CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-001

CHEMISTRY REVIEW(S)

DIVISION OF NEUROPHARMACOLOGICAL DRUG PRODUCTS

Review of Chemistry, Manufacturing, and Controls

NDA#: 21-001 **CHEMISTRY REVIEW: # 1** **DATE REVIEWED:** 15-MAY-2000

Submission Type	Document Date	CDER Stamp Date	Assigned Date
ORIGINAL	17-DEC-1999	20-DEC-1999	03-JAN-2000
Amendment (NC)	25-JAN-2000	27-JAN-2000	27-JAN-2000
Amendment (BC) — Stability update	10-MAY-2000	11-MAY-2000	15-MAY-2000

NAME AND ADDRESS OF APPLICANT: Pharmacia and Upjohn Company
7000 Portage Road
Kalamazoo, Michigan 49001

DRUG PRODUCT NAME:

Proprietary: AXERT™
Nonproprietary/Established/USAN: almotriptan malate – almotriptan is USAN malate salt status unclear
Code Name/#: PNU-180638E (also LAS 31416, T046, LAS W-322)
Chem. Type/Therapeutic Class: 1 S

DESI/PATENT STATUS: Almotriptan malate is claimed in U.S. Patent 5,565,447 (exp. 27-MAR-2014).

PHARMACOLOGICAL CATEGORY / INDICATION: Migraine
DOSAGE FORM: Tablet
STRENGTH(S): 6.25 mg and 12.5 mg
ROUTE OF ADMINISTRATION: Oral
DISPENSED: XX Rx ___ OTC
SPECIAL PRODUCTS: No

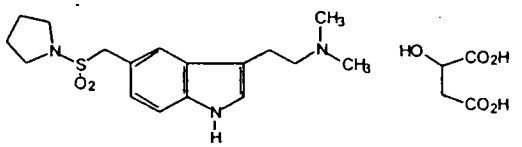
CHEMICAL NAME, STRUCTURAL FORMULA AND MOLECULAR FORMULA:

1-[[[3-(2-(dimethylamino)ethyl]-1H-indol-5-yl]-methyl]sulfonyl]pyrrolidine (±)-hydroxybutanedioate (1:1)

CAS No.: 181183-52-8

Mol. Formula: $C_{17}H_{25}N_3O_2S \cdot C_4H_6O_5$

Mol. Weight: 469.56 (salt), 335.47 (base)



SUPPORTING DOCUMENTS: [redacted]

RELATED DOCUMENTS: N/A

CONSULTS: Proposed tradename "Axert" consulted to OPDRA. Acceptable pending final OPDRA review at time of approval.

REMARKS / COMMENTS: NDA is deficient for drug substance manufacturing [redacted] and controls, drug product manufacture and controls, packaging, stability and labeling. Methods validation not initiated pending resolution of deficiencies in specifications and analytical procedures. Establishment inspections are pending.

CONCLUSIONS AND RECOMMENDATIONS:

NDA is not approvable for Chemistry at this time. Recommend information request letter to sponsor.

cc: Orig. NDA 21-001
HFD-120/Division File
HFD-120/MHeimann
HFD-120/LChen
HFD-120/MGuzewska/Init.by: MG
HFD-810/JSimmons

Martha R. Heimann, Ph.D., Review Chemist
Filename:

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

NDA#: 21-001 **CHEMISTRY REVIEW: # 2** **DATE REVIEWED:** 05-DEC-2000

Submission Type	Document Date	CDER Stamp Date	Assigned Date
Review #1			
ORIGINAL	17-DEC-1999	20-DEC-1999	03-JAN-2000
Amendment (NC)	25-JAN-2000	27-JAN-2000	27-JAN-2000
Amendment (BC) — Stability update	10-MAY-2000	11-MAY-2000	15-MAY-2000
Current Review (#2)			
Amendment (BC)	30-JUN-2000	03-JUL-2000	03-JUL-2000
Amendment (BC) — DMF update	26-JUL-2000	27-JUL-2000	31-JUL-2000
Amendment (BC)	25-AUG-2000	28-AUG-2000	06-SEP-2000
Amendment (BC)	29-AUG-2000	30-AUG-2000	08-SEP-2000

NAME AND ADDRESS OF APPLICANT: Pharmacia and Upjohn Company
7000 Portage Road
Kalamazoo, Michigan 49001

DRUG PRODUCT NAME:
Proprietary: AXERT™
Nonproprietary/Established/USAN: almotriptan malate
Code Name/#: PNU-180638E (also LAS 31416, T046, LAS W-322)
Chem. Type/Therapeutic Class: **1 S**

DESI/PATENT STATUS: Almotriptan malate is claimed in U.S. Patent 5,565,447 (exp. 27-MAR-2014).

PHARMACOLOGICAL CATEGORY / INDICATION: Migraine
DOSAGE FORM: Tablet
STRENGTH(S): 6.25 mg and 12.5 mg
ROUTE OF ADMINISTRATION: Oral
DISPENSED: XX Rx ___ OTC
SPECIAL PRODUCTS: No

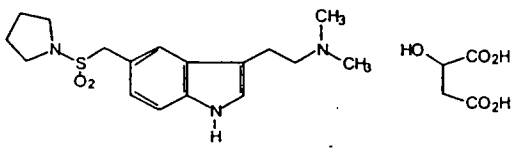
CHEMICAL NAME, STRUCTURAL FORMULA AND MOLECULAR FORMULA:

1-[[[3-(2-(dimethylamino)ethyl]-1H-indol-5-yl]-methyl]sulfonyl]pyrrolidine (±)-hydroxybutanedioate (1:1)

CAS No.: 181183-52-8

Mol. Formula: $C_{17}H_{25}N_3O_2S \cdot C_4H_6O_5$

Mol. Weight: 469.56 (salt), 335.47 (base)



SUPPORTING DOCUMENTS:

RELATED DOCUMENTS: N/A

CONSULTS:

Proposed tradename "Axert" consulted to OPDRA (by Project Manager). Acceptable pending final OPDRA review at time of approval.

Stability data and sponsor's statistical analysis was consulted to HFD-710 and reviewed by Dr. Yeh-Fong Chen. Statistical review and conclusions are included in Attachment 1.

REMARKS / COMMENTS:

NDA is deficient for drug substance manufacturing [redacted] and drug substance specification, drug product specification, packaging, stability and labeling. Methods validation not initiated pending resolution of deficiencies in specifications and analytical procedures. Expiration dating period requested by sponsor is not acceptable given long term data provided and results of statistical consult. Establishment inspections are completed and a satisfactory overall recommendation was received on 17-OCT-2000. [Refer to Attachment 2 for EER.]

CONCLUSIONS AND RECOMMENDATIONS:

NDA is not approvable for Chemistry at this time. Refer to review notes and list of deficiencies (Section H).

Martha R. Heimann, Ph.D., Review Chemist

cc: Orig. NDA 21-001
HFD-120/Division File
HFD-120/MHeimann
HFD-120/LChen
HFD-120/MGuzewska/Init. by: MG
HFD-810/JSimmons

Review completed: 12/05/00

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

NDA#: 21-001

CHEMISTRY REVIEW: # 3 **DATE REVIEWED:** 29-MAR-2001

Submission Type	Document Date	CDER Stamp Date	Assig ed Date
Review #1			
ORIGINAL	17-DEC-1999	20-DEC-1999	03-JAN-2000
Amendment (NC)	25-JAN-2000	27-JAN-2000	27-JAN-2000
Amendment (BC)	10-MAY-2000	11-MAY-2000	15-MAY-2000
Review #2			
Amendment (BC)	30-JUN-2000	03-JUL-2000	03-JUL-2000
Amendment (BC)	26-JUL-2000	27-JUL-2000	31-JUL-2000
Amendment (BC)	25-AUG-2000	28-AUG-2000	06-SEP-2000
Amendment (BC)	29-AUG-2000	30-AUG-2000	08-SEP-2000
Current Review (#3)			
Amendment (BZ)	23-JAN-2001	24-JAN-2001	24-JAN-2001
Amendment (AZ)	06-MAR-2001	07-MAR-2001	06-MAR-2001
Amendment (BC)	13-MAR-2001	14-MAR-2001	14-MAR-2001

NAME AND ADDRESS OF APPLICANT: Pharmacia and Upjohn Company
7000 Portage Road
Kalamazoo, Michigan 49001

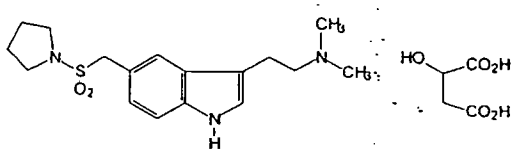
DRUG PRODUCT NAME:
Proprietary: AXERT™
Nonproprietary/Established/USAN: almotriptan malate
Code Name/#: PNU-180638E (also LAS 31416, T046, LAS W-322)
Chem. Type/Therapeutic Class: 1 S

DESI/PATENT STATUS: Almotriptan malate is claimed in U.S. Patent 5,565,447 (exp. 27-MAR-2014).

PHARMACOLOGICAL CATEGORY / INDICATION: Migraine
DOSAGE FORM: Tablet
STRENGTH(S): 6.25 mg and 12.5 mg
ROUTE OF ADMINISTRATION: Oral
DISPENSED: XX Rx ___ OTC
SPECIAL PRODUCTS: No

CHEMICAL NAME, STRUCTURAL FORMULA AND MOLECULAR FORMULA:

1-[[[3-(2-(dimethylamino)ethyl]-1H-indol-5-yl]-methyl]sulfonyl]pyrrolidine (±)-hydroxybutanedioate (1:1)



CAS No.: 181183-52-8

Mol. Formula: $C_{17}H_{25}N_3O_2S \cdot C_4H_6O_5$

Mol. Weight: 469.56 (salt), 335.47 (base)

SUPPORTING DOCUMENTS:

[redacted]

RELATED DOCUMENTS: [redacted]

CONSULTS:

Proposed tradename "Axert" was consulted to OPDRA by Ms. Chen (Project Manager). Tradename is acceptable pending final OPDRA review at time of approval.

REMARKS / COMMENTS:

NDA was previously considered deficient for drug substance manufacturing, drug substance specification, drug product specification, drug product packaging, stability (expiration dating), and labeling. Two submissions, dated 23-JAN-2001 and 06-MAR-2001, constitute a complete response to all CMC concerns conveyed in 20-DEC-2000 Approvable (AE) letter. The third amendment provides Spanish version of analytical procedures for the drug product as a follow-up to English translations that were submitted in 06-MAR-2001 amendment. The sponsor has corrected all outstanding deficiencies in the application. [Refer to review notes.]

Revised methods validation (MV) package was included in 06-MAR-2001 amendment. MV assignments were forwarded to field laboratories on 28-MAR-2001.

Dissolution specification proposed by firm, i.e., [redacted](Q), is acceptable to Biopharmaceutics reviewer.

Proposed expiration dating period of 24 months is acceptable based on additional stability data provided in 23-JAN-2001 amendment.

Establishment inspections are complete and a satisfactory overall recommendation was received on 17-OCT-2000. [EER detail report is appended to this review.]

CONCLUSIONS AND RECOMMENDATIONS:

Approval of NDA 21-001 is recommended. Standard paragraph regarding completion of methods validation should be included in action letter.

Martha R. Heimann, Ph.D., Review Chemist

cc: Orig. NDA 21-001
HFD-120/Division File
HFD-120/MHeimann
HFD-120/LChen
HFD-120/MGuzewska/Init. by: MG
HFD-810/JSimmons

Review completed: 03/29/01