CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-450

CHEMISTRY REVIEW(S)

CHEMISTRY REVIEW

NDA 21-450

Zomig® (zolmitriptan) Nasal Spray

AstraZeneca Pharmaceuticals LP as U.S. agent for:
IPR Pharmaceuticals

Martha R. Heimann, Ph.D.
Division of Neuropharmacological Drug Products

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Chemistry Review Data Sheet

1. **NDA #: 21-450**

2. **REVIEW #:** 1

3. **REVIEW DATE:** 09-DEC-2002

4. **REVIEWER:** Martha R. Heimann, Ph.D.

5. **PREVIOUS DOCUMENTS:**(This is review #1.)

6. **SUBMISSION(S) BEING REVIEWED:**

Submission(s) Reviewed	Document Date
Original NDA	06-MAR-2002
CMC Update	27-JUN-2002
Revised Package Insert	22-NOV-2002

7. **NAME and ADDRESS OF APPLICANT:**

Name:	IPR Pharmaceuticals, Inc
Address:	P.O. Box 1967 Carolina, PR 00984-1967
Representative:	Kevin McKenna, Executive Director-Regulatory Affairs AstraZeneca Pharmaceuticals LP 1800 Concord Pike, P.O. Box 8355
Telephone:	(302)886-2742

8. **DRUG PRODUCT NAME/CODE/TYPE:**

a) Proprietary Name: Zomig®
b) Non-Proprietary Name (USAN): zolmitriptan
c) Code Name/#: 311C90
d) Chem. Type/Submission Priority:
- Chem. Type: 3
- Submission Priority: S

9. LEGAL BASIS FOR SUBMISSION: N/A

10. PHARMACOLOGICAL CATEGORY:

Zolmitriptan is a selective 5-hydroxytryptamine IB/ID (5-$H_{T1B/1D}$) receptor agonist intended for the acute treatment of migraine.

11. DOSAGE FORM: Nasal Spray

12. STRENGTH/POTENCY: ——— 5 mg per single dose unit

13. ROUTE OF ADMINISTRATION: Nasal

14. Rx/OTC DISPENSED: _X_ **Rx** ___ **OTC**

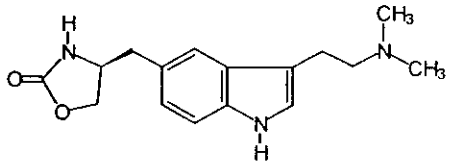
15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):

_____SPOTS product – Form Completed

__X__Not a SPOTS product

16. CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:

Structural Formula:



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

Molecular Formula: $C_{16}H_{21}N_3O_2$

Molecular Weight: 287.36

APPEARS THIS WAY
ON ORIGINAL

17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE [1]	STATUS [2]	DATE REVIEW COMPLETED	COMMENTS
[redacted]	3			3	Adequate	22-APR-2002 by Y. Yang	--
[redacted]	3			3	Adequate	16-FEB-2000 by L. Zhou	--
[redacted]	3			4	N/A	--	--

[1] Action codes for DMF Table:
1 – DMF Reviewed.
Other codes indicate why the DMF was not reviewed, as follows:
2 –Type 1 DMF
3 – Reviewed previously and no revision since last review
4 – Sufficient information in application
5 – Authority to reference not granted
6 – DMF not available
7 – Other (explain under "Comments")

[2] Adequate, Inadequate, or N/A (There is enough data in the application, therefore the DMF did not need to be reviewed)

B. Other Documents:

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
Zomig immediate release tablets	N20-768	Cross-referenced for drug substance CMC information
zolmitriptan tablet IND	I 45,147	
zolmitriptan NS IND	I53,848	

18. STATUS:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Biometrics	N/A	N/A	N/A
EES	Acceptable	19-NOV-2002	N/A
Pharm/Tox	---	Not completed [1]	L. Fossum
Biopharm	Not Approvable	07-NOV-2002, 02-DEC-2002	A. Jackson
Methods Validation	N/A	N/A	N/A
OPASS	N/A	N/A	N/A
EA	N/A	N/A	N/A
Microbiology	Approvable	17-JUN-2002	N. Sweeney

[1] Pharm/Tox issues related to qualification of degradants and specification limits were discussed with Dr. Fossum

The Chemistry Review for NDA 21-450

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

Approval of NDA 21-450 is recommended from a CMC perspective.

B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable

No Phase 4 commitments or risk management steps are indicated from a CMC perspective.

II. Summary of Chemistry Assessments

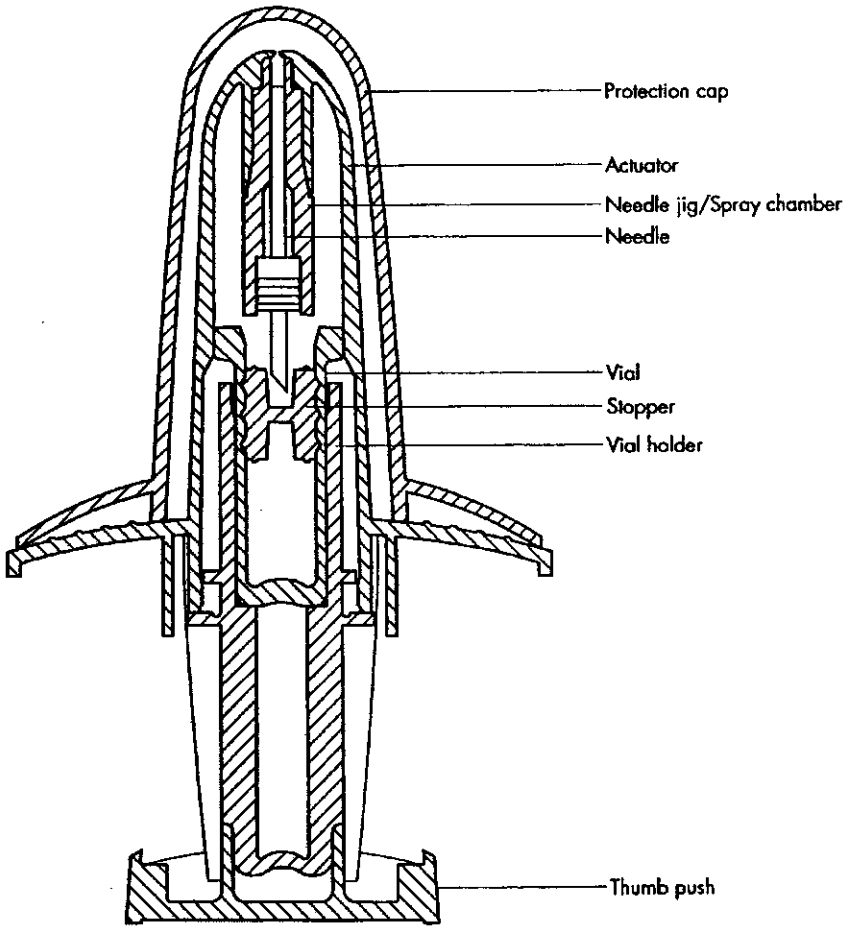
A. Description of the Drug Product(s) and Drug Substance

Zomig® NS (zolmitriptan) Nasal Spray will be marketed for acute treatment of migraine headache as a unit dose nasal spray device which will deliver [redacted] 5 mg of zolmitriptan in a 100 µL (0.1 mL), non-preserved aqueous solution. The product is not labeled as sterile. The nasal spray solution also contains citric acid and dibasic sodium phosphate. The solution is contained in a Type I clear glass vial with rubber stopper, which is then assembled into the nasal spray device.

The drug is administered used by removing the protective cap, placing the actuator into the nostril and pressing the thumb push, which breaks the break ring and actuates the device. Upon actuation, the rubber stopper is pierced and forced downward by the needle jig. The contents of the vial are forced up through the needle and out of the nozzle via the spray chamber. Refer to the figure on the following page for a cross-section view of the device. Spray characteristics (geometry and droplet size distribution) are determined by the size and shape of the spray chamber, the size of the needle orifice and actuation force.

Executive Summary Section

Cross Section View of Zomig NS Unit Dose Nasal Spray Device



The active ingredient of Zomig® NS, zolmitriptan, is currently marketed as Zomig Tablets (immediate release) under NDA 20-768 and Zomig ZMT (orally disintegrating tablets) under NDA 21-231. NDA 20-768 is cross-referenced for information regarding manufacture, characterization and control of the bulk drug substance.

Zolmitriptan ——— MW is 287.36). It is a basic compound ——— and solubility increases as solution pH decreases. In solution, the drug substance susceptible to both hydrolytic and oxidative degradation, especially at pH equal to or greater than——. Physical and chemical parameters critical to the nasal spray formulation include solubility in aqueous solutions and stability in solution. Intranasal delivery of the highest dose, 5 mg, in a suitable volume requires drug solubility greater than . ——— Use of as citric acid/ dibasic sodium phosphate based buffer system is necessary to achieve the required solubility while maintaining a solution pH (5) similar to that of human nasal mucosa. This target pH minimizes, but does not eliminate, product degradation.

Although the product is not labeled as [redacted] to ensure absence of microorganisms at time of manufacture. Based on process development studies, a number of parameters have been identified as critical to ensuring product quality. [redacted] Additional process parameters identified as critical include solution pH during compounding and vial fill weights.

The proposed commercial product and process differs from the product used in the single efficacy study (311CIL/0077) in two respects. [redacted] Additionally, although the internal mechanism of the proposed commercial nasal spray device is identical to the clinical study device, an external 'break ring" is incorporated into the commercial device. The sponsor has provided comparative *in-vitro* data in support bio-waiver request. The Office of Clinical Pharmacology and Biopharmaceutics (OCPB) reviewer, A. Jackson indicates in his review that a number of device equivalence criteria were not met.

B. Description of How the Drug Product is Intended to be Used

The product will be marketed in cartons containing six 5 mg unit dose devices. [redacted]

The recommended doses are [redacted] 5 mg administered intranasally [redacted] .. If the headache returns, the dose may be repeated after 2 hours. Total dose should not exceed 10 mg over 24 hours.

Based on stability data provided in the application, an expiration dating period of 24 months, when stored at controlled room temperature (20 - 25°C) is established for the 5 mg, [redacted]

C. Basis for Approvability or Not-Approval Recommendation

From a CMC perspective, the sponsor has provided adequate documentation of the composition of the proposed drug products, control of ingredients, the manufacturing process, control of critical manufacturing steps and control of the finished product. Dr. Sweeney's review of the microbiology controls did not identify any deficiencies that would affect approvability of the NDA. Adequate validation data to support the proposed regulatory methods was provided. Stability data are adequate to support the proposed expiry periods. Establishment inspections have been completed and an overall acceptable compliance recommendation was received. [Refer to Attachment 3.]

Although it does not affect the approvability of the current application, an error was noted in the drug substance specification, which was approved under NDA 20-768. The comment on page 60 of this review should be relayed to the sponsor.

III. Administrative

A. Reviewer's Signature

See electronic signatures in Division File System (DFS).

B. Endorsement Block

See electronic signatures in DFS.

C. CC Block

See DFS.

53 Page(s) Withheld

✓ § 552(b)(4) Trade Secret / Confidential

_____ § 552(b)(5) Deliberative Process

_____ § 552(b)(5) Draft Labeling