CENTER FOR DRUG EVALUATION AND RESEARCH

Application Number 21-231

CHEMISTRY REVIEW(S)

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

NDA #: 21-231

CHEMISTRY REVIEW: # 2

DATE REVIEWED: 7-FEB-2001

SUBMISSION TYPE	DOCUMENT DATE	CDER STAMP DATE	ASSIGNED DATE
N(BC)	19-JAN-2001	19-JAN-2001	23-JAN-2001
N(BC) (MV package)	02-FEB-2001	02-FEB-2001	05-FEB-2001

NAME AND ADDRESS OF APPLICANT: IPR Pharmaceuticals, Inc.
Attention: Judy Firor
US Agent—AstraZeneca Pharmaceuticals LP
1800 Concord Pike, P. O. Box 8355
Wilmington, DE 19803-8355

DRUG PRODUCT NAME:
Proprietary: **Zomig ZMT**
Nonproprietary/Established/USAN: zolmitriptan
Code Name/#: 311C90
Chem. Type/Therapeutic Class: **3 S**

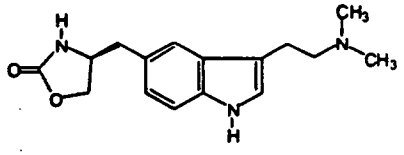
DESI/PATENT STATUS:

US Patent No. 5,466,699, expiration date November 14, 2012, covers compound per se, method of use and various formulations. Sponsor claims a three-year period of exclusivity for zolmitriptan orally disintegrating tablets under 21 CFR § 314.108(b)(4).

PHARMACOLOGICAL CATEGORY / INDICATION: [redacted]
DOSAGE FORM: Orally Disintegrating Tablet
STRENGTH(S): 2.5 mg
ROUTE OF ADMINISTRATION:
DISPENSED: XX Rx ___ OTC
SPECIAL PRODUCTS: No

CHEMICAL NAME, STRUCTURAL FORMULA AND MOLECULAR FORMULA:

(*S*)-4-{[3-[2-(Dimethylamino)ethyl]- 1*H*-indol-5-yl]methyl}-oxazolidinone



CAS No.: 139264-17-8

Mol. Formula: $C_{16}H_{21}N_3O_2$ Mol. Weight: 287.36

SUPPORTING DOCUMENTS:

Approved NDA #20-768 (Zomig® Tablets) is incorporated by reference for documentation of the characterization, manufacture and control of zolmitriptan bulk drug substance.

Type III DMFs referenced for packaging components [redacted]. Both files are adequate to support this NDA. [Refer to Section B.7 of MRH review #1, completed 13-DEC-2000.]

RELATED DOCUMENTS:

IND 45,147 (zolmitriptan tablets), IND 55,960 (zolmitriptan orally disintegrating tablets) [redacted]

CONSULTS:

No consults were initiated by Chemistry. Tradename consults to OPDRA, etc. were done by the Project Manager, Ms. Chen. The clinical division has not made a final decision regarding acceptability of the proposed tradename.

REMARKS / COMMENTS:

Zolmitriptan is currently marketed for treatment of migraine as a conventional immediate release formulation (Zomig® Tablets) under NDA 20-768. The orally disintegrating tablet is proposed as a convenience dosage form for patients who have difficulty in swallowing tablets during a migraine attack.

The 19-JAN-2001 amendment responds to deficiencies that were communicated in 13-DEC-2000 information request letter. The sponsor has provided adequate response to those deficiencies. [Refer to attached review notes.]

The proposed dissolution specification is acceptable to OCPB (Biopharmaceutics).

Establishment inspections are complete and an overall acceptable compliance recommendation was received on 10-AUG-2000. [EER is attached to MRH review #1.]

The 02-FEB-2001 amendment provides a revised method validation section. Validation assignments to FDA laboratories initiated on 07-FEB-2001.

CONCLUSIONS AND RECOMMENDATIONS:

Approval is recommended. Standard paragraph regarding cooperation with methods validation should be included in action letter.

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

cc: Orig. NDA 21-231
HFD-120/Division File
HFD-120/MHeimann
HFD-120/LChen
HFD-120/MGuzewska/Init.by: MG
HFD-810/JSimmons

Filename: D:\WORD\#NDA\N21-231\N21231_002.DOC

/s/

Martha Heimann
2/7/01 11:06:30 AM
CHEMIST

Maryla Guzewska
2/8/01 07:11:29 AM
CHEMIST

APPEARS THIS WAY
ON ORIGINAL

THIS SECTION WAS DETERMINED **NOT** TO BE RELEASABLE

5 pages

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

NDA #: 21-231

CHEMISTRY REVIEW: # 1

DATE REVIEWED: 12-DEC-2000

SUBMISSION TYPE	DOCUMENT DATE	CDER STAMP DATE	ASSIGNED DATE
ORIGINAL	14-APR-2000	14-APR-2000	09-MAY-2000
N(BC)	26-MAY-2000	31-MAY-2000	31-MAY-2000

NAME AND ADDRESS OF APPLICANT: IPR Pharmaceuticals, Inc.
Attention: Judy W. Firor
US Agent—AstraZeneca Pharmaceuticals LP
1800 Concord Pike, P. O. Box 8355
Wilmington, DE 19803-8355

DRUG PRODUCT NAME:
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Nonproprietary/Established/USAN: zolmitriptan
Code Name/#: 311C90
Chem. Type/Therapeutic Class: 3 S

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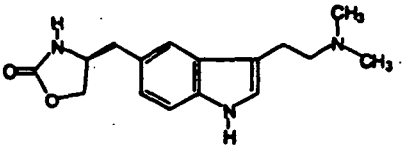

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REMARKS / COMMENTS:

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[redacted] is deficient for drug product manufacture and controls, product specification, and labeling. Methods validation was not initiated pending resolution of deficiencies in product specification and analytical procedures. Establishment inspections are complete and an overall acceptable compliance recommendation was received on 10-AUG-2000. [EER attached.]

CONCLUSIONS AND RECOMMENDATIONS:

Information Request letter to sponsor. Refer to deficiencies in Section H (pp. 19-20).

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

cc: Orig. NDA 21-231
HFD-120/Division File
HFD-120/MHeimann
HFD-120/LChen
HFD-120/MGuzewska/Init.by: MG
HFD-810/JSimmons

Filename: D:\WORD\#NDA\N21-231\N21231_001.DOC

/s/

Martha Heimann
12/12/00 04:57:13 PM
CHEMIST

Maryla Guzewska
12/13/00 07:37:13 AM
CHEMIST

APPEARS THIS WAY
ON ORIGINAL

THIS SECTION WAS DETERMINED **NOT** TO BE RELEASABLE

18 pages

B

ESTABLISHMENT EVALUATION REQUEST SUMMARY REPORT

Application: NDA 21231/000
Priority: S
Org Code: 120
Stamp: 14-APR-2000 Regulatory Due: 14-FEB-2001
Action Goal:
District Goal: 16-DEC-2000
Applicant: ASTRAZENECA PHARMS
1800 CONCORD PIKE
WILMINGTON, DE 198038355
Brand Name:
Established Name:
Generic Name: ZOLMITRIPTAN
Dosage Form: TAB (TABLET)
Strength: 2.5 MG

FDA Contacts:
L. CHEN (HFD-120) 301-594-5529 , Project Manager
M. HEIMANN (HFD-120) 301-594-2850 , Review Chemist
M. GUZEWSKA (HFD-120) 301-594-5571 , Team Leader

Overall Recommendation:

ACCEPTABLE on 10-AUG-2000 by J. D AMBROGIO (HFD-324) 301-827-0062

Establishment: 2133545
CIMA LABORATORIES INC
1000 VALLEY VIEW ROAD
EDEN PRARIE, MN 55344
DMF No:
AADA No:

Profile: TCM OAI Status: NONE
Last Milestone: OC RECOMMENDATION
Milestone Date 10-AUG-2000
Decision: ACCEPTABLE
Reason: DISTRICT RECOMMENDATION
Responsibilities: FINISHED DOSAGE MANUFACTURER

Establishment:
DMF No:
AADA No:

Profile: CTL OAI Status: NONE
Last Milestone: OC RECOMMENDATION
Milestone Date 24-JUL-2000
Decision: ACCEPTABLE
Reason: BASED ON PROFILE
Responsibilities:

Establishment:
DMF No:
AADA No:

Profile: CRU OAI Status: NONE
Last Milestone: OC RECOMMENDATION
Milestone Date 30-MAY-2000
Responsibilities:

ESTABLISHMENT EVALUATION REQUEST SUMMARY REPORT

Decision: **ACCEPTABLE**
Reason: **BASED ON PROFILE**

Establishment: **2650183**
IPR PHARMACEUTICALS INC
STATE ROAD 53 KM 84
GUAYAMA, PR 00784

DMF No:
AADA No:

Profile: **CSN** OAI Status: **NONE**
Last Milestone: **OC RECOMMENDATION**
Milestone Date **02-JUN-2000**
Decision: **ACCEPTABLE**
Reason: **DISTRICT RECOMMENDATION**

Responsibilities: **DRUG SUBSTANCE MANUFACTURER**

Establishment: **2517100**
ZENECA PHAMACEUTICALS
587 OLD BALTIMORE PIKE
NEWARK, DE 19702

DMF No:
AADA No:

Profile: **TCM** OAI Status: **NONE**
Last Milestone: **OC RECOMMENDATION**
Milestone Date **31-MAY-2000**
Decision: **ACCEPTABLE**
Reason: **BASED ON PROFILE**

Responsibilities: **FINISHED DOSAGE PACKAGER**

APPEARS THIS WAY
ON ORIGINAL