

**CENTER FOR DRUG EVALUATION AND RESEARCH**

**APPROVAL PACKAGE FOR:**

**APPLICATION NUMBER**

**21-409**

**Administrative/Correspondence**

## NDA/EFFICACY SUPPLEMENT ACTION PACKAGE CHECKLIST

Application Information		
NDA 21-409	Efficacy Supplement Type SE-	Supplement Number: Original NDA
Drug: Singulair (montelukast sodium) oral granules		Applicant: Merck Research Laboratories
RPM: Christine Yu, R.Ph.		HFD-570 <span style="float: right;">Phone # 301-827-1051</span>
Application Type: <input checked="" type="checkbox"/> 505(b)(1) <input type="checkbox"/> 505(b)(2)		Reference Listed Drug (NDA #, Drug name):
❖ Application Classifications:		
• Review priority		<input checked="" type="checkbox"/> Standard <input type="checkbox"/> Priority
• Chem class (NDAs only)		3
• Other (e.g., orphan, OTC)		
❖ User Fee Goal Dates		July 28, 2002
❖ Special programs (indicate all that apply)		<input checked="" type="checkbox"/> None Subpart H <input type="checkbox"/> 21 CFR 314.510 (accelerated approval) <input type="checkbox"/> 21 CFR 314.520 (restricted distribution) <input type="checkbox"/> Fast Track <input type="checkbox"/> Rolling Review
❖ User Fee Information		
• User Fee		<input checked="" type="checkbox"/> Paid
• User Fee waiver		<input type="checkbox"/> Small business <input type="checkbox"/> Public health <input type="checkbox"/> Barrier-to-Innovation <input type="checkbox"/> Other
• User Fee exception		<input type="checkbox"/> Orphan designation <input type="checkbox"/> No-fee 505(b)(2) <input type="checkbox"/> Other
❖ Application Integrity Policy (AIP)		
• Applicant is on the AIP		<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No
• This application is on the AIP		<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No
• Exception for review (Center Director's memo)		
• OC clearance for approval		
❖ Debarment certification: verified that qualifying language (e.g., willingly, knowingly) was not used in certification and certifications from foreign applicants are co-signed by U.S. agent.		<input checked="" type="checkbox"/> Verified
❖ Patent		
• Information: Verify that patent information was submitted		<input checked="" type="checkbox"/> Verified
• Patent certification [505(b)(2) applications]: Verify type of certifications submitted		21 CFR 314.50(i)(1)(i)(A) <input type="checkbox"/> I <input type="checkbox"/> II <input type="checkbox"/> III <input type="checkbox"/> IV  21 CFR 314 50(i)(1) <input type="checkbox"/> (ii) <input type="checkbox"/> (iii)
• For paragraph IV certification, verify that the applicant notified the patent holder(s) of their certification that the patent(s) is invalid, unenforceable, or will not be infringed (certification of notification and documentation of receipt of notice).		<input type="checkbox"/> Verified
Exclusivity Summary (approvals only)		July 26, 2002
❖ Administrative Reviews (Project Manager, ADRA) (indicate date of each review)		February 15 and July 26, 2002

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**General Information**

Actions	
• Proposed action	<input checked="" type="checkbox"/> AP <input type="checkbox"/> TA <input type="checkbox"/> AE <input type="checkbox"/> NA
• Previous actions (specify type and date for each action taken)	N/A
• Status of advertising (approvals only)	<input checked="" type="checkbox"/> Materials requested in AP letter <input type="checkbox"/> Reviewed for Subpart H
❖ Public communications	
• Press Office notified of action (approval only)	<input type="checkbox"/> Yes <input checked="" type="checkbox"/> Not applicable
• Indicate what types (if any) of information dissemination are anticipated	<input checked="" type="checkbox"/> None <input type="checkbox"/> Press Release <input type="checkbox"/> Talk Paper <input type="checkbox"/> Dear Health Care Professional Letter
❖ Labeling (package insert, patient package insert (if applicable), MedGuide (if applicable))	
• Division's proposed labeling (only if generated after latest applicant submission of labeling)	
• Most recent applicant-proposed labeling	July 25, 2002
• Original applicant-proposed labeling	September 28, 2001
• Labeling reviews (including DDMAC, Office of Drug Safety trade name review, nomenclature reviews) and minutes of labeling meetings ( <i>indicate dates of reviews and meetings</i> ) ODS Trade Name: Consult Response dated April 19, 2002 LNC established name consult sent: 4/25/02 Labeling meetings: July 15, 2002- Minutes included July 24, 2002- not completed July 25, 2002- not completed	
• Other relevant labeling (e.g., most recent 3 in class, class labeling)	
❖ Labels (immediate container & carton labels)	
• Division proposed (only if generated after latest applicant submission)	
• Applicant proposed	July 25, 2002
• Reviews- Project Manager	July 26, 2002
❖ Post-marketing commitments	
• Agency request for post-marketing commitments	
• Documentation of discussions and/or agreements relating to post-marketing commitments	
❖ Outgoing correspondence (i.e., letters, E-mails, faxes)	Included
❖ Memoranda and Telecons	Included
❖ Minutes of Meetings	
• EOP2 meeting (indicate date)	No EOP2 mtg
• Pre-NDA meeting (indicate date)	4/26/01
• Pre-Approval Safety Conference (indicate date; approvals only)	N/A
• Other	
❖ Advisory Committee Meeting	
• Date of Meeting	N/A
• 48-hour alert	N/A

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Federal Register Notices, DESI documents, NAS, NRC (if any are applicable)	N/A
<b>Clinical and Summary Information</b>	
❖ Summary Reviews (e.g., Office Director, Division Director, Medical Team Leader) (indicate date for each review)	July 26, 2002
❖ Clinical review(s) (indicate date for each review)	July 26, 2002
❖ Microbiology (efficacy) review(s) (indicate date for each review)	
❖ Safety Update review(s) (indicate date or location if incorporated in another review)	In Clinical Review
❖ Pediatric Page(separate page for each indication addressing status of all age groups)	July 26, 2002
❖ Statistical review(s) (indicate date for each review) Stability only	July 1, 2002
❖ Biopharmaceutical review(s) (indicate date for each review)	July 10 and 26, 2002
❖ Controlled Substance Staff review(s) and recommendation for scheduling (indicate date for each review)	N/A
❖ Clinical Inspection Review Summary (DSI)	None
• Clinical studies	
• Bioequivalence studies	
<b>CMC Information</b>	
❖ CMC review(s) (indicate date for each review)	5/6/02, 6/28/02, 7/26/02
❖ Environmental Assessment	
• Categorical Exclusion (indicate review date) Acceptable	5/6/02
• Review & FONSI (indicate date of review)	
• Review & Environmental Impact Statement (indicate date of each review)	
Micro (validation of sterilization & product sterility) review(s) (indicate date for each review) Informal consultation- see CMC review dated 7/26/02	7/25/02
❖ Facilities inspection (provide EER report)	Date completed: 4/23/02 (√) Acceptable ( ) Withhold recommendation
❖ Methods validation	( ) Completed ( ) Requested (√) Not yet requested
<b>Nonclinical Pharm/Tox Information</b>	
❖ Pharm/tox review(s), including referenced IND reviews (indicate date for each review)	7/19/02, 7/25/02
❖ Nonclinical inspection review summary	N/A
❖ Statistical review(s) of carcinogenicity studies (indicate date for each review)	N/A
❖ CAC/ECAC report	6/11/1997

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EXCLUSIVITY SUMMARY for NDA # 21-409 SUPPL # \_\_\_\_\_

Trade Name Singulair Oral Granules Generic Name Montelukast sodium

Applicant Name Merck Research Laboratories HFD- 570

Approval Date July 28, 2002

**PART I: IS AN EXCLUSIVITY DETERMINATION NEEDED?**

1. An exclusivity determination will be made for all original applications, but only for certain supplements. Complete Parts II and III of this Exclusivity Summary only if you answer "YES" to one or more of the following questions about the submission.

a) Is it an original NDA? YES / √ / NO / \_\_\_ /

b) Is it an effectiveness supplement? YES / \_\_\_ / NO / √ /

If yes, what type (SE1, SE2, etc.)? \_\_\_\_\_

c) Did it require the review of clinical data other than to support a safety claim or change in labeling related to safety? (If it required review only of bioavailability or bioequivalence data, answer "NO.")

YES / √ / NO / \_\_\_ /

If your answer is "no" because you believe the study is a bioavailability study and, therefore, not eligible for exclusivity, EXPLAIN why it is a bioavailability study, including your reasons for disagreeing with any arguments made by the applicant that the study was not simply a bioavailability study.

\_\_\_\_\_  
\_\_\_\_\_

If it is a supplement requiring the review of clinical data but it is not an effectiveness supplement, describe the change or claim that is supported by the clinical data:

\_\_\_\_\_  
\_\_\_\_\_

d) Did the applicant request exclusivity?

YES /  / NO /  /

If the answer to (d) is "yes," how many years of exclusivity did the applicant request?

6 months for Pediatric Exclusivity

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e) Has pediatric exclusivity been granted for this Active Moiety?

YES /  / NO /  /

**IF YOU HAVE ANSWERED "NO" TO ALL OF THE ABOVE QUESTIONS, GO DIRECTLY TO THE SIGNATURE BLOCKS ON Page 9.**

2. Has a product with the same active ingredient(s), dosage form, strength, route of administration, and dosing schedule previously been approved by FDA for the same use? (Rx to OTC Switches should be answered No - Please indicate as such).

YES /  / NO /  /

If yes, NDA # \_\_\_\_\_ Drug Name \_\_\_\_\_

**IF THE ANSWER TO QUESTION 2 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON Page 9.**

3. Is this drug product or indication a DESI upgrade?

YES /  / NO /  /

**IF THE ANSWER TO QUESTION 3 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON Page 9 (even if a study was required for the upgrade).**



If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA # \_\_\_\_\_  
NDA # \_\_\_\_\_  
NDA # \_\_\_\_\_

**IF THE ANSWER TO QUESTION 1 OR 2 UNDER PART II IS "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON Page 9. IF "YES," GO TO PART III.**

**PART III: THREE-YEAR EXCLUSIVITY FOR NDA'S AND SUPPLEMENTS**

To qualify for three years of exclusivity, an application or supplement must contain "reports of new clinical investigations (other than bioavailability studies) essential to the approval of the application and conducted or sponsored by the applicant." This section should be completed only if the answer to PART II, Question 1 or 2, was "yes."

1. Does the application contain reports of clinical investigations? (The Agency interprets "clinical investigations" to mean investigations conducted on humans other than bioavailability studies.) If the application contains clinical investigations only by virtue of a right of reference to clinical investigations in another application, answer "yes," then skip to question 3(a). If the answer to 3(a) is "yes" for any investigation referred to in another application, do not complete remainder of summary for that investigation.

YES /  / NO /  /

**IF "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON Page 9.**

2. A clinical investigation is "essential to the approval" if the Agency could not have approved the application or supplement without relying on that investigation. Thus, the investigation is not essential to the approval if 1) no clinical investigation is necessary to support the supplement or application in light of previously approved applications (i.e., information other than clinical trials, such as bioavailability data, would be sufficient to provide a basis

for approval as an ANDA or 505(b)(2) application because of what is already known about a previously approved product), or 2) there are published reports of studies (other than those conducted or sponsored by the applicant) or other publicly available data that independently would have been sufficient to support approval of the application, without reference to the clinical investigation submitted in the application.

For the purposes of this section, studies comparing two products with the same ingredient(s) are considered to be bioavailability studies.

- (a) In light of previously approved applications, is a clinical investigation (either conducted by the applicant or available from some other source, including the published literature) necessary to support approval of the application or supplement?

YES /  / NO /  /

If "no," state the basis for your conclusion that a clinical trial is not necessary for approval **AND GO DIRECTLY TO SIGNATURE BLOCK ON Page 9:**

\_\_\_\_\_

- (b) Did the applicant submit a list of published studies relevant to the safety and effectiveness of this drug product and a statement that the publicly available data would not independently support approval of the application?

YES /  / NO /  /

- (1) If the answer to 2(b) is "yes," do you personally know of any reason to disagree with the applicant's conclusion? If not applicable, answer NO.

YES /  / NO /  /

If yes, explain: \_\_\_\_\_

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ON ORIGINAL**

(2) If the answer to 2(b) is "no," are you aware of published studies not conducted or sponsored by the applicant or other publicly available data that could independently demonstrate the safety and effectiveness of this drug product?

YES /    /      NO /    /

If yes, explain: \_\_\_\_\_  
\_\_\_\_\_

(c) If the answers to (b)(1) and (b)(2) were both "no," identify the clinical investigations submitted in the application that are essential to the approval:

Investigation #1, Study #   P176  

3. In addition to being essential, investigations must be "new" to support exclusivity. The agency interprets "new clinical investigation" to mean an investigation that 1) has not been relied on by the agency to demonstrate the effectiveness of a previously approved drug for any indication and 2) does not duplicate the results of another investigation that was relied on by the agency to demonstrate the effectiveness of a previously approved drug product, i.e., does not redemonstrate something the agency considers to have been demonstrated in an already approved application.

(a) For each investigation identified as "essential to the approval," has the investigation been relied on by the agency to demonstrate the effectiveness of a previously approved drug product? (If the investigation was relied on only to support the safety of a previously approved drug, answer "no.")

Investigation #1      YES /    /      NO /    /

If you have answered "yes" for one or more investigations, identify each such investigation and the NDA in which each was relied upon:

NDA # _____	Study # _____
NDA # _____	Study # _____
NDA # _____	Study # _____

(b) For each investigation identified as "essential to the

approval," does the investigation duplicate the results of another investigation that was relied on by the agency to support the effectiveness of a previously approved drug product?

Investigation #1                      YES / \_\_\_ /                      NO / √ /

If you have answered "yes" for one or more investigations, identify the NDA in which a similar investigation was relied on:

NDA # \_\_\_\_\_ Study # \_\_\_\_\_

NDA # \_\_\_\_\_ Study # \_\_\_\_\_

NDA # \_\_\_\_\_ Study # \_\_\_\_\_

- (c) If the answers to 3(a) and 3(b) are no, identify each "new" investigation in the application or supplement that is essential to the approval (i.e., the investigations listed in #2(c), less any that are not "new"):

Investigation #1, Study #   P176  

4. To be eligible for exclusivity, a new investigation that is essential to approval must also have been conducted or sponsored by the applicant. An investigation was "conducted or sponsored by" the applicant if, before or during the conduct of the investigation, 1) the applicant was the sponsor of the IND named in the form FDA 1571 filed with the Agency, or 2) the applicant (or its predecessor in interest) provided substantial support for the study. Ordinarily, substantial support will mean providing 50 percent or more of the cost of the study.

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If yes, explain: \_\_\_\_\_  
\_\_\_\_\_  
\_\_\_\_\_

[ ~~/S/~~ ]  
\_\_\_\_\_  
Signature of Preparer  
Christine Yu, R.Ph.  
Regulatory Project Manager

July 26, 2002  
Date

[ ~~/S/~~ ]  
\_\_\_\_\_  
Signature of Office or Division Director *Acting Dir. Director*

July 26, 2002  
Date

cc:  
Archival NDA  
HFD- /Division File  
HFD- /RPM  
HFD-093/Mary Ann Holovac  
HFD-104/PEDS/T.Crescenzi

Form OGD-011347  
Revised 8/7/95; edited 8/8/95; revised 8/25/98, edited 3/6/00

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

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Badrul Chowdhury  
7/26/02 06:08:05 PM

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ON ORIGINAL**

# PEDIATRIC EXCLUSIVITY DETERMINATION CHECKLIST

## PART I - TO BE COMPLETED BY THE REVIEWING DIVISION.

Date of Written Request from FDA 3/4/99. Application Written Request was made to. NDA# 20-829, 20-830  
 Timeframe Noted in Written Request for Submission of Studies 12/31/2001.

NDA# 21-409 Supplement #N/A Choose one: SE1 SE2 SE3 SE4 SE5 SE6 SE7 SE8 SLR

Sponsor Merck Research Laboratories

Generic Name Montelukast sodium Trade Name Singular

Strength 4mg Dosage Form/Route Oral granules

Date of Submission of Reports of Studies 9/28/2001

Pediatric Exclusivity Determination Due Date (60 or 90 days from date of submission of studies) 12/27/01.

Was a formal Written Request made for the pediatric studies submitted?	Y <input checked="" type="checkbox"/>	N <input type="checkbox"/>
Were the studies submitted after the Written Request?	Y <input checked="" type="checkbox"/>	N <input type="checkbox"/>
Were the reports submitted as a supplement, amendment to an NDA, or NDA?	Y <input checked="" type="checkbox"/>	N <input type="checkbox"/>
Was the timeframe noted in the Written Request for submission of studies met?	Y <input checked="" type="checkbox"/>	N <input type="checkbox"/>
If there was a written agreement, were the studies conducted according to the written agreement?  OR If there was no written agreement, were the studies conducted in accord with good scientific principles?	Y <input checked="" type="checkbox"/>	N <input type="checkbox"/>
Did the studies fairly respond to the Written Request?	Y <input checked="" type="checkbox"/>	N <input type="checkbox"/>

SIGNED [ /S/ ]  
 (Reviewing Medical Officer)

DATE 11/6/01

**Do not enter in DFS - FORWARD TO PEDIATRIC EXCLUSIVITY BOARD, HFD-960.**

## PART II - TO BE COMPLETED BY THE PEDIATRIC EXCLUSIVITY BOARD

Pediatric Exclusivity                       **Granted**                       **Denied**

Existing Patent or Exclusivity Protection:

NDA/Product #	Eligible Patents/Exclusivity	Current Expiration Date
20-829, 20-830	NCE	20-Feb-2003
20-830	I-300	03-Mar-2003
20-829, 20-830	5565473	03-Feb-2012

SIGNED [ /S/ ]

DATE 12/10/2001

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

/s/

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Terrie Crescenzi  
12/10/01 01:51:44 PM

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**PEDIATRIC PAGE**

(Complete for all APPROVED original applications and efficacy supplements)

DA/BLA #: 21-409 Supplement Type (e.g. SE5): Original NDA Supplement Number: \_\_\_\_\_

Stamp Date: 7/28/02 Action Date: July 28, 2002

HFD -570 Trade and generic names/dosage form: Singulair (montelukast sodium) Oral Granules

Applicant: Merck Research Laboratories Therapeutic Class: 3S

Indication(s) previously approved: Treatment of asthma in asthma patients 2 years of age and older (tablets and chewable tablets, NDA 20-829 and 20-830)

Each approved indication must have pediatric studies: Completed, Deferred, and/or Waived.

Number of indications for this application(s): 1

Indication #1: Treatment of asthma in patients 12 months of age to adults

Is there a full waiver for this indication (check one)?

- Yes: Please proceed to Section A.
  - No: Please check all that apply:  Partial Waiver  Deferred  Completed
- NOTE: More than one may apply  
Please proceed to Section B, Section C, and/or Section D and complete as necessary.

**Section A: Fully Waived Studies**

Reason(s) for full waiver:

- Products in this class for this indication have been studied/labeled for pediatric population
- Disease/condition does not exist in children
- Too few children with disease to study
- There are safety concerns
- Other: \_\_\_\_\_

*If studies are fully waived, then pediatric information is complete for this indication. If there is another indication, please see Attachment A. Otherwise, this Pediatric Page is complete and should be entered into DFS.*

**Section B: Partially Waived Studies**

Age/weight range being partially waived:

Min <u>Birth</u>	kg _____	mo. _____	yr. _____	Tanner Stage _____
Max <u>&lt;6 mo</u>	kg _____	mo. _____	yr. _____	Tanner Stage _____

Reason(s) for partial waiver:

- Products in this class for this indication have been studied/labeled for pediatric population
- Disease/condition does not exist in children
- Too few children with disease to study
- There are safety concerns

- Adult studies ready for approval
- Formulation needed
- Other: \_\_\_\_\_

If studies are deferred, proceed to Section C. If studies are completed, proceed to Section D. Otherwise, this Pediatric Page is complete and should be entered into DFS.

**Section C: Deferred Studies**

Age/weight range being deferred:

Min \_\_\_\_\_ kg \_\_\_\_\_ mo. \_\_\_\_\_ yr. \_\_\_\_\_ Tanner Stage \_\_\_\_\_  
 Max \_\_\_\_\_ kg \_\_\_\_\_ mo. \_\_\_\_\_ yr. \_\_\_\_\_ Tanner Stage \_\_\_\_\_

Reason(s) for deferral:

- Products in this class for this indication have been studied/labeled for pediatric population
- Disease/condition does not exist in children
- Too few children with disease to study
- There are safety concerns
- Adult studies ready for approval
- Formulation needed

Other: \_\_\_\_\_

Date studies are due (mm/dd/yy): \_\_\_\_\_

If studies are completed, proceed to Section D. Otherwise, this Pediatric Page is complete and should be entered into DFS.

**Section D: Completed Studies**

Age/weight range of completed studies:

Min 6 months kg \_\_\_\_\_ mo. \_\_\_\_\_ yr. \_\_\_\_\_ Tanner Stage \_\_\_\_\_  
 Max adult kg \_\_\_\_\_ mo. \_\_\_\_\_ yr. \_\_\_\_\_ Tanner Stage \_\_\_\_\_

Comments:

Studies were completed down to patients 6 months of age, but approval of indication was only for patients 12 months and above. Patients under 6 months of age are waived with approval of this NDA.

If there are additional indications, please proceed to Attachment A. Otherwise, this Pediatric Page is complete and should be entered into DFS.

This page was completed by:

\_\_\_\_\_  
*(Signature)*  
 Regulatory Project Manager

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**I. Relevant regulatory history and time-lines:**

***NDA:***

On February, 20, 1998, Singulair (Montelukast sodium) 10 mg Film-Coated Tablets and 5 mg Chewable Tablets were approved for use in the prophylaxis and chronic treatment of asthma in adults and patients age 6 years of age and older (NDA 20-829 for 10 mg Film-Coated Tablets, and NDA 20-830 for 5 mg Chewable Tablets, submitted February 21, 1997). An efficacy supplement for 4 mg Chewable Tablets for use children in aged 2 to 5 years was approved on March 3, 2000 (NDA 20-830, SE1-008, submitted May 6, 1999). NDA 21-409 for Singulair 4 mg \_\_\_\_\_ was submitted September 28, 2001.

***Written Request:***

**Original Request (March 4, 1999):**

A Written Request (WR) was issued on March 4, 1999, and amended three times, on April 18, 2000, September 28, 2000, and September 7, 2001.

*Note: The original WR was issued two months prior to the submission of the NDA efficacy supplement for the 4 mg Chewable Tablets, which contained the Study Reports for Studies 3 and 4. All WR Amendments were issued after the Study Reports for Studies 3 and 4 were submitted.*

In the WR, the Division asked for two studies to assess the pharmacokinetics and safety of Singulair in children between the ages of  $\geq 2$  and  $< 6$  years, and two studies to assess the pharmacokinetics and safety of Singulair in infants and toddlers between  $\geq 6$  months and  $< 2$  years.

Study 1: Population pharmacokinetic (PK) study in pediatric asthma patients aged 6 months to  $< 2$  years old.

Study 2: Six-week safety study in pediatric asthma patients aged 6 months to  $< 2$  years.

Study 3: Population PK study in pediatric asthma patients aged  $\geq 2$  years to  $< 6$  years.

Study 4: Six-week safety study in pediatric asthma patients aged  $\geq 2$  years to  $< 6$  years.

**Amendment #1 (April 18, 2000):**

Changed the objective/rationale, study design, and entry criteria for Studies 1 and 3. In addition, the numbers of patients for all four studies were more clearly specified. Drug Information requested for Study 1 was amended. Finally, the timeframe for study reports was amended from January 2, 2001 to December 31, 2001. *Note: In retrospect, since Study 3 had already been submitted, no amendments should have been issued for this study.*

**Amendment #2 (September 7, 2000):**

Changed the entry criteria for Study 1.

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Amendment #3 (September 7, 2001):

Changed study evaluations for Study 1, and Clinical Endpoints for Study 2. This Amendment also denied a request for post-hoc changes to Studies 3 and 4 since the studies had already been submitted to an approved NDA.

**Study Reports:**

The final report for Study 3 (Study P066) was submitted to IND \_\_\_\_\_ on November 18, 1998. The results of the first two studies were submitted to NDA 20-830 on May 6, 1999 as supplement SE1-008 for Singulair 4mg chewable tablets, which was approved on March 3, 2000. The study report for Study 4 (P072) submitted to the NDA supplement was an interim analysis report, with the final study report submitted May 25, 2000 as NDA 20-830, SE8-011.

Studies 1 and 2 were submitted on September 28, 2001 to NDA 21-409, N-000.

**Table of Timelines**

	Date	Comments
NDA 20-829 and NDA 20-830 submitted	2/21/1997	10 mg Film-Coated Tablets and 5 mg Chewable Tablets for ages 6 through adult
NDA 20-829 and NDA 20-830 approved	2/20/1998	10 mg Film-Coated Tablets and 5 mg Chewable Tablets for ages 6 through adult
Written Request	3/4/1999	4 studies outlined
NDA 20-830, SE1-008 submitted	5/6/1999	4 mg Chewable Tablets for ages 2 to 5 years Final Study Report for Study 3 (PK ages 2-5 years) Interim Study Report for Study 4 (Safety ages 2-5 years)
WR Amendment #1	4/18/2000	Changed the objective/rationale, study design, and entry criteria for Studies 1 and 3, and numbers of patients for all four studies were more clearly specified. Drug Information requested for Study 1. Timeframe for study reports was amended from January 2, 2001 to December 31, 2001
NDA 20-830, SE1-008 approved	3/3/ 2000	4 mg Chewable Tablets for ages 2 to 5 years
NDA 20-830, SE8-011 submitted	5/25/2000	Final Report for Study 4 (Safety ages 2-5 years)
Original WR Due Date	1/2/2001	Applies to Studies 3 and 4
WR Amendment #2	9/28/2000	Changed Entry Criteria for Study 1
WR Amendment #3	9/7/2001	Changed Study Evaluations for Study 1, and Clinical Endpoints for Study 2
NDA 21-409 submitted	9/28/2001	4 mg _____ for ages 6 to 23 months Final Study Report for Study 1 (PK ages 6 to 23 months) Final Study Report for Study 2 (Safety 6 to 23 months)
Amended WR Due Date	12/31/2001	Applies to Studies 1 and 2

**II. Amended Written Request:**

Note: Original WR is in normal font. *Italics font reflects WR Amendment.*

***Types of studies to be performed:***

Study 1: Population pharmacokinetic (PK) study in pediatric asthma patients aged 6 months to <2 years old.

Study 2: Safety study in pediatric asthma patients aged 6 months to <2 years.

Study 3: Population PK study in pediatric asthma patients aged  $\geq 2$  years to <6 years.

Study 4: Safety study in pediatric asthma patients aged  $\geq 2$  years to <6 years.

**Types of studies performed:**

	<u>Study</u>	<u>Protocol</u>	<u>Study Description</u>
✓	1	P136C1	Population PK study in pediatric asthma patients aged 6 months to 23 months old.
✓	2	P176	Safety study in pediatric asthma patients aged 6 months to 24 months.
✓	3	P066	Population PK study in pediatric asthma patients aged $\geq 2$ years to <6 years.
✓	4	P072	Safety study in pediatric asthma patients aged $\geq 2$ years to <6 years.

***Objective/rationale:***

*Study 1: To estimate the total plasma clearance of montelukast in children aged 6 months to <2 years as compared to those seen in adults given labeled doses of Singulair 10 mg film-coated (FC) tablets. These data should be used to determine the appropriate dosage (by age and/or by weight) for Studies 2 and 4. (Amendment #1)*

*Study 3: To estimate the total plasma clearance and to assess the linearity of pharmacokinetics of montelukast in children aged  $\geq 2$  years to <6 years as compared to those seen in adults given labeled doses of Singulair 10 mg film-coated (FC) tablets. These data should be used to determine the appropriate dosage (by age and/or by weight) for Studies 2 and 4.*

*To estimate the total plasma clearance of montelukast in children aged >2 years to <6 years as compared to those seen in adults given labeled doses of Singulair 10 mg film-coated (FC) tablets. These data should be used to determine the appropriate dosage (by age and/or by weight) for Studies 2 and 4. (Amendment #1)*

**Studies 2 & 4: To evaluate the safety of montelukast in children aged 6 months to <2 years (Study 2) and aged  $\geq 2$  years to <6 years (Study 4) when administered at an age- and/or weight-appropriate dose.**

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ON ORIGINAL**

**Objective/rationale evaluated:**

- ✓ Study 1: Estimated the population AUC of montelukast in children aged 6 months to <2 years as compared to those seen in adults given labeled doses of Singulair 10 mg film-coated (FC) tablets. These data were used to determine the appropriate dosage (by age and/or by weight) for Study 2.
- ✓ Study 3: Estimated the population AUC of montelukast in children aged 2 years to <6 years and compared the results to those seen in adults given labeled doses of Singulair 10 mg film-coated (FC) tablets. The population AUC “was determined by a non-linear mixed-effect 1-compartment pharmacokinetic model and were compared using a 2-sample t-test. The ratio of the geometric means (GMR) for the AUCs (AUC<sub>pop</sub>) was also computed along with the 90% confidence interval for the GMR, which was compared to the prespecified interval (0.5, 2.0). C<sub>max</sub> and T<sub>max</sub> were also derived from this model. The half-life was derived separately by fitting a linear mixed-effect model to the natural log concentration over time using data in the terminal phase.” These data were used to determine the appropriate dosage (by age) for Study 4.

*Note: A single-dose study cannot address linearity of pharmacokinetics. This was a mistake in the wording of the original Written Request, which was corrected in the WR Amendment after the fact.*

- ✓ Study 2: To evaluate the safety of montelukast in children aged 6 months to <2 years when administered at an age- and/or weight-appropriate dose.
- ✓ Study 4: To evaluate the safety of montelukast in children aged ≥2 years to <6 years when administered at an age- and/or weight-appropriate dose.

***Indication(s) to be studied:***

Studies 1-4: Asthma.

**Indication(s) studied:**

- ✓ Studies 1-4: Asthma.

***Study design:***

*Study 1: A single-dose population PK study including 3 sparse blood samples postdose per patient. In designing the population PK study, please refer to the Agency's Guidance for Industry: Population Pharmacokinetics, published on February 15, 1999. Using previous PK data for montelukast in adults, employ an optimized sampling strategy to accurately estimate population pharmacokinetics. [For example, there may be 6 sampling timepoints chosen. The timepoints may then be divided into two schedules: Schedule A: 1st, 3rd, and 5th timepoints; and Schedule B: 2nd, 4th, and 6th timepoints. Pediatric patients from each age group should be randomly assigned to Schedule A or B. For both schedules, draw three sparse blood samples per patient.] Record dosing and sampling times accurately. (Amendment #1)*

Study 3: A single-dose population PK study should include 3 sparse blood samples postdose per patient to evaluate the dose level(s) of montelukast. Using previous PK data for montelukast in adults, an optimized sampling strategy based on time brackets should be employed in order to accurately estimate population pharmacokinetics. [For example, there may be 6 sampling time brackets chosen: dose-1.0 hr (1st), 1.0-3.0 hr (2nd), 3.0-5.0 hr (3rd), 5.0-9.0 hr (4th), 9.0-15.0 hr (5th), and 15.0-24.0 hr (6th). The time brackets should be divided into two schedules, i.e., Schedule A: 1st, 3rd, and 5th time brackets and Schedule B: 2nd, 4th, and 6th time brackets. Pediatric patients should be randomly assigned to Schedule A or B. For both schedules, three sparse blood samples per patient (one sample per time bracket) should be taken.]. Dosing and sampling times should be recorded accurately.

*A single-dose population PK study including 3 sparse blood samples postdose per patient to evaluate one or more dose level(s) of montelukast. Using previous PK data for montelukast in adults, employ an optimized sampling strategy to accurately estimate population pharmacokinetics. [For example, there may be 6 sampling timepoints chosen. The timepoints may then be divided into two schedules: Schedule A: 1st, 3rd, and 5th timepoints; and Schedule B: 2nd, 4th, and 6<sup>th</sup> timepoints. Pediatric patients should be randomly assigned to Schedule A or B. For both schedules, draw three sparse blood samples per patient.] Record dosing and sampling times accurately. (Amendment #1)*

Studies 2 & 4: Randomized, double-blind, placebo-controlled, and parallel-group safety study. The study subjects are to be randomized into 2 groups: an active treatment group and a placebo group with a 2:1 ratio. The double-blind treatment period must be at least 6 weeks.

**Study design used:**

- ✓ *Study 1: A single-dose population PK study including 3 blood samples post-dose (and one pre-dose) per patient to evaluate one dose level of montelukast. Using previous PK data for montelukast in adults, an optimized sampling strategy to accurately estimate population pharmacokinetics was developed. There were 6 sampling timepoints chosen, divided into two schedules: Schedule A: 1st, 3rd, and 5th timepoints; and Schedule B: 2nd, 4th, and 6<sup>th</sup> timepoints. Patients were randomly assigned to Schedule A or B. For both schedules, four blood samples per patient were drawn, including the pre-dose sample, with a total maximum of 12.0 ml of blood withdrawn during the study. Dosing and sampling times were recorded. After 18 patients had completed treatment and sampling, an interim analysis was performed to determine whether a lower or higher dosage would be studied in subsequent patients. Based on this analysis, the 4 mg dosage used for the first 18 patients was continued for the rest of the study.*
- ✓ *Study 3: A single-dose population PK study including 3 blood samples post-dose (and one pre-study) per patient to evaluate one dose level of montelukast. (Note: Only one dose level was used.) Using previous PK data for montelukast in adults, an optimized sampling strategy to accurately estimate population pharmacokinetics was developed. There were 6 sampling timepoints chosen*

in addition to the pre-study sample (1.5, 2, 4, 8, 12, 24 hours). Plasma sampling was divided into two schedules: Schedule A: 1<sup>st</sup> (1.5 hours), 3<sup>rd</sup> (4 hours), and 5<sup>th</sup> (12 hours) timepoints; and Schedule B: 2<sup>nd</sup> (2 hours), 4<sup>th</sup> (8 hours), and 6<sup>th</sup> (24 hour) timepoints. Patients were randomly assigned to Schedule A or B. For both schedules, four blood samples per patient were drawn, including the pre-study sample, with a total maximum of 12.0 ml of blood withdrawn during the study. Dosing and sampling times were recorded.

*Note: Study 3 did not follow the original WR regarding suggested sampling times. However, these times were only given as examples, and the quality of the data were sufficient for approval of the 4 mg chewable tablet NDA. Therefore, the intent of the population pharmacokinetic study (to obtain adequate population pharmacokinetic data for interpretation) was met.*

- ✓ Study 2: Randomized, double-blind, placebo-controlled, and parallel-group safety study. Study subjects were randomized into 2 groups: an active treatment group and a placebo group with a 2:1 ratio. The double-blind treatment period was 6 weeks.
- ✓ Study 4: Randomized, double-blind, placebo-controlled, and parallel-group safety study. Study subjects were randomized into 2 groups: an active treatment group and a placebo group with a 2:1 ratio. The double-blind treatment period was 12 weeks, with a 36-week open-label controlled extension. An interim analysis of at least 6 weeks of blinded data was performed and submitted.

***Age group in which the studies will be performed:***

Studies 1 & 2: Children with asthma aged 6 months to <2 years. Approximately equal distribution of subjects into 2 age groups:  $\geq 6$  months to <1 year (with sufficient representation of younger subjects) and  $\geq 1$  year to <2 years.

Study 3: Children with asthma aged  $\geq 2$  to < 6 years (with sufficient representation of younger subjects).

Study 4: Children with asthma aged  $\geq 2$  years to <6 years. Approximately equal distribution of subjects into 2 age groups:  $\geq 2$  years to <4 year and  $\geq 4$  years to <6 years.

**Age group studied:**

See Demographics of Patients Studied in the section below.

***Number of subjects to be studied or power of study to be achieved:***

*Study 1: A minimum of 24 patients should complete the study. At least 12 patients for each age group ( $\geq 6$  months to <1 year and 1 year to <2 years) should complete the study. (Amendment #1)*

*Study 2: A minimum of 150 patients should complete the study. At least 38 patients (25 in the treatment group and 13 in the placebo group) 6 months and <12 months of age must complete the study. (Amendment #1)*

Study 3: A minimum of 12 patients should complete the study. (Note: The exact same requirement was repeated in Amendment #1.)

Study 4: A minimum of 150 patients per study. At least 75 patients (50 in the treatment group and 25 in the placebo group) per age group. (Note: The exact same requirement was repeated in Amendment #1.)

**Demographics of subjects studied:**

**✓ Study 1 (Protocol P136C1) Patients distribution [p136c.pdf]**

Ages:	≥6 mo to <1 yr	≥1 yr to <2 yr	Totals
WR Requirement (completed)	12	12	24
Entered	14	18	32
Boys	9 (6 to 11)	5 (17 to 23)	
Girls	5 (8 to 11)	13 (12 to 23)	
Completed	13	17	30
Discontinued	1	1	2
Data available for PK analysis	12	14	26

**✓ Study 2 (Protocol P176) Patient disposition**

	Montelukast 4mg	Placebo	Totals
WR Requirement (completed)	100	50	150
≥6 months to <1 year	25	13	
≥1 to <2 years			
Baseline (entered) Totals:	175	81	256
Boys	116 (6 to 23) *	59 (6 to 24) *	175 (6 to 24) *
Girls	59 (6 to 24) *	22 (6 to 23) *	81 (6 to 24) *
Age at Randomization			
≥6 months to <1 year	51	33	84 (32.8%)
Boys	35	24	
Girls	16	9	
≥1 to <2 years	124	48	172
Boys			
Girls			
Completed	169	74	243 (94.9%)
Discontinued	6	7	13
* Age range in months			

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## ✓ Study 3 (Protocol P066) Patients

	Schedule A	Schedule B	Totals
WR Requirement (completed)			12
Entered	8	7	15
Boys	5 (2 to 5) *	2 (4 to 5) *	7 (2 to 5) *
Girls	3 (2 to 5) *	5 (2 to 5) *	8 (2 to 5) *
Age (years)			
2			5
3			1
4			2
5			7
6			0
Completed	8	7	15
* Age range in years			

## ✓ Study 4 (Protocol P072) Patient breakdown: Interim analysis of 6 weeks of patient data [from Interim Study Report, NDA 20-830, S-008, pages 31-4; P072.pdf]

	Montelukast 4mg Chewables	Placebo	Totals
WR Requirement (completed ≥6 weeks treatment)			150
2 to 3 (<4) years	50	25	
4 to 5 (<6) years	50	25	
Baseline (entered) Totals:	212	102	314
Boys	130 (2 to 6)	57 (2 to 6)	187 (2 to 6)
Girls	82 (2 to 6)	45 (2 to 5)	127 (2 to 6)
Age (years) at baseline			
2	45	16	61
3	51	26	77
Subtotal 2 to 3 years	96	42	138
4	62	35	97
5	50	24	74
Subtotal 4 to 5 years	112	59	171
6 (4 patients turned age 6 between Visit 1 and Randomization Visit 3, 1 had a wrong birth date)	4	1	5
Completed ≥ 6 weeks of Period II (treatment period)	199	96	295
Completed Period II (12 weeks)	139	71	210
Discontinued	22	11	33

No data regarding compliance were stated for Study 4. The protocol states that compliance with administration of study drug during Period I, the run-in period, was required for randomization, but does not give the specific requirement or results. Study 4 provided far more information than was requested in the Written Request. It continued for 12 weeks, with an open safety extension out to 12 months. Many more patients were enrolled than were requested in the Written Request, as noted in the following table extracted from the final Study Report.

✓ **Study 4 (Protocol P072) Patient breakdown: Final Study Report** [from supplement to NDA 21-409, SE-8, May 25, 2000; p072.pdf]

	Montelukast 4mg	Placebo	Totals
WR Requirement (completed ≥6 weeks treatment)			150
2 to 3 years	50	25	
4 to 6 years	50	25	
Baseline (entered)      Totals:	461	228	689 *
Boys	272	131	403
Girls	189	97	286
Completed Period II (12 weeks)	416	202	618
Discontinued	45	26	71
* Of which, 9 patients were age 6 at time of randomization			

**Entry criteria:**

*Study 1: Male and female patients aged 6 months to <2 years with a history of physician-diagnosed asthma or "asthma-like" symptoms consistent with the need for chronic anti-asthma controller therapy (in the judgement of the physician), including, but not limited to, cough, wheezing, and shortness of breath. Each patient should be judged to be otherwise in good health on the basis of medical history and physical examination. (Amendment #2)*

**Study 3: Male and female patients aged ≥2 years to <6 years with stable asthma and without any other clinically significant disease. (Note: The exact same requirement was repeated in Amendment #1.)**

**Studies 2 & 4: Male and female patients aged 6 months to <2 years (Study 2) and aged ≥2 years to <6 years (Study 4) with stable asthma and without any other clinically significant disease, whose symptoms are consistent with the need for chronic anti-asthmatic therapy.**

**Note: Amendment #3 allowed the use of the term 'asthma-like' symptoms for Study 1, but the request for amendment for Studies 2 and 4 was disallowed since the amendment occurred after the study reports were filed.**

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ON ORIGINAL**

**Entry criteria used:**

- ✓ Study 1: Male and female patients aged 6 months to <2 years, between 6 and 15 kg (5<sup>th</sup> to 95<sup>th</sup> percentile of height for weight) with "a history of physician-diagnosed asthma" (defined in the protocol as  $\geq 3$  discrete episodes of wheezing after 8 weeks of age with episodes separated by a symptom-free interval of at least 7 days), or "'asthma-like' symptoms consistent with the need for chronic anti-asthma controller therapy (in the judgement of the physician), including, but not limited to, cough, wheezing, and shortness of breath". Each patient was judged to be otherwise in good health on the basis of medical history and physical examination.
- ✓ Study 3: Male and female patients aged  $\geq 2$  years to <6 years, between 10 and 20 kg, with stable asthma as defined in the protocol as 3 or more episodes of cough, wheezing, and shortness of breath, within one year of the study period, and without any other clinically significant disease.
- ✓ Study 2: Male and female patients aged 6 months to <2 years, and without any other clinically significant disease, and with "physician-diagnosed asthma or asthma-like symptoms including, but not limited to, cough, wheezing, and shortness of breath. The patient must also have had at least 3 episodes of asthma or 'asthma-like' symptoms, all occurring after 8 weeks of age; at least one of the episodes must have occurred within 6 months of the Prestudy Visit." While the term "symptoms consistent with the need for chronic anti-asthmatic therapy" was not specifically used in this protocol, and while the term "'asthma-like' symptoms" was used in the study, the intent of the Written Request was met in that enrollees were patients who were required to have the need for recurrent bronchodilator treatment for respiratory symptoms, and many were on previous controller therapy.
- ✓ Study 4: Male and female patients aged  $\geq 2$  years to <6 years with stable asthma and without any other clinically significant disease. The term "symptoms consistent with the need for chronic anti-asthmatic therapy" was not used in the protocol. Instead, asthma and the need for controller therapy was pre-defined as at least 3 episodes within 1 year prior to the study, with a pre-specified asthma symptom score of 1 or more on 6-9 days during the run-in period and beta-agonist use of 6-9 times during the run-in period, depending upon the length of the run-in of between 11-17 days. Therefore, many enrollees were patients who were on previous controller therapy, and the enrollment criteria were strict enough to meet the current NAEPP/NHLBI guidelines of the need for controller therapy.

**Clinical endpoints:**

- Studies 1 & 3: Determination of plasma concentrations of montelukast using the same validated assay method(s) employed previously or using an adequately cross-validated assay method.
- Study 2: Adverse events (recorded at each examination on Adverse Event Case Report forms), changes in physical examinations (including vital signs, body weight,

*and height), and clinical hematology and chemistry tests (at baseline and last study visit for each participant). (Amendment #3)*

Study 4: Adverse events (recorded daily in a diary by the patient's parent or caretaker), changes in physical examinations (including vital signs, body weight, and height), and clinical hematology and chemistry tests (at baseline and last study visit for each participant).

**Clinical endpoints used:**

- ✓ Study 1: Determination of plasma concentrations of montelukast used \_\_\_\_\_ with \_\_\_\_\_
- ✓ Study 3: Determination of plasma concentrations of montelukast used \_\_\_\_\_ with \_\_\_\_\_
- ✓ Study 2: Adverse events (recorded at each examination on Adverse Event Case Report forms), changes in physical examinations (including vital signs, body weight, and height), and clinical hematology and chemistry tests (at baseline and last study visit for each participant).
- ✓ Study 4: Adverse events (recorded daily in a diary by the patient's parent or caretaker), changes in physical examinations (including vital signs, body weight, and height), and clinical hematology and chemistry tests (at baseline and last study visit for each participant).

**Study evaluations:**

Study 1: Report of plasma concentrations and estimated clearance of montelukast.

Population PK data analysis should utilize prior PK data available in adults.  
(Amendment #3)

Study 3: Report of plasma concentrations and estimated clearance of montelukast. Population PK data analysis should utilize all prior PK data available in adolescents and adults.

Studies 2 & 4: Safety data including adverse events, changes in physical examinations, and clinical laboratory tests.

**Study evaluations used:**

- ✓ Study 1: Report of plasma concentrations and estimated clearance of montelukast. Population PK data analysis utilized prior PK data available in adults.
- ✓ Study 3: Report of plasma concentrations and estimated clearance of montelukast. Population PK data analysis utilized all prior PK data available in adolescents and adults.
- ✓ Studies 2 & 4: Safety data including adverse events, changes in physical examinations, and clinical laboratory tests.

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ON ORIGINAL**

**Drug information:**

## Studies 1 &amp; 2:

- Dosage form: Appropriate dosage form (e.g., \_\_\_\_\_ for administration to children aged 6 months to <2 years.
- Route of administration: Oral
- Regimen:     *Study 1:* *Single dose administration of (an) age- and/or weight-appropriate dose level(s) (after correction for relative bioavailability to achieve AUCs similar to that in adults receiving Singulair 10 mg FC tablet dose). (Amendment #1)*
- Study 2:* Administration of an age- and/or weight-appropriate dose (as determined by Study 1) at an appropriate dosing interval.

## Studies 3 &amp; 4:

- Dosage form: Appropriate dosage form (e.g., chewable tablets) for administration to children aged  $\geq 2$  years to <6 years.
- Route of administration: Oral
- Regimen:     *Study 3:* Single dose administration of an age- and/or weight appropriate dose level (after correction for relative bioavailability to achieve AUCs similar to that in adults receiving Singulair 10 mg FC tablet dose).
- Study 4:* Administration of an age- and/or weight-appropriate dose (as determined by Study 3) at an appropriate dosing interval.

**Drug information evaluated:**

## Studies 1 &amp; 2:

- ✓ Dosage form: 4 mg \_\_\_\_\_ for administration to children aged 6 months to <2 years.
- ✓ Route of administration: Oral
- Regimen:     ✓ *Study 1:* *Single dose administration of (an) age- and/or weight-appropriate dose level(s) (after correction for relative bioavailability to achieve AUCs similar to that in adults receiving Singulair 10 mg FC tablet dose).*
- ✓ *Study 2:* Administration of an age- and/or weight-appropriate dose (4 mg, as determined by Study 1) at an appropriate dosing interval (daily).

Studies 3 & 4:

- ✓ Dosage form: 4 mg chewable tablets for administration to children aged  $\geq 2$  years to  $< 6$  years.
- ✓ Route of administration: Oral
- Regimen: ✓ Study 3: Single dose administration of an age- and/or weight appropriate dose level (after correction for relative bioavailability to achieve AUCs similar to that in adults receiving Singulair 10 mg FC tablet dose).
- ✓ Study 4: Administration of an age- and/or weight-appropriate dose (4 mg, as determined by Study 3) at an appropriate dosing interval (daily).

***Safety concerns:***

Unanticipated adverse reactions (e.g., gastritis, enteritis, neurologic symptoms/signs, eosinophilia, elevated liver enzymes, etc.).

**Safety information submitted:**

- ✓ Unanticipated adverse reactions, as well as clinical and laboratory safety measurements.

***Statistical information:***

Studies 1 & 3: Population analysis of the plasma clearance for montelukast.

Studies 2 & 4: Descriptive statistics of adverse events and changes in physical examinations and clinical laboratory tests.

**Statistical information submitted:**

- ✓ Studies 1 & 3: Population analysis of the plasma clearance for montelukast.
- ✓ Studies 2 & 4: Descriptive statistics of adverse events and changes in physical examinations and clinical laboratory tests.

***Labeling that may result from the studies:***

Information on pharmacokinetics, dosing regimen and safety in children with asthma aged 6 months to  $< 6$  years.

**Labeling that has resulted or may result from the studies:**

- ✓ Studies 1 and 3: Proposed labeling for Singulair labeling for
- ✓ Studies 2 and 4: Present labeling for Singulair labeling for 4mg chewable tablets for ages 2 to 5 years.

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ON ORIGINAL**

***Format of reports to be submitted:***

Full study reports addressing all issues outlined in this request.

***Format of submitted reports:***

See below under Timeframe for submitting study reports.

***Timeframe for submitting reports of the studies:***

Full study reports should be submitted to the Agency by January 2, 2001.

*Full study reports should be submitted to the Agency by December 31, 2001. (Amendment #1)*

*(Note: Study Reports for Studies 3 and 4 were submitted before this amendment. Therefore, this amendment only applies to Studies 1 and 2. The Final Study Report for Study 4 was submitted after Amendment #1, but before January 2, 2001, the original cutoff date.)*

***Timeframe of submitted study reports:***

- ✓ Study 1: Complete uncontrolled study report submitted September 28, 2001, and stamped October 1, 2001, to NDA 21-409, N-000. (Study P136C1)
- ✓ Study 2: Complete controlled study report submitted September 28, 2001, and stamped October 1, 2001, to NDA 21-409, N-000. (Study P176)
- ✓ Study 3: Complete controlled study report submitted May 6, 1999 to NDA 20-830, SE1-008. (Study P066)
- ✓ Study 4: Interim analysis controlled study report submitted May 6, 1999 to NDA 20-830, SE1-008. Final study report submitted May 25, 2000 to NDA 20-830, SE8-011. (Study P072)

***Other Requirements:***

Must conduct the following studies prior to initiation of these studies.

1. The relative bioavailability of an appropriate dosage form (e.g., a \_\_\_\_\_ formulation for pediatric patients aged 6 months to <2 years) compared with the currently marketed Singulair (montelukast) 10 mg FC tablet or an appropriate chewable tablet formulation must be determined in normal adults.
2. The relative bioavailability of an appropriate dosage form (for pediatric patients aged  $\geq 2$  years to <6 years) compared with the currently marketed Singulair (montelukast) 10 mg FC tablet or Singulair 5 mg chewable tablet formulation must be determined in normal adults if the above appropriate dosage form (e.g., a smaller chewable tablet) is not compositionally and proportionally the same as the currently marketed 5 mg chewable tablet formulation.

***Other Requirements completed:***

- ✓ 1. The relative bioavailability of an appropriate dosage form (4 mg \_\_\_\_\_ formulation) for pediatric patients aged 6 months to <2 years) compared 4 mg chewable tablet formulation was determined in normal adults.

- ✓ 2. The relative bioavailability of an appropriate dosage form (4 mg chewable tablets for pediatric patients aged  $\geq 2$  years to  $< 6$  years) compared with Singulair 10 mg FC tablet formulation was estimated based on linear regression analysis of AUC vs. weight from 5 previously conducted pharmacokinetic studies. This was done as part of NDA 20-830, S-008, with the population PK study (Study 3 – P066) in 2-5 year olds serving as confirmation that the correct dose had been chosen.

### **III. Recommendation**

The Division believes that all four studies satisfied the Written Request and appropriate WR Amendments. Pediatric Exclusivity should be granted.

**APPEARS THIS WAY  
ON ORIGINAL**

NDA 21-409  
NDA Regulatory Filing Review  
(Includes Filing Meeting Minutes)  
Page 1

Original NDA 21-409, Singulair (montelukast sodium) Oral Granules

Applicant: Merck Research Laboratories  
Date of Application: September 28, 2001  
Date of Receipt: September 28, 2001  
Date of Filing meeting: November 16, 2001  
Filing Date: November 27, 2001

Indication(s) requested:

Type of Application: Full NDA   X   Supplement \_\_\_\_\_  
(b)(1)   X   (b)(2) \_\_\_\_\_  
[If the Original NDA of the supplement was a (b)(2), all subsequent supplements are (b)(2)s; if the Original NDA was a (b)(1), the supplement can be either a (b)(1) or (b)(2)]

If you believe the application is a 505(b)(2) application, see the 505(b)(2) requirements at the end of this summary.

Therapeutic Classification: S   X   P \_\_\_\_\_  
Resubmission after a withdrawal or refuse to file   No    
Chemical Classification: (1,2,3 etc.)   3    
Other (orphan, OTC, etc.)   None  

Has orphan drug exclusivity been granted to another drug for the same indication? YES  NO

If yes, is the drug considered to be the same drug according to the orphan drug definition of sameness [21 CFR 316.3(b)(13)]? YES  NO

If the application is affected by the application integrity policy (AIP), explain.  NO

User Fee Status: Paid  Waived (e.g., small business, public health) \_\_\_\_\_  
Exempt (orphan, government) \_\_\_\_\_  
Form 3397 (User Fee Cover Sheet) submitted: YES  NO \_\_\_\_\_  
User Fee ID#   4179    
Clinical data? YES  NO \_\_\_\_\_ Referenced to NDA# \_\_\_\_\_  
Date clock started after UN \_\_\_\_\_

User Fee Goal date:   July 28, 2002  

Action Goal Date (optional) \_\_\_\_\_

- Does the submission contain an accurate comprehensive index?  YES  NO
- Form 356h included with authorized signature?  
If foreign applicant, the U.S. Agent must countersign.  YES  NO
- Submission complete as required under 21 CFR 314.50?  YES  NO

NDA 21-409  
 NDA Regulatory Filing Review  
 (Includes Filing Meeting Minutes)  
 Page 2

If no, explain:

- If electronic NDA, does it follow the Guidance? YES NO NA  
**If an electronic NDA: all certifications must be in paper and require a signature.**
- If Common Technical Document, does it follow the guidance? YES NO NA
- Patent information included with authorized signature? YES NO

• Exclusivity requested? YES; If yes, 6 months NO  
 Note: An applicant can receive exclusivity without requesting it, therefore, requesting exclusivity is not a requirement.

- Correctly worded Debarment Certification included with authorized signature? YES NO  
**If foreign applicant, the U.S. Agent must countersign.**

Debarment Certification must have correct wording, e.g.: "I, the undersigned, hereby certify that Merck & Co, Inc. did not and will not use in any capacity the services of any person debarred under section 306 of the Federal Food, Drug and Cosmetic Act in connection with the studies listed in Appendix \_\_\_\_." Applicant may not use wording such as, "To the best of my knowledge, ...."

- Financial Disclosure included with authorized signature? YES NO  
 (Forms 3454 and/or 3455)  
**If foreign applicant, the U.S. Agent must countersign.**
- Has the applicant complied with the Pediatric Rule for all ages and indications? YES NO  
 If no, for what ages and/or indications was a waiver and/or deferral requested:  
*Waiver is granted for patients \_\_\_\_\_ with this NDA approval.*  
*Although patients \_\_\_\_\_ of age did not get approval, pediatric study requirements have been fulfilled.*

- Field Copy Certification (that it is a true copy of the CMC technical section)? YES NO

**Refer to 21 CFR 314.101(d) for Filing Requirements**

PDUFA and Action Goal dates correct in COMIS? YES NO  
 If not, have the document room staff correct them immediately. These are the dates EES uses for calculating inspection dates.

Drug name/Applicant name correct in COMIS? If not, have the Document Room make the corrections.

List referenced IND numbers: IND 39,568    IND     IND 58,819    -

End-of-Phase 2 Meeting? Date \_\_\_\_\_ NO  
 If yes, distribute minutes before filing meeting.

Pre-NDA Meeting(s)? Date(s) 4/26/01 NO  
 If yes, distribute minutes before filing meeting.

NDA 21-409  
NDA Regulatory Filing Review  
(Includes Filing Meeting Minutes)  
Page 3

**Project Management**

- Copy of the labeling (PI) sent to DDMAC?  YES  NO
- Trade name (include labeling and labels) consulted to ODS/Div. of Medication Errors and Technical Support?  YES  NO
- MedGuide and/or PPI consulted to ODS/Div. of Surveillance, Research and Communication Support?  YES  NO  NA
- OTC label comprehension studies, PI & PPI consulted to ODS/ Div. of Surveillance, Research and Communication Support?  YES  NO  NA
- Advisory Committee Meeting needed? YES, date if known \_\_\_\_\_  NO

**Clinical**

- If a controlled substance, has a consult been sent to the Controlled Substance Staff?  YES  NO

**Chemistry**

- Did sponsor request categorical exclusion for environmental assessment?  YES  NO  
If no, did sponsor submit a complete environmental assessment?  YES  NO  
If EA submitted, consulted to Nancy Sager (HFD-357)?  YES  NO
- Establishment Evaluation Request (EER) package submitted?  YES  NO
- Parenteral Applications Consulted to Sterile Products (HFD-805)?  YES  NO  NA

**If 505(b)(2), complete the following: *Not Applicable***

Describe the change from the listed drug(s) provided for in this (b)(2) application (for example, "This application provides for a new indication, otitis media" or "This application provides for a change in dosage form, from capsules to solution").

Name of listed drug(s) and NDA/ANDA #:

Is the application for a duplicate of a listed drug and eligible for approval under section 505(j)?  
(Normally, FDA will refuse-to-file such applications.)

YES  NO

Is the extent to which the active ingredient(s) is absorbed or otherwise made available to the site of action less than that of the reference listed drug (RLD)?

If yes, the application must be refused for filing under 314.54(b)(1)  YES  NO

Is the rate at which the product's active ingredient(s) is absorbed or otherwise made available to the site of action unintentionally less than that of the RLD?

YES  NO

Which of the following patent certifications does the application contain? Note that a patent certification must contain an authorized signature.

- 21 CFR 314.50(i)(1)(i)(A)(1): The patent information has not been submitted to FDA.
- 21 CFR 314.50(i)(1)(i)(A)(2): The patent has expired.
- 21 CFR 314.50(i)(1)(i)(A)(3): The date on which the patent will expire.
- 21 CFR 314.50(i)(1)(i)(A)(4): The patent is invalid, unenforceable, or will not be infringed by the manufacture, use, or sale of the drug product for which the application is submitted.

*If filed, and if the applicant made a "Paragraph IV" certification [21 CFR 314.50(i)(1)(i)(A)(4)], the applicant must submit a signed certification that the patent holder was notified the NDA was filed [21 CFR 314.52(b)]. Subsequently, the applicant must submit documentation that the patent holder(s) received the notification ([21 CFR 314.52(e)].*

- 21 CFR 314.50(i)(1)(ii): No relevant patents.
- 21 CFR 314.50(i)(1)(iii): Information that is submitted under section 505(b) or (c) of the act and 21 CFR 314.53 is for a method of use patent, and the labeling for the drug product for which the applicant is seeking approval does not include any indications that are covered by the use patent.
- 21 CFR 314.54(a)(1)(iv): The applicant is seeking approval only for a new indication and not for the indication(s) approved for the listed drug(s) on which the applicant relies.

Did the applicant:

- Identify which parts of the application rely on information the applicant does not own or to which the applicant does not have a right of reference?  
YES NO
- Submit a statement as to whether the listed drug(s) identified has received a period of marketing exclusivity?  
YES NO
- Submit a bioavailability/bioequivalence (BA/BE) study comparing the proposed product to the listed drug?  
YES NO

Has the Director, Div. of Regulatory Policy II, HFD-007, been notified of the existence of the (b)(2) application?

YES NO

**APPEARS THIS WAY  
ON ORIGINAL**

ATTACHMENT

MEMO OF FILING MEETING

DATE: November 16, 2001

BACKGROUND:

Singulair is approved for treatment of asthma down to 2 years old of age (tablets and chewable tablets, NDA 20-829 and 20-830)

Merck proposes Singulair Oral Granules for use in patients ages \_\_\_\_\_ to under 2 years old and as an alternate dosage form to the chewable tablets for patients 2-5 years old.

ATTENDEES:

Prasad Peri  
Timothy McGovern  
Joseph Sun  
Sandra Suarez-Sharp  
Tayo Fadiran  
Jim Gebert  
Peter Starke  
Badrul Chowdhury  
Robert Meyer  
Laurie Lenkel  
Christine Yu

**APPEARS THIS WAY  
ON ORIGINAL**

ASSIGNED REVIEWERS:

Discipline

Medical:  
Secondary Medical:  
Statistical (Stability):  
Pharmacology:  
Statistical Pharmacology:  
Chemist:  
Environmental Assessment (if needed):  
Biopharmaceutical:  
Microbiology, sterility:  
Microbiology, clinical:  
DSI:  
Project Manager:  
Other Consults:

Reviewer

Peter Starke  
Badrul Chowdhury  
Ted Guo  
Luqi Pei  
  
Prasad Peri  
Categorical exclusion requested  
Sandra Suarez-Sharp  
  
Christine Yu  
ODS, DMETS (Scott Dallas)  
LNC (Dan Boring)

Per reviewers, all parts in English, or English translation? YES  NO

CLINICAL – File  Refuse to file

• Clinical site inspection needed: YES  NO

MICROBIOLOGY CLINICAL – File  N/A  Refuse to file

STATISTICAL – File N/A Refuse to file \_\_\_\_\_

BIOPHARMACEUTICS – File ✓ Refuse to file \_\_\_\_\_

• Biopharm. inspection Needed: YES \_\_\_\_\_ NO ✓

PHARMACOLOGY – File ✓ Refuse to file \_\_\_\_\_

CHEMISTRY –

• Establishment(s) ready for inspection? YES ✓ NO \_\_\_\_\_ File ✓ Refuse to file \_\_\_\_\_

REGULATORY CONCLUSIONS/DEFICIENCIES:

✓ The application, on its face, appears to be well-organized and indexed. The application appears to be suitable for filing.

\_\_\_\_\_ The application is unsuitable for filing. Explain why:

[ /S/ ]

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

**APPEARS THIS WAY  
ON ORIGINAL**

## Memorandum of Telephone Facsimile Correspondence

Date: July 31, 2002

To: David Altarac, M.D., MPA  
Director, Regulatory Affairs

Fax: 732-594-1030

From: Christine Yu, R.Ph. **/S/**  
Regulatory Project Manager

Subject: NDA 21-409 for Singulair Oral Granules  
Memorandum of July 15, 2002, teleconference

Reference is made to the meeting held between representatives of your company and this Division on July 15, 2002. Attached is a copy of our final minutes for that meeting/teleconference. These minutes will serve as the official record of the meeting/teleconference. If you have any questions or comments regarding the minutes, please call me at (301) 827-1051.

**THIS DOCUMENT IS INTENDED ONLY FOR THE USE OF THE PARTY TO WHOM IT IS ADDRESSED AND MAY CONTAIN INFORMATION THAT IS PRIVILEGED, CONFIDENTIAL AND PROTECTED FROM DISCLOSURE UNDER APPLICABLE LAW.**

If you are not the addressee, you are hereby notified that any review, disclosure, dissemination, copying, or other action based on the content of this communication is not authorized. If you received this document in error, please immediately notify us by telephone at (301) 827-1050 and return it to us at FDA, 5600 Fishers Lane, HFD-570, DPDP, Rockville, MD 20857.

Thank you.

**APPEARS THIS WAY  
ON ORIGINAL**

**MEMORANDUM OF TELECONFERENCE**

DATE: July 15, 2002  
APPLICATION: NDA 21-409  
DRUG NAME: Singulair (montelukast sodium) Oral Granules  
SPONSOR: Merck Research Laboratories (Merck)

BETWEEN: David Altarac, Director, Regulatory Affairs  
Dawn Bartizal, Labeling  
Diane Benezra-Kurshan, Labeling  
Carolyn Daly, Regulatory Coordination  
Richard Couch, Regulatory and Analytical Sciences  
Dennis Erb, Regulatory Affairs  
Barry Gertz, Clinical Research  
Shefali Goyal, Labeling  
Alan Hartford, Biostatistics,  
Michelle Kloss, Regulatory Affairs  
Barbara Knorr, Respiratory and Allergy  
Elizabeth Migoya, Clinical Pharmacology  
Janet Van Adelsberg, Respiratory and Allergy  
Jaap Verbeek, Editing  
Lynn Wei, Biostatistics  
Ji Zhang, Biostatistics

AND Division of Pulmonary & Allergy Drug Products, HFD-570, unless noted

Prasad Peri, Chemistry Reviewer  
Guirag Poochikian, Chemistry Team Leader  
Luqi Pei, Pharmacology & Toxicology Reviewer  
Emmanuel Fadiran, Clinical Pharmacology & Biopharmaceutics TL  
James Gebert, Biostatistics  
Peter Starke, Medical Officer  
Badrul Chowdhury, Acting Director  
Christine Yu, Regulatory Project Manager  
Laurie Lenkel, Regulatory Review Officer, Division of Drug Marketing,  
Advertising, and Communications

**APPEARS THIS WAY  
ON ORIGINAL**

This NDA 21-409 was submitted September 28, 2001. The PDUFA due date is July 28, 2002. The Division's proposal for labeling and other labeling comments were faxed to Merck on July 12, 2002. The teleconference minutes captures the key issues discussed, agreements and action items.

Merck identified 5 areas of discussion:

1. Terminology (oral granules vs \_\_\_\_\_)
2. Stability comments on mixing the oral granules on page 1 of the package insert (PI)
3. Packaging comments from Division facsimile correspondence dated July 12, 2002, "Carton & Packaging labeling comments"
4. Indication
5. Pharmacokinetic data on page 3 of the PI

1. Drug dosage form terminology

Merck stated that "\_\_\_\_\_" is a good description of how the drug product would be used and that other products are currently marketed with the same term.

The Division responded that the two examples of drug products cited by Merck that contains \_\_\_\_\_ as part of the drug name are \_\_\_\_\_. Accordingly, the dosage form \_\_\_\_\_ is part of the established name. Additionally, the Division stated that the USP Expert Committee on Nomenclature & Labeling, as well as the Agency agree that the established name for this drug is "montelukast sodium oral granules."

Merck asked whether other products using \_\_\_\_\_ would be requested to modify the product name and if \_\_\_\_\_ may be part of a trademark.

The Division stated that it will contact the appropriate FDA division who may want to pursue follow-up action on the other products using the name \_\_\_\_\_ at a future date. Using \_\_\_\_\_ as part of a trademark may be considered.

Merck stated that they will take the "oral granules" issue back for internal discussion.

2. Stability comments on mixing the oral granules with other foods under the DESCRIPTION section, last paragraph on page 1 of the PI.

Merck stated that this information is more appropriate under the DOSAGE & ADMINISTRATION section.

The Division responded that Merck can move this information out of the DESCRIPTION section, but none of the informational content should be lost in moving this information to the DOSAGE & ADMINISTRATION section.

Merck agreed to remove any redundancy and make any minor editorial revisions.

3. Packaging comments from Division facsimile correspondence dated July 12, 2002, "Carton & Packaging labeling comments"

Merck agreed with all other comments except for those listed below.

- Comment 3- Merck responded that other products are on the market, where the drug name is in more than one color.
- Comment 7- Merck would like clarification of this comment.

The Division stated that instructions on the packet on how the packet should be opened are not clear. There is a vertical line in the front without a scissor mark, but a horizontal line in the back with a scissor mark.

Merck replied that the vertical line is intended to be a folding mark, but that they will improve the packet opening instructions.

- Comment 11- Merck stated that pictures of children on complementary cartons have been approved in previous applications for Singulair tablets and chewable tablets and that they do not agree to deleting the pictures.

The Division responded that the pictures of happy children on the complementary cartons would not be informative to the physicians or other users of Singulair oral granules. Rather, the pictures may give false impressions about the content or intended use (i.e., that a toy or candy is inside the carton). The purpose of printed materials on the carton should be to provide information that will aid in the safe and appropriate use of the product. It is the Division's opinion that the pictures distract from this purpose and should be removed from the complementary cartons.

Merck will provide the NDA numbers and the dates in which the other complementary cartons with pictures of people were approved.

4. Indication

Merck requested Division's rationale for providing indication for 12 months to 5 year olds only \_\_\_\_\_).

The Division responded that the rationale and evidence submitted was adequate for approval \_\_\_\_\_; but the evidence provided was not adequate to support an approval \_\_\_\_\_ of age for the following reasons.

- Asthma as defined in adults and older children has certain pathophysiology associated with the diagnosis of asthma. It is uncertain whether "asthma" in children \_\_\_\_\_ of age is the same.
  - The safety study submitted had randomization problems for the sub-group of patients \_\_\_\_\_ of age, i.e., corticosteroid use at baseline was not equal. Therefore, the exploratory efficacy endpoints could not be evaluated. There were no supportive evidences of efficacy in the \_\_\_\_\_ patients, rather, some of the exploratory efficacy endpoints went in the opposite direction in favor of placebo. Furthermore, fewer patients randomized to the placebo group received glucocorticoids in comparison to the montelukast group.
5. Pharmacokinetic data on page 3 of the PI, CLINICAL PHARMACOLOGY section, Adolescents and Pediatric Patients subsection.

Merck requested clarifications of how AUCs and Cmax were calculated.

From the data submitted to the NDA, the Division stated that it appeared Merck had pooled individual data then performed an analysis. The Division used the population pharmacokinetics analysis approach to calculate individual AUCs and Cmax's, then pooled the results for greater accuracy. The Division will provide the procedure that was followed to calculate the Division's AUC and Cmax.

Merck requested the intent of the Division for including the information about the 6-11 month patients in the PI.

The Division responded that the studies for this NDA were conducted in response to a Written Request from the Agency. The Division recognizes that even if approval is for 12 months and older, physicians may choose to use this drug in patients down to 6 months of age. Since there is significant variability in systemic exposure after administration of montelukast in the 6 to 11 month age group, the Division considers it a public health issue to provide the pharmacokinetic information for this age group in the label even though the drug is not approved for this age range.

Merck proposed that since pharmacokinetic data about the 6 to 11 month age group is being included, that safety data for this age group for both studies be also provided in the label.

The Division responded that Merck may include a brief statement regarding safety results from the single-dose pharmacokinetic study. However, the Division stated that the safety data from the 6-week safety study for the 6 to 11 month age group could not be included in the description of the safety study in the Adverse Events section. The study had a randomization imbalance, thus, the safety information from this study is not considered valid. In addition, in considering the inclusion of this information in the label, several of

the exploratory efficacy data results that also relate to safety, were not in favor of montelukast.

Merck agreed to add a sentence to the CLINICAL PHARMACOLOGY SECTION, Adolescents and Pediatric Patients subsection of the PI, describing the safety results from the single-dose pharmacokinetic study in the 6 to 11 month age group. Additional safety information about the 6 to 11 month age group from the 6-week safety study will not be included.

Merck noted that exposure ratios in the PRECAUTIONS section, Carcinogenesis, Mutagenesis, Impairment of Fertility subsection, have been modified and requested a summary of how the new ratios were calculated.

The Division responded that exposure ratios were recalculated based on the pharmacokinetic data from the younger age group. The Division will provide information on how the ratios were calculated.

**Post-teleconference follow-up**

The Division provided the following information by facsimile:

- July 19, 2002- Pharmacology & Toxicology and Biopharmaceutical calculations
- July 24, 2002- Pharmacology & Toxicology calculation for AUC value of 116.7  $\mu\text{g}\cdot\text{hr}/\text{ml}$

**APPEARS THIS WAY  
ON ORIGINAL**

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

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Christine Yu  
7/31/02 01:47:59 PM  
CSO

**APPEARS THIS WAY  
ON ORIGINAL**

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

7/30/02

Project Manager Labeling Review

NDA: Singulair (montelukast sodium) oral granules

SPONSOR: Merck Research Laboratories

SUBMITTED: September 28, 2001 RECEIVED: September 28, 2001

This original NDA provides for the use of Singulair (montelukast sodium) oral granules in treatment of asthma as the primary formulation for patients 12 months to <2 years of age, and as an alternate formulation for patients 2 to 5 years of age. With approval of this NDA, labeling has been revised for the Singulair product line [10 mg film-coated tablets (NDA 20-829), 4 mg and 5 mg chewable tablets (NDA 20-830)].

I compared the submitted package insert (PI) and patient package insert (PPI) to the last approved labeling (approved November 23, 2001, for NDA 20-830/S-011). Please note that this NDA was submitted before the approval of NDA 20-830/S-011, so the labeling changes approved with NDA 20-830/S-011 were not incorporated into Merck's proposed PI and PPI. Other than the changes from NDA 20-830/S-011 and the changes agreed upon during teleconferences dated July 15, 24, and 25, 2002, there are no changes other than those requested by this NDA. The Medical Officer's Review dated July 26, 2002, the Chemistry Review dated July 26, 2002, the Addendum to the Pharmacologist's review dated July 25, 2002, and the Addendum to the Clinical Pharmacology Review dated July 26, 2002, found the agreed upon labeling acceptable and recommended approval of this NDA.

The immediate container \_\_\_\_\_, trade and complimentary carton are acceptable as agreed upon during teleconferences July 15 and 24, 2002. Note that the Division does not like the complimentary carton with pictures of happy children, but since previous complimentary cartons for application NDA 20-829 and 20-830 have been approved for several years now with picture of people, and since there are no regulations in place for the Division to mandate the removal of these pictures, the Division's position is captured in the teleconference minutes dated July 15 and 24, 2002. The approval letter dated July 26, 2002, requests that Merck submit the mock-up of the complimentary carton to Division of Drug Marketing, Advertising and Communications (DDMAC) for evaluation and review. Three of the pictures of children on the originally proposed complimentary carton are to be replaced with older children, since approval was down to 12-months of age only \_\_\_\_\_.

I recommend approval of the PI, PPI, packet, and the trade and complimentary cartons for this NDA, as long as Merck appropriately implements the agreed upon changes.

Christine Yu, R.Ph.  
Regulatory Project Manager  
Division of Pulmonary and Allergy Drug Products

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

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Christine Yu  
7/30/02 11:49:00 AM  
CSO

**APPEARS THIS WAY  
ON ORIGINAL**

**DIVISION DIRECTOR'S MEMORANDUM**

DATE: July 26, 2002  
TO: NDA 21-409  
FROM: Badrul A. Chowdhury, MD, PhD  
Acting Director, Division of Pulmonary and Allergy Drug Products  
PRODUCT: Singulair (montelukast sodium) Oral Granules 4mg  
APPLICANT: Merck Research Laboratories, Rahway, New Jersey

**Introduction**

Merck Research Laboratories submitted NDA 21-409 for Singulair (montelukast sodium) Oral Granules 4mg on September 28, 2001, as primary formulation for pediatric asthma patients ages \_\_\_\_\_ to <2 years, and as alternate formulation to the currently approved Singulair Chewable Tablets 4mg for ages 2 to 5 years. Singulair Tablets 10mg (NDA 20-829) and Singulair Chewable Tablets 4mg and 5mg (NDA 20-830) are currently approved for asthma patients 2 years of age and older. With this application Merck also requested pediatric exclusivity, which was granted on December 10, 2001.

The clinical program of this NDA is based on three adult pharmacokinetic and bioequivalence studies to support the use of Singulair Oral Granules 4mg for ages 2 to 5 years, and one pediatric population pharmacokinetic study and one pediatric safety study to support the use of Singulair Oral Granules 4mg for ages \_\_\_\_\_ to <2 years. The submitted data support the approval of Singulair Oral Granules 4mg down to 12 months of age, \_\_\_\_\_

\_\_\_\_\_ The CMC data support the approval of the new Oral Granule formulation.

**Chemistry and Manufacturing**

Singulair Oral Granules 4mg is composed of montelukast sodium \_\_\_\_\_ mannitol \_\_\_\_\_ hydroxypropyl cellulose \_\_\_\_\_ magnesium stearate \_\_\_\_\_, and purified water to a total weight of \_\_\_\_\_ mg. The granule formulation is based on a \_\_\_\_\_ formed from mannitol with the active drug substance coated on the \_\_\_\_\_ The market image product consists of \_\_\_\_\_ of \_\_\_\_\_ white granules packaged in a \_\_\_\_\_ foil child-resistant packet with a \_\_\_\_\_ for ease of opening.

The commercial batch size is \_\_\_\_\_ The proposed shelf life of the drug product is \_\_\_\_\_ The CMC reviewer Dr. Peri, in consultation with the biometrics reviewer Dr. Guo, has concluded that the proposed shelf life is supported by the stability data. The

applicant has agreed to study and provide results of the validation studies with

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Stability of Singulair Oral Granules mixed with some foods such as applesauce, ice cream, carrot, and rice was studied. Data show that \_\_\_\_\_ are formed when the drug mixed with food is left for \_\_\_\_\_ time period. For example, the \_\_\_\_\_ impurity reaches \_\_\_\_\_ when the Singulair Oral Granules are mixed with applesauce and left exposed to light for \_\_\_\_\_ minutes, and \_\_\_\_\_ when mixed with rice under the same conditions. As a reference, the proposed limit of this impurity is \_\_\_\_\_ after \_\_\_\_\_ months of shelf life. This issue is reflected in the product label and patient instruction, which states that the drug should be consumed within 15 minutes of opening the pouch.

#### **Clinical Pharmacology and Biopharmaceutics**

The applicant submitted results from three adult pharmacokinetic and bioequivalence studies to support the Singulair Oral Granules 4mg as an alternate formulation for ages 2 to 5 years. The studies were a single dose, dose proportionality study of 2mg, 4mg, and 6mg Singulair Oral Granules (Study P127); a single dose, food-effect, bioavailability and bioequivalency study of 4mg Singulair Oral Granules given with and without applesauce, and Singulair 4mg Chewable Tablets (Study P090); and a single dose food effect, bioavailability and bioequivalence study of 4mg Singulair Oral Granules given with and without high fat meal, and 4mg Singulair Chewable Tablets (Study P183). Office of Clinical Pharmacology and Biopharmaceutics (OCBP) reviewer Dr. Suarez reviewed these studies in detail and concluded these studies provide adequate pharmacokinetic and bioequivalence data to support the approval of Singulair Oral Granules 4mg as an alternate formulation for ages 2 to 5 years. The 4mg Oral Granule formulation of montelukast was bioequivalent to the already approved 4mg Chewable Tablet, and the C<sub>max</sub> and AUC of the Oral Granule formulation were proportional within the 2- to 6-mg dose range. Applesauce did not affect the bioavailability of montelukast delivered from the Oral Granule formulation, and food did not effect the AUC of montelukast delivered from the Oral Granule formulation. The clinical reviewer Dr. Starke also reached the same conclusion, and did not identify any safety issues in these studies. The OCBP team and the clinical reviewer have recommended approval of Singulair Oral Granules 4mg for age 2 to 5 years and I concur with the recommendation.

The applicant submitted results from one pharmacokinetic study and one safety study to support the Singulair Oral Granules 4mg as the primary formulation for ages \_\_\_\_\_ to <2 years. The pharmacokinetic study was a single dose population pharmacokinetic study in children 6 months to <2 years of age (Study P136C1). This study showed that children 6 to <12 months of age had mean AUC values 60% higher than that observed in adults, and mean Cmax values 89% higher than that observed in adults. The systemic exposure in children 12 months to <2 years of age was also higher than those observed in adults (AUC 33% higher, Cmax 60% higher). There was no relationship between exposure and weight or age of the children. The pharmacokinetic parameters in children 6 to <12 months of age were highly variable, compared to the older age group and adults and adolescents. Although the supporting safety study (discussed in the following section) did not support approval of Singulair \_\_\_\_\_ the pharmacokinetic data in children 6 to <12 months of age are nevertheless informative for prescribing physicians and will be included in the product label.

#### Clinical and Statistical

The applicant submitted results from a multi center, double blind, parallel group safety and tolerability study comparing Singulair Oral Granules 4mg with placebo in patients 6 months to <2 years of age (Study P176). This study and the clinical pharmacokinetics and biopharmaceutics study are reviewed in Dr. Starke's excellent medical review. Only brief comments are made in this memorandum on Study P176 that justifies the action to approve the product down to 12 months of age but not \_\_\_\_\_ of age. This action overrides Dr. Starke's recommendation \_\_\_\_\_

In study 176 a total of 256 children 6 months to <2 years of age with history suggestive of asthma or with asthma like symptoms were treated with either montelukast 4mg (n=175, 51 below 12 months of age) or placebo (n=81, 33 below 12 months of age) for six weeks. Montelukast was well tolerated by the study patients and there no specific safety signals noted. Efficacy variables were evaluated as secondary endpoints in this study. The efficacy variables were supportive in children 12 months to <2 years of age, \_\_\_\_\_ (Table1). Children 6 to <12 months of age had more asthma exacerbations and required more oral corticosteroid rescue. The study was further confounded because there was a randomization imbalance for the 6 to <12 months age group. More children in the 6 to <12 months age group who had used oral corticosteroids were randomized to the montelukast arm. The mean total courses of oral corticosteroids for one year prior to randomization were 1.41 for the montelukast arm and 0.67 for the placebo arm for this age group.

Table 1. Summary of secondary efficacy variables by age group

	6-11 months		12-23 months	
	Montelukast	Placebo	Montelukast	Placebo
Oral corticosteroid rescue (%)	22.0	0.0	12.1	12.5
Asthma attacks (%)	24.0	12.1	13.7	22.9
Unscheduled visit for asthma (%)	12.0	12.1	8.9	16.7
Beta-agonist treatments per day	0.79	0.90	0.73	0.86

	6-11 months		12-23 months	
	Montelukast	Placebo	Montelukast	Placebo
Days without beta-agonist use (%)	63.13	57.29	67.88	61.07

Asthma is a difficult disease to diagnose in very young children. The asthma phenotype is also different in younger ages, and the response to therapy is also expected to be different. Therefore, in addition to safety and pharmacokinetic data, the Division relies on supportive efficacy data to decide on approvability of an asthma medication in young children. For ages 12 months to <2 years the applicant has provided adequate pharmacokinetic data and adequate supportive efficacy data to support the approval of montelukast for down to 12 months. However, the efficacy data in children for ages \_\_\_\_\_, as reviewed above and in depth in Dr. Starke's clinical review, do not support the efficacy of montelukast in this very young age range. Rather, some of the efficacy results go in the opposite direction in favor of placebo. The baseline randomization imbalance for oral corticosteroid use also confounds the results for the 6 months to <12 months age group. Furthermore, the pharmacokinetic data, reviewed in depth by Drs. Suarez'a and Starke, show that children between the ages of 6 and <12 months are exposed to higher levels of montelukast relative to children older than 12 months, and have higher variability, which makes dose recommendation for this very young age group difficult. The applicant has reasonable safety database to support the 4mg dose in children below the age of 12 months, but would require supportive efficacy data in order to gain an asthma indication for montelukast for children \_\_\_\_\_. The higher frequency of asthma exacerbation and higher oral corticosteroid use in the 6 to <12 months age group also make safety assessment difficult.

No safety information for ages 6 to <12 months from study P176 will be included in the product label because the randomization imbalance makes the study results invalid.

#### **Pharmacology and Toxicology**

There are no outstanding preclinical issues. No preclinical pharmacology or toxicology studies were conducted in support of this application. Preclinical data support the use of montelukast \_\_\_\_\_ of age in humans. Dr. Pei has concluded that the proposed drug product is safe and I concur with that conclusion.

#### **Data Quality and Integrity**

No DSI audits of clinical trial sites were requested or conducted for this NDA. Singulair is not a new molecular entity, and during the review process no irregularities that would raise question on the data integrity were found. No ethical issues are present. No financial disclosure issues are present.

#### **Establishment Evaluation**

The drug substance is manufactured and packaged in \_\_\_\_\_. This site has been inspected and found to have an acceptable status on April 19, 2002. The drug product is manufactured by Merck Manufacturing, West Point, Pennsylvania, packaged at \_\_\_\_\_, and stability tested in Merck Manufacturing

Division, Wilson, North Carolina. All of these sites have acceptable establishment evaluation status.

### **Labeling**

The applicant has submitted product label, patient product information, and carton and container labels. In the product label substantial changes or additions or both are proposed in the description, pharmacokinetics subsection under clinical pharmacology, pediatric use subsection under precaution, adverse events, and dosage and administration sections. These changes and additions were reviewed by various disciplines, and the Division and Merck have agreed on the final version of the label. The age of approval is lowered to 12 months. Information from the submitted studies is incorporated to various sections of the label. Although the product is not approved, \_\_\_\_\_ the clinical pharmacology section contains pharmacokinetic information for ages 6 to <12 months, because these are relevant for prescribing physicians. The dosage and administration section contains explicit information on use of the Oral Granule formulation to account for the limited stability of the product when taken out of the pouch and mixed with food. The patient product information also contains relevant information for patients.

### **Product Name**

The proprietary name of Singulair is approved and used by Merck for the line of products containing montelukast. Merck submitted this NDA using the term "\_\_\_\_\_" as a suffix to Singulair. During labeling stage of the NDA review a determination was made that the appropriate name for this formulation would be "Oral Granule." This terminology was vetted on by the USP Expert Committee on Nomenclature. Merck agreed to the change, but expressed an interest to come back later with the word "\_\_\_\_\_" in the trade name.

### **Pediatric Consideration**

On March 4, 1999, the Agency issued a pediatric written request to Merck on montelukast asking for clinical studies down to the age of 6 months. Merck submitted results from part of the requested clinical studies to NDA 20-830 on May 6, 1999. On the basis of that submission Singulair Chewable Tablet was approved down to the age of 2 years. Results from rest of the requested clinical studies down to the age of 6 months and other studies are submitted with this NDA. Merck has satisfied the requirements of the written request and was granted exclusivity based on the submitted clinical studies. The Agency's determination that montelukast should be studied down to 6 months of age has therefore been satisfied.

### **Recommendation**

The applicant has submitted adequate rationale and data to support the approval of Singulair (montelukast sodium) Oral Granules 4mg for treatment of asthma in children down to the age of 12 months. The submitted data support the use of Singulair Oral Granules 4mg as the primary formulation for ages 12 months to <2 years, and as an alternate formulation for ages 2 to 5 years.

\_\_\_\_\_ The action on this application is therefore an  
APPROVAL down to the age of 12 months. \_\_\_\_\_

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Badrul Chowdhury  
7/26/02 02:30:30 PM  
MEDICAL OFFICER

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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: Dr. David Altman

Organization Name/Dept: Director, Regulatory Affairs

CC: \_\_\_\_\_

Phone number: 732-594-0135

Fax number: 732-544-1030

From: \_\_\_\_\_ /S/ \_\_\_\_\_

**FAX: 301 - 827 - 1271**

**Phone: 301 - 827 - 1050**

- Urgent
- For Review
- Please Comment
- Please Reply
- OTHER: \_\_\_\_\_

Date sent: July 24, 2002

Number of pages including cover page: 19

Message: Changes tracked PC and PPI

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

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/s/

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Christine Yu

7/25/02 08:28:56 AM

CSO

Faxed 7/24/02 for labelg TC. The Division also requested  
Merck to edit some AEs listed in the  
PPI to less technical language. NOTE: this fax  
did not incorporate Div's AUC & Cmax values  
(Merck was looking at our calculations.) under CLIN  
PHARM sectn.



**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: Dr. David Altman

Organization Name/Dept: Div, RA

CC: \_\_\_\_\_

Phone number: 732-544-0135

Fax number: 732-544-1030

From: [ /S/ ]

**FAX: 301 - 827 - 1271**

**Phone: 301 - 827 - 1050**

- Urgent
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Date sent: 7/24/02

Number of pages including cover page: 2

Message: Pharmacology and Toxicology Calculations

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## Estimating Mouse Montelukast AUC at 100 mg/kg/day

July 24, 2002

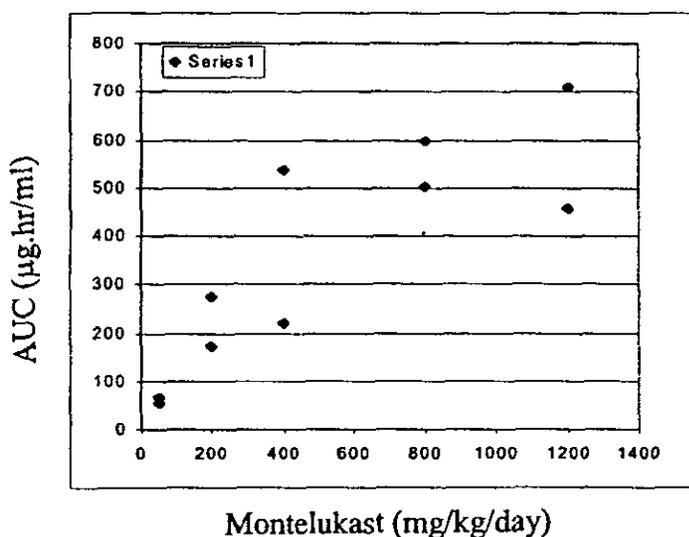
Plasma montelukast AUC value at an oral dose of 100 mg/kg/day in the mouse carcinogenicity study was extrapolated from a 4-week oral gavage study (Study No. T93-034-0) using the following model:

$$\text{AUC} = \text{Dose} \times 0.9033 + 26.35$$

The model was a linear regression of a section of the dose-concentration curve (50 – 400 mg/kg/day) of Study T93-034-0 using both sexes. An AUC value of 116.7 was obtained when 100 replaces “Dose”. The reason for the extrapolation is that the carcinogenicity study lacks the assessment of systemic exposure of the drug. Table 1 presents the AUC values in Study T93-034-0. The figure below is a graphical presentation of the data in Table 1.

**Table 1. Plasma Montelukast AUC in Mice (Study Y93-034-0)**

Montelukast (mg/kg/day, PO)	Plasma AUC <sub>0-24 hr</sub> (µg.hr/ml)				
	50	200	400	800	1200
Male	67.8	173.2	538.4	503.7	709.8
Female	54.9	276.4	221.7	598.5	457.0



Both the Agency and Sponsor have accepted and used the AUC value of 116.7 µg.hr/ml for labeling purpose for all montelukast products.

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/s/

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Christine Yu  
7/25/02 12:20:50 PM  
CSO  
Faxed to sponsor 7/24/02.

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## Memorandum of Telephone Facsimile Correspondence

Date: July 23, 2002

To: David Altarac, M.D., MPA  
Director, Regulatory Affairs

Fax: 732-594-1030

From: Christine Yu, R.Ph. [ /S/ ]  
Regulatory Project Manager

Subject: NDA 21-409  
Memorandum of December 12, 2001, teleconference

Reference is made to the meeting held between representatives of your company and this Division on December 12, 2001. Attached is a copy of our final minutes for that meeting/teleconference. These minutes will serve as the official record of the meeting/teleconference. If you have any questions or comments regarding the minutes, please call me at (301) 827-1051.

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Thank you.

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**MEMORANDUM OF TELECONFERENCE**

DATE: December 12, 2001  
APPLICATION: NDA 21-409  
DRUG NAME: Singulair (montelukast sodium) Oral Granules  
SPONSOR: Merck Research Laboratories

BETWEEN: David Altarac, Director, Regulatory Affairs

AND Christine Yu, Regulatory Project Manager, DPADP, HFD-570

Merck submitted the above NDA on September 28, 2001, containing final study reports for pediatric studies conducted in accordance with Section 505A of the FD&C Act and the March 4, 1999, FDA Written Request letter (as amended on April 18, September 28, 2000, and September 7, 2001).

The Division of Pulmonary and Allergy Drug Products compared these study reports against the terms of the Written Request and determined that the terms of the Written Request (as amended) have been met. This finding was confirmed at a meeting with the CDER Pediatric Exclusivity Board on December 10, 2001.

By recommendation of the Board, I contacted Dr. David Altarac, Director, Regulatory Affairs, on December 12, 2001, and informed him that exclusivity has been granted for this NDA for meeting the terms of the pediatric Written Request letter. I informed him that notice of this additional exclusivity award should appear on the CDER Pediatric internet web site within a few days and will also appear in the next supplemental printing of the Orange Book.

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

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**FACSIMILE TRANSMITTAL SHEET**

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**DATE:** July 19, 2002

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

**Subject:** NDA 21-409 Singulair Oral Granules  
Pharmacology/Toxicology and Biopharmaceutics calculations MRL requested during  
the July 15, 2002, labeling teleconference

**Total no. of pages including cover:** 3

**Comments:**

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**Document to be mailed:**  YES  NO

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**Clinical Pharmacology & Biopharmaceutics**

The following delineates the procedure for NONMEM calculation of population pharmacokinetic parameters for children 6 months to 2 years receiving 4 mg of Singulair oral granules and for adult receiving 10 mg of Singulair tablets.

- A 1-compartment model with first-order absorption and elimination better described the concentration-time data submitted by Merck for children 6 month to 2 years of age.
- The analysis was done with exclusion of subjects 101 and 132 who appear to be outliers. The exclusion of these subjects did not affect the outcome of the average population PK parameters.
- There was an improvement in the fit when the rate of absorption was fixed ( $K_a=1.5$ ).
- NONMEM output provided individual values of the following PK parameters:  $K_e$ , CL, Vd, and AUC.
- AUC<sub>pop</sub> for children 6 months to 1 year of age and for children 1 year to 2 years of age was calculated by averaging the individual AUC obtained from the NONMEM output.
- C<sub>max</sub> was calculated based on the estimates of  $K_e$ ,  $K_a$  and Vd for each subject.
- A 2-compartment model with first order absorption and elimination better described the adult data from protocol 034.
- The adult C<sub>max</sub> was calculated using non-compartmental methods.
- The effect of covariates, such as weight and age were introduced into the basic adult and children models. The analysis showed no correlation between C<sub>max</sub> or AUC and weight in the group of children 6 months to < 2 years of age receiving Singulair — 4mg.

**Pharmacology/Toxicology**

The following provides the calculations for exposure (AUC) ratios in the Carcinogenesis and Overdose sections of the labeling for montelukast. The exposure ratios were calculated by dividing the mean AUCs in animals by the mean AUC (3.04  $\mu\text{g}\cdot\text{hr}/\text{ml}$ ) in children 12 - 23 months of age and then rounding to the nearest 10. Table 1 presents parameters used in the calculation.

**Table 1. Parameters for Deriving AUC Ratios of Montelukast**

Labeling Section	Species	Dose (mg/kg)	AUC ( $\mu\text{g}\cdot\text{hr}/\text{ml}$ ) <sup>a</sup>	AUC Ratio (animal/human)	
				Calculated	Rounded to
Carcinogenesis	Mice	100	116.7 <sup>b</sup>	38.4	40
	Rat	200	326.9 <sup>c</sup>	107.5	110 <sup>c</sup>
Overdosage	Mice	5000	616.5 <sup>d</sup>	202	200
	Rat	5000	901.7 <sup>d</sup>	296.7	300

*numbers were flipped PI has the correct #'s*

- a. Montelukast AUCs in mice and rats have been used to calculate exposure ratios of the approved labeling.
- b. Average of the male and female AUCs in Study T93-034-0.
- c. Average of the male (404.8  $\mu\text{g}\cdot\text{h}/\text{ml}$ ) and female AUCs (248.9  $\mu\text{g}\cdot\text{h}/\text{ml}$ ) in Study T93-054-0.
- d. AUC values at 800 mg/kg in both species, for AUC values plateaus in mice and rats following a single dose of 800 mg/kg and higher of montelukast.
- e. This number is different from the ratio proposed by the Division in the July 12, 2002, facsimile which included the Division's proposal for labeling.

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/s/

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Christine Yu  
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CSO