CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: 20-829

CHEMISTRY REVIEW(S)

DEC 19 1997

DIVISION OF PULMONARY DRUG PRODUCTS

Review of Chemistry, Manufacturing, and Controls

NDA #: 20-829 **CHEM.REVIEW #:** 3 **REVIEW DATE:** 15-Dec-97

SUBMISSION TYPE	DOCUMENT DATE	CDER DATE	ASSIGNED DATE
ORIGINAL	21-FEB-97	21-FEB-97	28-FEB-97
AMENDMENT	17-JUN-97	18-JUN-97	25-JUN-97
AMENDMENT	30-JUL-97	31-JUL-97	07-AUG-97
AMENDMENT	23-SEP-97	24-SEP-97	02-OCT-97
		SUBJECT OF THIS REVIEW	
AMENDMENT N(BC)	13-NOV-97	14-NOV-97	19-NOV-97
AMENDMENT N(BC)	26-NOV-97	28-NOV-97	05-DEC-97
AMENDMENT N(BL)	25-NOV-97	26-NOV-97	08-DEC-97
AMENDMENT N(BC)	14-OCT-97	15-OCT-97	21-OCT-97
AMENDMENT N(BL)	11-DEC-97	12-DEC-97	16-DEC-97

NAME & ADDRESS OF APPLICANT: Merck Research Laboratories
Sumneytown Pike
West Point, PA 19486

DRUG PRODUCT NAME

Proprietary:	Singular Tablets
Nonproprietary/USAN:	montelukast sodium
Code Name/#:	MK-476
Chem.Type/Ther.Class:	1 S

ANDA Suitability Petition/DESI/Patent Status: N/A

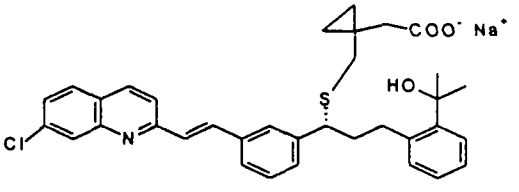
PHARMACOL.CATEGORY/INDICATION: Treatment of asthma (leukotriene antagonist)

DOSAGE FORM: tablet (I.R.)
STRENGTHS: 10 mg
ROUTE OF ADMINISTRATION: oral, one tablet per day
DISPENSED: X Rx _____ OTC

CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOL.WT:

Sodium 1-[[[(R)-*m*-[(E)-2-(7-chloro-2-quinolyl)vinyl]-α-[*o*-(1-hydroxy-1-methylethyl)phenethyl]benzyl]thio]methyl]cyclopropaneacetate

Molecular Formula: $C_{35}H_{35}ClNNaO_3S$
Molecular Weight: 608.18



RELATED DOCUMENTS (if applicable):
Supporting INDs & NDAs included above.

CONSULTS:

ENVIRONMENTAL ASSESSMENT:	requested 3/12/97; FONSI completed 5/16/97
METHODS VALIDATION:	requested 4/4/97; pending from St. Louis lab; Philadelphia lab reported 11/12/97 that methods are suitable for regulatory control of this product.
ESTABLISHMENT INSPECTION:	requested 3/6/97; pending
NOMENCLATURE COMMITTEE:	requested 3/13/97; The Committee finds the proposed name unacceptable 3/27/97. Division decision to accept of proposed name (Singulair™) 5/19/97.
PHARM/TOX IMPURITY CONSULT:	requested 9/26/97; the 10/31/97 review concluded that the proposed specifications for impurities are acceptable from a preclinical standpoint.
BIOMETRICS STABILITY:	requested 10/3/97; review dated 12/15/97 concludes that the data supports 24 months expiry for bottles and 12 months for blisters.

REMARKS/COMMENTS:
Previous chemist's review (JLeak, 10/7/97) found the application deficient and an information request letter dated October 22, 1997 was sent to the applicant. The 11/13/97 response will be covered in this review. There was also a meeting with the applicant on 11/7/97 to discuss the items in our letter dated October 22, 1997. Additional stability data was submitted in the 11/26/97 amendment and draft labels were submitted in the 11/25/97 amendment. The labels contain all the information required by 21CFR 201.100.

Proposed expiry (7/30/97):
for HDPE bottles - 24 months based on submitted data for 18 months (24 months 11/13/97),
and for blisters - 12 months based on submitted data for 12 months.

Additional data is to be submitted with the proposal to extend the expiry. Three months stability data has been submitted 7/31/97 and 11/13/97 and six months stability data has been submitted 11/26/97 on batches of drug product manufactured at the commercial manufacturing site.

CONCLUSIONS & RECOMMENDATIONS:
From a chemistry and manufacturing basis, the application may be approved. The approval letter should include a statement that the validation of the methods by our laboratories has not been completed, and should problems be found in the methods, the applicant will cooperate to solve the problems. The allowed expiry for the drug product should be stated in the approval letter as 24 months based on submitted data for HDPE bottles and 12 months based on submitted data for blisters. The package insert should be modified as indicated in the attached draft letter.

cc:
Orig. NDA 20-829
HFD-570/Division File
HFD-570/JLeak/
HFD-570/CSO
HFD-570/GPoochikian
HFD-820/JGibbs
R/D Init by /S/ 1/8/97

/S/
John C. Leak, Review Chemist
filename: 20829B.NDA

OCT 15 1997

DIVISION OF PULMONARY DRUG PRODUCTS
Review of Chemistry, Manufacturing, and Controls

NDA #: 20-829 **CHEM.REVIEW #:** 2 **REVIEW DATE:** 07-OCT-97

SUBMISSION TYPE	DOCUMENT DATE	CDER DATE	ASSIGNED DATE
ORIGINAL	21-FEB-97	21-FEB-97	28-FEB-97
		SUBJECT OF THIS REVIEW	
AMENDMENT	17-JUN-97	18-JUN-97	25-JUN-97
AMENDMENT	30-JUL-97	31-JUL-97	07-AUG-97
AMENDMENT	23-SEP-97	24-SEP-97	02-OCT-97

NAME & ADDRESS OF APPLICANT: Merck Research Laboratories
Sumneytown Pike
West Poimt, PA 19486

DRUG PRODUCT NAME

Proprietary:	Singular Tablets
Nonproprietary/USAN:	montelukast sodium
Code Name/#:	MK-476
Chem.Type/Ther.Class:	1 S

ANDA Suitability Petition/DESI/Patent Status: N/A

PHARMACOL.CATEGORY/INDICATION: Treatment of asthma (leukotriene antagonist)

DOSAGE FORM: tablet (I.R.)
STRENGTHS: 10 mg
ROUTE OF ADMINISTRATION: oral, one tablet per day
DISPENSED: X Rx _____ OTC

CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOL.WT:

Sodium 1-[[[(R)-*m*-[(E)-2-(7-chloro-2-quinolyl)vinyl]-α-[*o*-(1-hydroxy-1-methylethyl)phenethyl]benzyl]thio]methyl]cyclopropaneacetate

Molecular Formula: $C_{35}H_{35}ClNNaO_3S$
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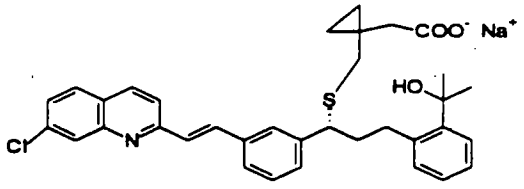

RELATED DOCUMENTS (if applicable):
Supporting INDs & NDAs included above.

CONSULTS:

ENVIRONMENTAL ASSESSMENT:	requested 3/12/97; FONSI completed 5/16/97
METHODS VALIDATION:	requested 4/4/97; pending
ESTABLISHMENT INSPECTION:	requested 3/6/97; pending
NOMENCLATURE COMMITTEE:	requested 3/13/97; The Committee finds the proposed name unacceptable 3/27/97. Division decision to accept of proposed name (Singulair™) 5/19/97.
PHARM/TOX IMPURITY CONSULT:	requested 9/26/97; pending (see p 14 of this review)
BIOMETRICS STABILITY:	requested 10/3/97; pending

REMARKS/COMMENTS:
Previous chemist's review (JLeak, 5/21/97) found the application deficient and an information request letter dated June 18, 1997 was sent to the applicant. The June 17 amendment stated that 3 month stability data on batches of drug product manufactured at the commercial plant (Wilson, NC) would be submitted by October 1. The July 30 amendment addressed the items in the information request letter dated June 18, 1997 which will be covered in this review.

Proposed expiry:
for HDPE bottles - 24 months based on submitted data for 18 months, and for blisters - 12 months based on submitted data for 12 months. Additional data is to be submitted with the proposal to extend the expiry. Three months stability data has been submitted 7/31/97 on batches of drug product manufactured at the commercial manufacturing site.

Agreements and commitments by the applicant in the July 30 amendment:

1. A 6 month re-test date is assigned to the purchased starting materials for the synthesis of the drug substance.
2. testing will be included as part of the supportive studies in the event of any proposed change to the container/closure system which impacts the materials in direct contact with the drug substance.
3. The specifications for and total impurities in the bulk drug substance will be tightened after reassessment within one year of approval.
4. Only purchased from purchased from will be used in the synthesis of the bulk drug substance.
5. The specification for the

6. A specification of will be established for release, and over the shelf-life of the montelukast sodium tablet formulations. Merck agrees to maintain the specification in stability studies after validation to indicate if a problem arises in future commercial batches.
7. A reevaluation of the release specifications for impurity levels in the coated tablets should occur within a year of approval and presented to the Agency, based on results for production lots prepared at full scale.

CONCLUSIONS & RECOMMENDATIONS:
Deficiencies found in the following review should be sent to the applicant for correction. The project manager should forward to the applicant the items in the attached draft letter.

cc:
Orig. NDA 20-829
HFD-570/Division File

NDA 20-829

HFD-570/JLeak/
HFD-570/CSO
HFD-570/GPoochikian
HFD-820/JGibbs
R/D Init by: /S/ 10/15/97

/S/

John C. Leak, Review Chemist
filename: 20829A.NDA

APPEARS THIS WAY
ON ORIGINAL

MAY 22 1997

DIVISION OF PULMONARY DRUG PRODUCTS
Review of Chemistry, Manufacturing, and Controls

NDA #: 20-829 **CHEM.REVIEW #:** 1 **REVIEW DATE:** 21-MAY-1997

SUBMISSION TYPE	DOCUMENT DATE	CDER DATE	ASSIGNED DATE
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Molecular Formula: $C_{35}H_{35}ClNNaO_3S$
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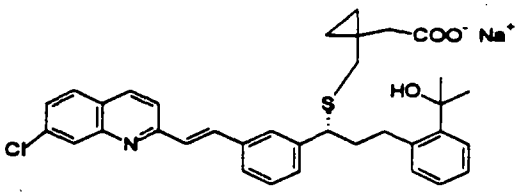

RELATED DOCUMENTS (if applicable):
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CONSULTS:

ENVIRONMENTAL ASSESSMENT:	requested 3/12/97; pending
METHODS VALIDATION:	requested 4/4/97; pending
ESTABLISHMENT INSPECTION:	requested 3/6/97; pending
NOMENCLATURE COMMITTEE:	requested 3/13/97; The Committee finds the proposed name unacceptable 3/27/97. Pending division decision regarding acceptance of proposed name.

REMARKS/COMMENTS:
Proposed expiry:
for HDPE bottles - 24 months based on submitted data for 18 months,
and for blisters - 12 months based on submitted data for 12 months.
Additional data is to be submitted with the proposal to extend the expiry. No data has been submitted on batches of drug product manufactured at the commercial manufacturing site.

CONCLUSIONS & RECOMMENDATIONS:
Deficiencies found in the following review should be sent to the applicant for correction. The project manager should forward to the applicant the items in the attached draft letter.

cc:
Orig. NDA 20-829
HFD-570/Division File
HFD-570/JLeak
HFD-570/CSO 5/22/97
HFD-570/GPoochikian

R/D Init by:

/S/

John C. Leak, Review Chemist
filename: 20829.NDA