of Pulmonary & Allergy Drug Products
Fax number: 732-594-1030	Fax number: 301-827-1271
Phone number: 732-594-0135	Phone number: 301-827-1051
Subject: NDA 21-409 Singulair . — Request for information	

Total no. of pages including cover: 2

Comments:

Document to be mailed: YES NO

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We refer to your NDA 21-409, submitted and received on September 28, 2001, for Singulair
(montelukast sodium) oral granules. We have the following requests for information.

- will get*
1. One Case Report Form is missing, for one patient who discontinued due to an AE in Study P136C1. Please supply this Case Report Form.
 2. If possible, provide dissolution profiles of the Singulair — formulation.
 3. Provide data files, control stream files and output NONMEM files generated from protocol 136/138 (population pharmacokinetics in children 6-months to 2-years of age).

Tag C-43

pp C-69 C-70

did not do NONMEM

stats?

stats log files

what specific look for

do we have output files

312.160

for in vitro

Merck up?

1/16/02

Spoke to D. Altman

*Told him SAs may need to look into a bit more
before we can fully address #3*

MRC will submit #9

10/30/01



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

NDA 21-409

Merck Research Laboratories
Division of Merck & Company, Inc.
RY 33-720
P.O. Box 2000
Rahway, NJ 07065

Attention: David Altarac, M.D., M.P.A.
Director, Regulatory Affairs

Dear Dr. Altarac:

We have received your new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for the following:

Name of Drug Product: Singlair (montelukast sodium) oral granules

Review Priority Classification: Standard (S)

Date of Application: September 28, 2001

Date of Receipt: September 28, 2001

Our Reference Number: NDA 21-409

Unless we notify you within 60 days of our receipt date that the application is not sufficiently complete to permit a substantive review, this application will be filed under section 505(b) of the Act on November 27, 2001, in accordance with 21 CFR 314.101(a). If the application is filed, the primary user fee goal date will be July 28, 2002, and the secondary user fee goal date will be September 28, 2002.

Please cite the NDA number listed above at the top of the first page of any communications concerning this application. All communications concerning this NDA should be addressed as follows:

U.S. Postal/Courier/Overnight Mail:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Pulmonary and Allergy Drug Products, HFD-570
Attention: Division Document Room
5600 Fishers Lane
Rockville, Maryland 20857

NDA 21-409

Page 2

If you have any questions, call Christine Yu, R.Ph., Regulatory Project Manager, at (301) 827-1051.

Sincerely,

(See appended electronic signature page)

Sandy Barnes
Supervisory CSO
Division of Pulmonary and Allergy Drug Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

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this page is the manifestation of the electronic signature.

/s/

Christine Yu
10/30/01 04:42:43 PM
Signing for Sandy Barnes, CPMS

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USER FEE COVER SHEET

See Instructions on Reverse Side Before Completing This Form

completed form must be signed and accompany each new drug or biologic product application and each new supplement. See exceptions on the reverse side. If payment is sent by U.S. mail or courier, please include a copy of this completed form with payment. Payment instructions and fee rates can be found on CDER's website: <http://www.fda.gov/cder/pdofa/default.htm>

1. APPLICANT'S NAME AND ADDRESS

Merck & Co., Inc.
Sumneytown Pike, BLA-10
P.O. Box 4
West Point, PA 19486

4. BLA SUBMISSION TRACKING NUMBER (STN) / NDA NUMBER

NDA 21-409

5. DOES THIS APPLICATION REQUIRE CLINICAL DATA FOR APPROVAL?

YES NO

IF YOUR RESPONSE IS "NO" AND THIS IS FOR A SUPPLEMENT, STOP HERE AND SIGN THIS FORM

IF RESPONSE IS "YES", CHECK THE APPROPRIATE RESPONSE BELOW.

THE REQUIRED CLINICAL DATA ARE CONTAINED IN THE APPLICATION.

THE REQUIRED CLINICAL DATA ARE SUBMITTED BY REFERENCE TO:

(APPLICATION NO. CONTAINING THE DATA).

2. TELEPHONE NUMBER (Include Area Code)

(484) 344-2383

3. PRODUCT NAME

Singulair™

6. USER FEE I.D. NUMBER

4179

7. IS THIS APPLICATION COVERED BY ANY OF THE FOLLOWING USER FEE EXCLUSIONS? IF SO, CHECK THE APPLICABLE EXCLUSION.

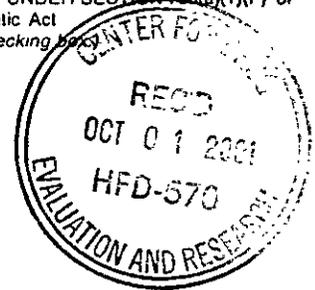
A LARGE VOLUME PARENTERAL DRUG PRODUCT APPROVED UNDER SECTION 505 OF THE FEDERAL FOOD, DRUG, AND COSMETIC ACT BEFORE 9/1/92 (Self Explanatory)

A 505(b)(2) APPLICATION THAT DOES NOT REQUIRE A FEE (See item 7, reverse side before checking box.)

THE APPLICATION QUALIFIES FOR THE ORPHAN EXCEPTION UNDER SECTION 736(a)(1)(E) of the Federal Food, Drug, and Cosmetic Act (See item 7, reverse side before checking box.)

THE APPLICATION IS A PEDIATRIC SUPPLEMENT THAT QUALIFIES FOR THE EXCEPTION UNDER SECTION 736(a)(1)(F) of the Federal Food, Drug, and Cosmetic Act (See item 7, reverse side before checking box.)

THE APPLICATION IS SUBMITTED BY A STATE OR FEDERAL GOVERNMENT ENTITY FOR A DRUG THAT IS NOT DISTRIBUTED COMMERCIALY (Self Explanatory)



8. HAS A WAIVER OF AN APPLICATION FEE BEEN GRANTED FOR THIS APPLICATION?

YES NO

(See Item 8, reverse side if answered YES)

Public reporting burden for this collection of information is estimated to average 30 minutes 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:

Department of Health and Human Services
Food and Drug Administration
CBER, HFM-99
1401 Rockville Pike
Rockville, MD 20852-1448

Food and Drug Administration
CDER, HFD-94
and
12420 Parklawn Drive, Room 3046
Rockville, MD 20852

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SIGNATURE OF AUTHORIZED COMPANY REPRESENTATIVE

TITLE Bonnie J. Goldmann, MD
Vice President, Domestic Liaison
Regulatory Affairs

DATE

September 19, 2001

Pre-NDA MEETING MINUTES

IND # 58,819
 Serial #: 033
 Sponsor: Merck and Co., Inc.
 Drug: 4 mg montelukast sodium formulation
 Indication: C

3

Meeting Information

Date: April 26, 2001
 Time: 9:30-11:00 a.m.
 Place: 5600 Fishers Lane, Rockville, Maryland

Meeting Attendees

<p>FDA:</p> <p>Young-Moon Choi</p> <p>Lydia Gilbert-McClain</p> <p>Huiqing Hao</p> <p>David Hilfiker</p> <p>Timothy McGovern</p> <p>Robert Meyer</p> <p>Guirag Poochikian</p> <p>Mary Purucker</p> <p>Juanita Ross</p> <p>C. Joseph Sun</p> <p>Steve Wilson</p>	<p>Clinical Pharmacology and Biopharmaceutics Reviewer</p> <p>Clinical Reviewer</p> <p>Pharmacology/Toxicology Reviewer</p> <p>Regulatory Project Manager</p> <p>Pharmacology/Toxicology Reviewer</p> <p>Division Director</p> <p>CMC Team Leader</p> <p>Clinical Team Leader</p> <p>CMC Reviewer</p> <p>Pharmacology/Toxicology Team Leader</p> <p>Biometrics Team Leader</p>
<p>Merck:</p> <p>David Altarac</p> <p>Steven Caffé</p> <p>John Curran</p> <p>Thomas Hassell</p> <p>Sam McClintock</p> <p>Barbara Knorr</p> <p>Elizabeth Migoya</p> <p>Theodore Reiss</p> <p>J. Douglas Rogers</p> <p>Janet Van Adelsberg</p> <p>Lynn Wei</p> <p>Ji Zhang</p>	<p>Regulatory Affairs</p> <p>Regulatory Affairs</p> <p>Regulatory and Analytical Sciences – CMC</p> <p>Regulatory Agency Relations</p> <p>Pharmaceutical Research and Development</p> <p>Clinical Research</p> <p>Clinical Pharmacology</p> <p>Clinical Research</p> <p>Drug Metabolism</p> <p>Clinical Research</p> <p>Clinical Biostatistics</p> <p>Clinical Biostatistics</p>

Meeting Background

On March 4, 1999, in accordance with Section 505A of the Federal Food, Drug, and Cosmetic Act, FDA issued a Written Request for pediatric studies to be conducted and submitted for montelukast. Part of this Written Request required pharmacokinetic and safety information in patients 6 months to 24 months of age using an "age-appropriate" formulation.

In response, Merck filed IND 58,819 on August 16, 1999, for a new ~~_____~~ formulation for use in children ~~_____~~ years of age. The ~~_____~~ formulation is a granular formulation of montelukast sodium that can be administered with food or alone. Through pharmacokinetic and safety data, Merck intends to support the use of 4 mg of montelukast in children from ~~_____~~ months to 5 years of age.

In a supplemental NDA 20-830/S-008, Merck provided for a 4-mg chewable tablet for use in children 2 to 5 years of age. That supplemental application was approved on March 3, 2000. Therefore, the pending NDA for the ~~_____~~ formulation will be designed to support the extension of safety and efficacy of 4-mg montelukast from 2 years of age down to ~~_____~~ months of age, and to provide an alternative formulation to the 4-mg chewable tablets for use in children 2 to 5 years of age.

On March 20, 2001, Merck submitted a request for a pre-NDA meeting to discuss the proposed format and content of an NDA for the montelukast sodium ~~_____~~ formulation.

Meeting Summary

Merck presented an overview of the aims for the montelukast ~~_____~~ program and a summary of the clinical studies used to support the proposed NDA (see attachment 1).

FDA asked for clarification on Merck's intentions for the labeling in the NDA. Merck stated that they plan to propose an indication for ~~_____~~

~~_____~~ the 4 mg approved
chewable tablet formulation for children 2 to 5 years of age.

FDA then responded to the issues for discussion proposed by Merck. The issues for discussion are presented in italics followed by a summary of FDA responses and discussion.

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CLINICAL/CLINICAL PHARMACOLOGY/STATISTICS

Issue 1: Table of Contents

Merck Research Laboratories (MRL) proposes to file a New Drug Application (NDA) to (1) fulfill the Written Request for Pediatric Studies with montelukast as outlined in the Food and Drug Administration (FDA) Written Request dated March 4, 1999 and amended April 18, 2000 and September 28, 2000; (2) gain approval of a new ~~oral~~ formulation of a 4-mg dose of montelukast as an alternate to the 4-mg chewable tablet in 2 to 5 year old children; and, (3) obtain labeling for 4-mg montelukast ~~in~~ in the treatment of asthma for children from ~~6~~ months to <2 years of age. The proposed submission will include the results from 4 clinical pharmacology studies (Protocols 090, 183, 127 and 136/138) and 1 pediatric safety study (Protocol 176). The proposed table of contents for this submission is outlined in this background package [Tab 5].

Question 1:

Is the proposed presentation format, as outlined in the table of contents, acceptable to the Agency?

Yes, FDA stated that the proposed format is acceptable and had no comments or concerns.

Issue 2: Efficacy Tables

Efficacy data will be presented for the Pediatric Safety Study (Protocol 176). The endpoints for the efficacy data are exploratory. The endpoints analyzed will be: days without β -agonist use, oral corticosteroid rescues, discontinuations from the study due to worsening asthma symptoms, number of unscheduled physician visits or emergency room visits or hospital visits due to worsening asthma symptoms, total peripheral blood eosinophil counts, and asthma attacks. Table 7 (page 13) and Table 8 (page 13) of the background package show the format in which efficacy data will be displayed in this application [Tab 4].

Question 2:

Is the format of the efficacy tables planned for this submission acceptable to the Agency?

Yes, FDA stated that the proposed format is acceptable and had no comments or concerns.

Issue 3: Safety Tables

Pediatric safety data will be presented separately for the pediatric population PK study (Protocol 136/138) and the pivotal safety study (Protocol 176) because of the different designs and extent of exposure in these studies. Adult safety data from the two bioequivalence studies and the dose proportionality study will be pooled. Tables 10 (page 14), 11 (page 15) and 12 (page 16) of the background package show the format in which safety data will be displayed in the application [Tab 4].

Question 3:

Is the format of the safety tables planned for this submission acceptable to the Agency?

Yes, FDA stated that the proposed format is acceptable and had no comments or concerns.

Issue 4: Data Analysis Plan for Protocol 176 (Pediatric Safety Study)

The strategy, statistical techniques, and rationales to be used to assess the clinical safety and efficacy of montelukast in pediatric patients ≥ 6 months to < 2 years of age with asthma are described in the Data Analysis Plan (DAP) for Protocol 176 [Tab 6].

Question 4:

Do the procedures for statistical analysis as outlined in the DAP in this package satisfy the needs for analyzing the clinical safety and efficacy in pediatric patients ≥ 6 months to < 2 years of age with asthma?

FDA stated that the efficacy endpoints evaluated in this study primarily designed to assess safety are considered secondary and supportive. Therefore, any proposal to include these data in the product labeling should bear in mind the exploratory nature of these data and the lack of pre-specified plans for inferential testing.

FDA agreed with Merck's plans to prespecify a range for the safety endpoints in the trial and evaluate subjects and means according to the prespecified normal range. FDA recommended that Merck also consider evaluating mean and individual differences in safety parameters across treatment groups.

FDA stated that further comments may be forthcoming as post-meeting notes to these minutes.

BEST POSSIBLE COPY

POST-MEETING NOTES:

The sponsor's methods of statistical analysis for safety and efficacy are reasonable. However, the efficacy analyses are termed "exploratory" by the sponsor. This is important because there are five efficacy endpoints with no plans to account for multiple endpoints, thus not controlling the resultant Type I error of the study at 5%. Further, the sample sizes of 100 in the active arm and 50 in the placebo arm derive only from the need to have an "adequate number of patients exposed for a sufficient period to address the safety evaluation." Various detectable differences in adverse event rates (with 80% power) between montelukast and placebo are presented.

The details of the efficacy analyses are detailed enough to suggest that the data will likely be submitted as substantial evidence of efficacy in this population of patients if the results are nominally statistically positive; i.e., if p-values below .05 are generated for any of the efficacy endpoints. This situation will cause problems in interpretation of the results. The Medical Division may choose to ask the sponsor for a more rigorous plan in order to allay ambiguities in the future.

Issue 5: Clinical Pharmacology – Bioequivalence

The NDA will contain three clinical pharmacology studies to support use of the 4-mg [redacted] formulation of montelukast as an alternate to the 4-mg chewable tablet (CT). These studies include two bioequivalence studies comparing 4-mg doses of the [redacted] formulation of montelukast to the CT, including a pilot study in 24 adults (Protocol 090) and a second study in 31 adults with the final market image of the [redacted] formulation (Protocol 183). The results of a dose proportionality study in 16 adults (Protocol 127) will also be presented.

Question 5:

Are the data from the bioequivalence study between the [redacted] and chewable tablet formulations of montelukast in the format acceptable for the agency to address the use of the [redacted] as an alternate formulation in 2- to 5-year-old children with asthma?

FDA stated that the proposed format for the data is appropriate. FDA provided two additional comments:

1. FDA recommended that Merck include separate analyses of the population pharmacokinetic data for the 6 month to 12 month age group and the 12 month to 24 month age group, in addition to the overall analyses of the 6 to 24 month age group.

2. FDA stated that the proposed 70%-143% confidence interval to provide for dose proportionality is not acceptable. Merck should employ the 80%-125% confidence interval.

LABELING

Issue 6: Labeling

[]

Question 6:

Does the Agency agree that these clinical data would support labeling for pediatric use of montelukast 4-mg _____ in patients aged _____ months to <2 years old?

[]

Issue 7: Package Labeling

As part of the manufacturing and validation process it will be necessary for Merck Manufacturing Division (MMD) to package the montelukast 4-mg _____ formulation in _____ prior to the completion of the review and approval of the NDA. MRL acknowledges that the Agency will require the review and approval of the supporting documentation for the Chemistry, Manufacturing and Control information from the NDA to approve the information described on the montelukast 4-mg _____ packet. However, MRL would like to minimize the need for _____ to be revised during the review and approval process of the NDA. The proposed text for the montelukast 4-mg _____ packet has been included for Agency comment (Tab 3a).

Question 7:

Does the Agency agree that the proposed text for the montelukast 4-mg _____ packet is appropriate?

FDA provided three general comments on the proposed labeling:

1. The list of excipients should be included on the package labeling.
2. The proposed storage statement is not adequate. FDA referred Merck to a 1998 draft Guidance for the appropriate storage information.

3. The last statement on the back of the pouch may need to be modified.

In addition, FDA recommended that Merck not print any labeling materials at this time, because some of the information containing in the package label may be data-driven, and adequate statements of this nature cannot be determined until the NDA has been reviewed. FDA stated that Merck should submit the NDA and provide FDA with sufficient time to review the application before proposing discussions to finalize the package labeling.

CHEMISTRY, MANUFACTURING AND CONTROL

Issue 8: Dissolution Testing



Question 8:

Does the Agency agree with Merck that a dissolution control at release and during shelf-life is not necessary based on the characteristics of this formulation and the purpose of a dissolution test (i.e. measurement of the drug substance release from the drug product matrix)?

FDA stated that Merck should continue dissolution testing at release and through the expiry period, based on the experience that excipients and manufacturing process can effect dissolution rates. FDA stated that Merck may submit data to support a justification in the NDA that dissolution testing should be waived.

ELECTRONIC SUBMISSION

Issue 9: Electronic Submission

As we have done for NDAs and sNDAs, MRL proposes to file this application as an electronic submission as outlined in the Summary of Plans for Electronic Submissions [Tab 7].

Question 9: Electronic Submission

Does the Agency concur with this plan to file the NDA electronically?

FDA stated that all materials submitted electronically as reviewer aids should also be submitted in the archival electronic copy in the archival formats outlined in the current Guidance to Industry for electronic submissions. As an example, FDA reminded Merck that data analysis programs should be submitted in .pdf files to the archival electronic copy to accompany the SAS transport data files.

FDA requested that Merck ensure that all datasets, including input, control, and output files for population pharmacokinetic analyses, as well as data files for bioequivalence and dose proportionality studies, are submitted in accordance with the Guidance to Industry and in accordance with the above comments.

End of Meeting Summary

Attachments: (1) Presentation Slides presented by Merck (2 pages, hard copy only)

Draft by: HFD-570/Hilfiker/4-27-01
Initialed by: HFD-570/Choi/4-27-01
HFD-570/Gilbert-McClain
HFD-570/Meyer/5-4-01
HFD-570/Poochikian/4-27-01
HFD-570/Purucker
HFD-570/Ross/4-27-01
HFD-570/Wilson
Final: HFD-570/Hilfiker/5-4-01

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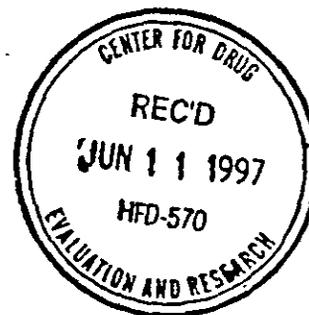
/s/

David Hilfiker
5/4/01 05:09:35 PM

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Executive CAC
December 3, 1996

ORIGINAL



Committee members:

Joseph DeGeorge, Ph.D., HFD-024, Chair
Joseph Contrera, Ph.D., HFD-900, Rotating Member
Albert DeFelice, PhD, HFD-110, Rotating Member
Hilary Sheevers., Ph.D., HFD-570, Division Team Leader
Reviewer and Preparer of Draft Report: Shannon Williams, Ph.D., HFD-570

IND 39,568, IND — and — (Williams; HFD-570)
MK-0476 (L-706,631)
Merck Research Laboratories.

Executive CAC meeting was convened, in part, to assess the results from two carcinogenicity studies conducted using the Leukotriene D4/E4 receptor antagonist, MK-0476 (L-706,631), one 92-week study in CD-1 mice and a second 2-year study in Sprague-Dawley rats. The committee members were provided with a pharmacology and statistical reviews of both studies submitted to IND 39,568.

The carcinogenic potential of MK-0476 was evaluated in a 92- week oral carcinogenic study in CD-1 mice conducted at Merck Research Laboratories, West Point, PA during 1993-96. MK-0476, administered by gavage at doses of 25, 50, and 200/100 mg/kg/day, produced a large reduction in body weights at the 200 mg/kg high dose such that the high dose was reduced from 200 to 100 mg/kg in week 10 of dosing. There were no treatment-related incidences of neoplastic tumors.

The carcinogenic potential of MK-0476 was evaluated in a 2-year oral carcinogenic study in Sprague Dawley rats, conducted at Merck Research Laboratories, West Point, PA during 1993-96. MK-0476 was administered by gavage at doses of 50, 100, and 200 mg/kg/day to rats maintained on a "diet optimization feeding regimen" in which males were given 24 g food/day and females 17 g/day. Both the dose selection and the diet optimization feeding/dosing regimen were previously approved by the Exec. CAC. MK-0476 produced no significant effects on body weights or other evidence of toxicity. In addition, no statistically significant differences in the incidence of neoplastic lesions between control and treated groups were observed, such that MK-0476 (L-706,631) was regarded as negative for tumorigenic activity in the rat carcinogenicity study

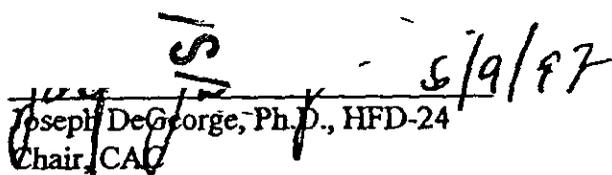
The Executive CAC advised that:

1. The Exec. CAC concurred that MK-0476 (L-706-631) was not tumorigenic in Sprague Dawley rats given doses up to 200 mg/kg under the conditions of a dietary optimization feeding regimen employed in the study, given that both the doses tested and the diet optimization feeding regimen were previously agreed upon by the Exec. CAC.

2. The Exec. CAC expressed concern that weight reductions in mice treated at the high dose in the 92-week mouse carcinogenicity study could have resulted in reduced tumor incidence at this dose and thus obscured detection of statistical significance using the linear trend test. In this regard the Committee recommended that the incidence of tumors at the mid dose be reexamined for comparability to the control group and that the results of this reexamination be communicated to the committee through Sharon Olmstead (acting secretary for the committee at that time)

Reviewers response to #2 above:

Reinspection of the tumor incidence for MK-0476 at both the mid and low doses in mouse study revealed no difference in the tumor incidence in either group relative to the incidence in either the control or high dose groups. (original data was included in the package; Pages 7 and 8 of the statistical review of IND 39,568 by Barbara Bono dated 8/12/96). In addition, there was no indication of a reduction in the spontaneous incidence of tumors in mice at the high dose relative to that in the control or mid and low dose groups. Collectively these observations suggested that the body weight reductions observed at the high dose had not artificially yielded a false negative linear trend test. Thus, the final recommendation to the Exec CAC is that MK-0476 be regarded as negative for tumorigenic effects in the Mouse Carcinogenicity study.


Joseph DeGeorge, Ph.D., HFD-24
Chair, CAC

41 pages redacted from this section of
the approval package consisted of draft labeling