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APPLICATION NUMBER:

21-450

PHARMACOLOGY REVIEW

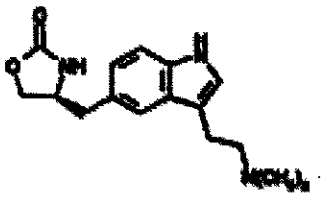
PHARMACOLOGY/TOXICOLOGY COVER SHEET

NDA 21-450.
Review number:
Sequence number/date/type of submission: N-000 / stamp date 2-27-02 / New Drug Application, Original.
Information to sponsor: Yes () No (X).
Sponsor and/or agent: IPR Pharmaceuticals Inc., Carolina, Puerto Rico; Authorized US Agent: AstraZeneca Pharmaceuticals LP, 1800 Concord Pike, Wilmington, DE 19803.
Manufacturer for drug substance: same as for already marketed oral products.

Reviewer name: Linda H. Fossom, Ph.D.
Division name: Neuropharmacological Drug Products.
HFD #: 120.
Review completion date: 12/18/02.

Drug:

Trade name: Zomig Nasal Spray.
Generic name (list alphabetically): zolmitriptan.
Code names: 311C90 (Wellcome); ZD8250 (AstraZeneca).
Chemical name: 2-Oxazolidinone, 4-((3-(2-(dimethylamino)ethyl)-1H-indol-5-yl)methyl)-, (S)-.
CAS registry number: 139264-17-8.
Mole file number: unknown.
Molecular formula/molecular weight: C_{16}-H_{21}-N_3-O_2; 28′/—g/mol.
Structure:



Relevant INDs/NDAs/DMFs: NDA 20-768 (2.5 and 5 mg oral tablets for acute treatment of migraine attacks with or without aura; approved 11-25-97); NDA 21-231 (orally disintegrating tablets; approved 2-13-01); IND 45,147 (tablets); IND 53,8848 (nasal spray); IND 55,960 (fast-melt tablets).

Drug class: Agonist at serotonin receptor subtypes 5-HT1B/D.

Indication: Acute treatment of migraine with or without aura in adults.

Clinical formulation: aqueous solution, buffered to pH 5 using citrate phosphate buffer; preservative-free. Provided as a unit dose nasal spray, designed to deliver —— r 5 mg zolmitriptan in a dose volume of 100 µl, to the nasal cavity.

Route of administration: intranasal, as spray.

Disclaimer: Tabular and graphical information is excerpted directly from Sponsor's submission where ever feasible and noted as such.

Executive Summary

I. RECOMMENDATIONS

A. Recommendation on Approvability:

Approval.

B. Recommendation for Nonclinical Studies:

No additional pharmacology/toxicology studies are recommended.

C. Recommendations on Labeling:

[These labeling recommendations are compared with the Sponsor's proposed labeling and justified in the body of this review.]

CLINICAL PHARMACOLOGY/Mechanism of Action: Accept Sponsor's labeling, which is the same as the existing labeling for oral formulations.

Clinical Phamacokinetics and Bioavailability/Metabolism: [redacted]

WARNINGS/Local Adverse Reactions: [redacted]

PRECAUTIONS/Binding to Melanin-containing Tissues: Accept Sponsor's labeling including insertion of lack of effect on retina in intranasal animal studies; existing labeling for oral formulations includes this information for oral animal studies.

Carcinogenesis, Mutagenesis, Impairment of Fertility/ Carcinogenesis: [redacted]

Carcinogenesis, Mutagenesis, Impairment of Fertility/ Mutagenesis: [redacted]

Mutagenesis: Zolmitriptan was mutagenic in an Ames test, in 2 of 5 strains of S. typhimurium tested, in the presence of, but not in the absence of, metabolic activation. It was not mutagenic in an *in vitro* mammalian gene cell mutation (CHO/HGPRT) assay. Zolmitriptan was clastogenic in an *in vitro* human lymphocyte assay both in the absence of and the presence of metabolic activation. Zolmitriptan was not clastogenic in *in vivo* mouse and rat micronucleus assays. Zolmitriptan was not genotoxic in an unscheduled DNA synthesis study.

Carcinogenesis, Mutagenesis, Impairment of Fertility/ Impairment of Fertility: Accept Sponsor's labeling, which is the same as the existing labeling for the oral formulations.

Pregnancy: Pregnancy Category C: Recommended labeling (existing labeling for oral formulations) below:

Pregnancy: Pregnancy Category C: There are no adequate and well controlled studies in pregnant women; therefore, zolmitriptan should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

In reproductive toxicity studies in rats and rabbits, oral administration of zolmitriptan to pregnant animals was associated with embryolethality and fetal abnormalities. When pregnant rats were administered oral zolmitriptan during the period of organogenesis at doses of 100, 400, and 1,200 mg/kg/day, there was a dose-related increase in embryolethality which became statistically significant at the high dose. The maternal plasma exposures at these doses were approximately 280, 1,100, and 5,000 times the exposure in humans receiving the maximum recommended total daily dose of 10 mg. The high dose was maternally toxic, as evidenced by a decreased maternal body weight gain during gestation. In a similar study in rabbits, embryolethality was increased at the maternally toxic doses of 10 and 30 mg/kg/day (maternal plasma exposures equivalent to 11 and 42 times exposure in humans receiving the maximum recommended total daily dose of 10 mg), and increased incidences of fetal malformations (fused sternebrae, rib anomalies) and variations (major blood vessel variations, irregular ossification pattern of ribs) were observed at 30 mg/kg/day. Three mg/kg/day was a no effect dose (equivalent to human exposure at a dose of 10 mg). When female rats were given zolmitriptan during gestation, parturition, and lactation, an increased incidence of hydronephrosis was found in the offspring at the maternally toxic dose of 400 mg/kg/day (1,100 times human exposure).

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