CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: 20-829

CHEMISTRY REVIEW(S)
DIVISION OF PULMONARY DRUG PRODUCTS  
Review of Chemistry, Manufacturing, and Controls

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

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<th>NAME &amp; ADDRESS OF APPLICANT:</th>
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<td>Merck Research Laboratories</td>
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<td>Summitown Pike</td>
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<td>West Point, PA 19486</td>
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<th>DRUG PRODUCT NAME</th>
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<td>Nonproprietary/USAN:</td>
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| ANDA Suitability Petition/DESI/Patent Status: N/A |

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

| DOSAGE FORM: |
| tablet (I.R.) |
| 10 mg |

| STRNGTHS: |
| oral, one tablet per day |

| ROUTE OF ADMINISTRATION: |
| X Rx |
| OTC |

| DISPENSED: |

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

| Molecular Formula: | C_{39}H_{33}ClNNO_{3}S |
| Molecular Weight: | 608.18 |
NDA 20-829

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

CONSULTS:

ENVIRONMENTAL ASSESSMENT:
requested 3/12/97; FONSI completed 5/16/97
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.

METHODS VALIDATION:

ESTABLISHMENT INSPECTION:
requested 3/6/97; pending
requested 3/13/97; The Committee finds the
proposed name unacceptable 3/27/97. Division
decision to accept proposed name (Singulair™)
5/19/97.

NOMENCLATURE COMMITTEE:

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.
requested 10/3/97; review dated 12/15/97 concludes
that the data supports 24 months expiry for
bottles and 12 months for blisters.

BIOMETRICS STABILITY:

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/GSO
HFD-570/GPoochikian
HFD-820/JGibbs
R/D Init by 11/19/97

[Signature]
John C. Leak, Review Chemist

filename: 20829B.NDA
DIVISION OF PULMONARY DRUG PRODUCTS
Review of Chemistry, Manufacturing, and Controls

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

SUBMISSION TYPE  DOCUMENT DATE  CDRR 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

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/DBSI/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

CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOL.WT:
Sodium 1-[[{(R)-m-[[E]-2-(7-chloro-2-quinolyl)vinyl]-α-[0-(1-hydroxy-1-methylethyl)phenethyl]benzyl]thio)methyl]cyclopropaneacetate

Molecular Formula: C_{32}H_{31}ClNNaO_{3}S
Molecular Weight: 608.18

[Chemical structure diagram]
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 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
DIVISION OF PULMONARY DRUG PRODUCTS
Review of Chemistry, Manufacturing, and Controls

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

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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: S

ANDA Suitability Petition/DBSI/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: C₃₁H₂₉ClNNaO₅S
Molecular Weight: 608.18
RELATED DOCUMENTS (if applicable):
Supporting INDs & NDAs included above.

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/ 5/22/97
HFD-570/CSO
HFD-570/GPoochikiah

R/D Init by:

John C. Leak, Review Chemist

filename: 20829.NDA