CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: 20-830/S008

ADMINISTRATIVE DOCUMENTS

SUBMISSION OF PATENT INFORMATION
pursuant to 21 C.F.R. 314.53
for
NDA# 20-830

Trade Name:	SINGULAIR®
Active Ingredient:	Montelukast sodium
Strength(s)	4 mg
Dosage Form:	Chewable tablets
Approval Date:	Pending
US Patent Number:	5,565,473
Expiration Date	30 November 2010
Type of Patent	Drug substance, drug product and method of use
Approved Method of Use Covered by Patent:	Asthma
Name of Patent Owner:	Merck Frosst Canada & Co.
US Agent:	Merck & Co., Inc.

The undersigned declares that the above stated United States Patent Number 5,565,473 covers the composition, formulation and/or method of use of SINGULAIR®. This product is currently approved under section 505 of the Federal Drug, and Cosmetic Act.

Signed: Mollie A

Date: April 7, 1999
Title: Senior Patent Attorney, Merck & Co., Inc.
Telephone Number: 732-594-6343

APPEARS THIS WAY
ON ORIGINAL

EXCLUSIVITY SUMMARY FOR NDA # 20-830 SUPPL # 008

Trade Name Singulair Generic Name montelukast sodium

Applicant Name Merck and Co., Inc. HFD # 570

Approval Date If Known _____

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 question about the submission.

a) Is it an original NDA?

YES /___/ NO /_X_/

b) Is it an effectiveness supplement?

YES /_X_/ NO /___/

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

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 /_X_/ 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 /_X_/

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

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

NO

IF YOU HAVE ANSWERED "NO" TO ALL OF THE ABOVE QUESTIONS, GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

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 /_X_/

If yes, NDA #_____. Drug Name _____.

IF THE ANSWER TO QUESTION 2 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

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

YES /___/ NO /_X_/

IF THE ANSWER TO QUESTION 3 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8 (even if a study was required for the upgrade).

PART II FIVE-YEAR EXCLUSIVITY FOR NEW CHEMICAL ENTITIES

(Answer either #1 or #2 as appropriate)

1. Single active ingredient product.

Has FDA previously approved under section 505 of the Act any drug product containing the same active moiety as the drug under consideration? Answer "yes" if the active moiety (including other esterified forms, salts, complexes, chelates or clathrates) has been previously approved, but this particular form of the active moiety, e.g., this particular ester or salt (including salts with hydrogen or coordination bonding) or other non-covalent derivative (such as a complex, chelate, or clathrate) has not been approved. Answer "no" if the compound requires metabolic conversion (other than deesterification of an esterified form of the drug) to produce an already approved active moiety.

YES /_X_/ NO /___/

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

NDA# 20-829 Singulair 10 mg Tablets

NDA# 20-830 Singulair 5 mg Chewable Tablets

2. Combination product.

If the product contains more than one active moiety(as defined in Part II, #1), has FDA previously approved an application under section 505 containing any one of the active moieties in the drug product? If, for example, the combination contains one never-before-approved active moiety and one previously approved active moiety, answer "yes." (An active moiety that is marketed under an OTC monograph, but that was never approved under an NDA, is considered not previously approved.)

YES /___/ NO /___/

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 8. 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 /_X_/ NO /___/

IF "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

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.

(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 /_X_/ 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 8:

_____

(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 /_X_/ 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 /_X_/

If yes, explain:

(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:

Protocol 066: population PK study

Protocol 072: safety and tolerability study (interim analysis)

Studies comparing two products with the same ingredient(s) are considered to be bioavailability studies for the purpose of this section.

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 /_X_/

Investigation #2 YES /___/ NO /_X_/

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

_____ _____

_____ _____

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 /_X_/

Investigation #2 YES /___/ NO /_X_/

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

_____ _____

_____ _____

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"):

Protocol 066 Protocol 072

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.

a) For each investigation identified in response to question 3(c): if the investigation was carried out under an IND, was the applicant identified on the FDA 1571 as the sponsor?

Investigation #1

IND # _____ YES /_X_/ NO /___/ Explain: _____

Investigation #2

IND # _____ YES /_X_/ NO /___/ Explain: _____

(b) For each investigation not carried out under an IND or for which the applicant was not identified as the sponsor, did the applicant certify that it or the applicant's predecessor in interest provided substantial support for the study?

Investigation #1

YES /___/ Explain _____ NO /___/ Explain _____

_____ _____

_____ _____

Investigation #2

YES /___/ Explain _____ NO /___/ Explain _____

_____ _____
_____ _____

(c) Notwithstanding an answer of "yes" to (a) or (b), are there other reasons to believe that the applicant should not be credited with having "conducted or sponsored" the study? (Purchased studies may not be used as the basis for exclusivity. However, if all rights to the drug are purchased (not just studies on the drug), the applicant may be considered to have sponsored or conducted the studies sponsored or conducted by its predecessor in interest.)

YES /___/ NO /_X_/

If yes, explain: _____

/S/
Signature
Title: Regulatory Project Manager

2/25/00
Date

_____ _____
Signature of Division Director Date

cc: Original NDA 20-830/S-008
HFD-570/Division File
HFD-570/Hilfiker
HFD-93 Mary Ann Holovac

APPEARS THIS WAY
ON ORIGINAL

PEDIATRIC PAGE

(Complete for all original application and all efficacy supplements)

NDA/BLA Number:	20830	**Trade Name:**	SINGULAIR(MONTELUKAST SODIUM) CHEWABLE TA
Supplement Number:	8	**Generic Name:**	MONTELUKAST SODIUM CHEWABLE TABS
Supplement Type:	SE1	**Dosage Form:**	——— Tablet; Tablet, Chewable; Oral
Regulatory Action:	AP	**Proposed Indication:**	prophylaxis from episodes of bronchospasm associated with asthma

ARE THERE PEDIATRIC STUDIES IN THIS SUBMISSION?

YES, Pediatric data exists for at least one proposed indication which supports pediatric approval

What are the INTENDED Pediatric Age Groups for this submission?

____NeoNates (0-30 Days)
____Infants (1-24 Months)
____Children (25 Months-12 years)
____Adolescents (13-16 Years)
_X_ Other Age Groups (listed): 2-5 years of age

Label Adequacy	Adequate for ALL pediatric age groups
Formulation Status	NEW FORMULATION developed with this submission
Studies Needed	STUDIES needed. Applicant has COMMITTED to doing them
Study Status	Protocols are under discussion. Comment attached

Are there any Pediatric Phase 4 Commitments in the Action Letter for the Original Submission? YES

COMMENTS:

Studies submitted within partially fulfill the terms of a Written Request DH, 1/27/00 A P4 commitment to conduct a pediatric growth study with montelukast was committed at the time of approval of the original NDA and is still pending. DH, 3/6/00

This Page was completed based on information from a PROJECT MANAGER/CONSUMER SAFETY OFFICER, DAVID HILFIKER

/S/ 3/6/00

Signature Date

Montelukast Sodium 2- To 5-Year-Old Patients
Debarment Certification

As required by §306(k)(1) of 21 U.S.C. 335a(k)(1), we hereby certify that, in connection with this application, Merck & Co., Inc did not and will not use in any capacity the services of any person debarred under subsections 306(a) or (b) of the Act.

APPEARS THIS WAY
ON ORIGINAL

Division Director's Memorandum

Date:	Wednesday, March 01, 2000
NDA:	20-830; efficacy supplement S-008
Sponsor:	Merck
Proprietary Name:	Singulair (montelukast sodium) 4 mg Chewable Tablets
From:	Robert J. Meyer, MD Director, Division of Pulmonary and Allergy Drug Products

/S/

Introduction: This is a supplemental NDA for Singulair tablets that seeks approval for the prophylaxis and chronic treatment of asthma in children between the ages of 2 - 5 (currently Singulair is approved down to age 6). It also proposes a new dosage strength – a 4 mg chewable tablet, in addition to the approved 5 mg chewable tablet (approved for 6 – 14 year olds) and the 10 mg tablet product (for 15 year olds and older).

CMC: The CMC review by Dr. Khorshidi reveals the new tablet to be approvable from the CMC standpoint. The pharmaceutics of the tablets are very similar and proportional to the 5 mg chewable tablet, except for the dosage strength itself (i.e., it is simply 80% of the total formulation of the 5 mg tablet).

Pharmacology/toxicology: No new issues, given the lower age range proposed is 2 and above. Labeling multiples of human dosage will need to be revised as appropriate (i.e., other than reproductive and pregnancy sections).

Biopharmaceutics review: Dr. Albert Chen did the primary review. Essentially, the sponsor has provided evidence that children aged 2 - 5 years have similar systemic exposure to montelukast following the 4 mg chewable tablet as adults who have taken the 10 mg dosage, and 6 – 14 year olds exposed to the 5 mg chewable tablet. It is notable that these younger children had a higher Cmax and lower Cmin based on the modeling and limited data than that seen in adults, though the AUC was similar. However, given the similarity of these data to the 6 – 14 year olds, given the modeling aspects and the lack of clear definition of Cmin and the lack of clear definition of what a critical Cmin is, these PK data support the efficacy of this dosage regimen in this age range.

Clinical / Stastical: Drs. Gilbert-McClain was the primary reviewer, with me serving as the secondary reviewer. Since the clinical review was performed solely for safety (with efficacy inferred from the PK study and prior definitive efficacy with this drug in older children and adults), no statistical review was performed. In essence, the data provided were mainly derived from an interim analysis for safety of a 12-week safety and efficacy study in this age range and for this product. This study provide data only for patients exposed to at least 6-weeks of randomized treatment. These data, derived from 212 subjects randomized to montelukast, coupled with all other SRS data and short-term exposure data, suggest a safety profile comparable to that seen in older children and adults.

Auditing / Data Checking: The Division elected not to request routine DSI audits of these studies, due to the known efficacy of montelukast and the nature of the data supporting this application. No circumstances that would have elicited a "for cause" audit were

discovered in the review. The medical officer performed her own auditing/checking of the CRF data and did not identify any crucial problems that would invalidate the conclusions regarding the safety profile of this compound compared to that seen in other populations.

EERS: Acceptable EERs are in place, with an overall approval recommendation from Jan. 21, 2000.

Labeling: The labeling as proposed needed minor revisions, including revisions to the PPI suggested by a consult from Dr. Lechter of DDMAC to make the language clearer and more consumer friendly.

Conclusions: The sponsor has provide adequate clinical evidence of efficacy for Singulair in the 2 - 5 year old age group. This approval is based partly on the Pediatric Rule, based on the similarity of asthma in this population compared to older patients and the assumption that the efficacy response to montelukast will be similar in this younger population compared to older children and adults. Therefore, the approval relies on a PK study to establish the correct dose and on safety data sufficient to address overall conclusions on the similarity of the safety profile in this population compared to older children and adults. It should be noted that these data fulfill a part of the Agency's pediatric written request for Montelukast,

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ON ORIGINAL

FDA CDER EES
ESTABLISHMENT EVALUATION REQUEST
SUMMARY REPORT

Application: NDA 20830/008
Stamp: 07-MAY-1999 Regulatory Due: 07-MAR-2000
Applicant: MERCK RES
BLA-30
WEST POINT, PA 19486

Priority: 3S Org Code: 570
Action Goal: District Goal: 01-FEB-2000
Brand Name: SINGULAIR(MONTELUKAST SODIUM)CHEWABLE TA
Established Name:
Generic Name: MONTELUKAST SODIUM CHEWABLE TABS
Dosage Form: TAB (TABLET)
Strength: 5 MG/CHEWABLE

FDA Contacts:
D. HILFIKER (HFD-570) 301-827-1050 , Project Manager
H. KHORSHIDI (HFD-570) 301-827-1096 , Review Chemist
G. POOCHIKIAN (HFD-570) 301-827-1050 , Team Leader

Overall Recommendation:

ACCEPTABLE on 21-JAN-2000 by S. FERGUSON (HFD-324) 301-827-0062

Establishment: [redacted]
DMF No:
AADA No:

Profile: CTL OAI Status: NONE
Last Milestone: OC RECOMMENDATION
Milestone Date: 08-OCT-1999
Decision: ACCEPTABLE
Reason: DISTRICT RECOMMENDATION

Responsibilities: FINISHED DOSAGE STABILITY TESTER

Establishment: 1036761
MERCK AND CO INC
4633 MERCK RD
WILSON, NC 27893
DMF No:
AADA No:

Profile: TCM OAI Status: NONE
Last Milestone: OC RECOMMENDATION
Milestone Date: 21-JAN-2000
Decision: ACCEPTABLE
Reason: DISTRICT RECOMMENDATION

Responsibilities: FINISHED DOSAGE MANUFACTURER
FINISHED DOSAGE PACKAGER
FINISHED DOSAGE RELEASE TESTER

Establishment: 2510592
MERCK AND CO INC
SUMNEYTOWN PIKE BLA20
WEST POINT, PA 19486
DMF No:
AADA No:

Profile: TCM OAI Status: NONE
Last Milestone: OC RECOMMENDATION

Responsibilities: FINISHED DOSAGE MANUFACTURER

FDA CDER EES
ESTABLISHMENT EVALUATION REQUEST
SUMMARY REPORT

Milestone Date: **08-OCT-1999**
Decision: **ACCEPTABLE**
Reason: **DISTRICT RECOMMENDATION**

Establishment [ ]
DMF No:
AADA No:

Profile: —
OAI Status: —
Responsibilities: [ ]
Last Milestone:
Milestone Date:
Decision:
Reason:

Establishment: **9610180**
MERCK SHARP AND DOHME IRELAI
TIPPERARY, CLONMEL COUNTY, EI
DMF No:
AADA No:

Profile: **CSN** OAI Status: **NONE**
Last Milestone: **OC RECOMMENDATION**
Milestone Date: **07-OCT-1999**
Decision: **ACCEPTABLE**
Reason: **BASED ON PROFILE**
Responsibilities: **DRUG SUBSTANCE MANUFACTURER**
DRUG SUBSTANCE OTHER TESTER

Profile: **TCM** OAI Status: **NONE**
Last Milestone: **OC RECOMMENDATION**
Milestone Date: **13-OCT-1999**
Decision: **ACCEPTABLE**
Reason: **DISTRICT RECOMMENDATION**

Establishment [ ]
DMF No:
AADA No:

Profile: **TCM** OAI Status: **NONE**
Last Milestone: **OC RECOMMENDATION**
Milestone Date: **08-OCT-1999**
Decision: **ACCEPTABLE**
Reason: **DISTRICT RECOMMENDATION**
Responsibilities: **FINISHED DOSAGE PACKAGER**
