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APPLICATION NUMBER:

21-450

STATISTICAL REVIEW(S)

STATISTICAL REVIEW AND EVALUATION

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

MEDICAL DIVISION: Neuropharmacological Drug Products (HFD-120)
BIOMETRICS DIVISION: Division of Biometrics I (HFD-710)

NDA NUMBER: NDA 21-450

DRUG NAME: Zomig (zolmitriptan) Nasal Spray

INDICATION: Treatment of migraine with/without aura in adults

SPONSOR: AstraZeneca Pharmaceuticals LP

DOCUMENTS REVIEWED: Cover letter and documents (CDER REC'D Dates: 27-Mar-2003, 17-Apr-2003 and 25-Apr-2003) including SAS data base

STATISTICAL KEY WORDS: χ^2-test, logistic regression, odds ratio, Bonferroni adjustment, spending function, interim analysis

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Table of Contents

STATISTICAL REVIEW AND EVALUATION

1 Executive Summary of Statistical Findings

1.1 Recommendations and Conclusions

Based on the collective evidences and findings, in this statistical reviewer's opinion the interim data and results of study 311CUS/0022 support the sponsor's efficacy claim of ZOMIG® (zolmitriptan) 5 mg nasal with respect to the headache response endpoint for the adult patients with migraine, using first attack analysis. The data and results of the study show that the primary endpoint, 2 hour headache response, is statistically significantly improved in the treatment arm to the placebo arm for the intention-to-treat (ITT) population (p-value=0.0006).

There was no statistically significant differences demonstrated for Zolmitriptan Nasal Spray dose of 5.0 mg to placebo in the secondary variable of nausea at 2 hours post dose. There was statistically significant differences demonstrated for Zolmitriptan Nasal Spray doses of 5.0 mg to placebo in the secondary variable of photophobia at 2 hours post-dose. There was no evidence to demonstrate the statistically significant difference for Zolmitriptan Nasal Spray dose of 0.5 mg to placebo in phonophobia at 2 hours post-dose.

Those results are consistent with the original NDA submission of Zolmitriptan Nasal Spray. We therefore recommend Approval for the treatment of adult patients with migraine.

1.2 Brief Overview of Clinical Studies

The zolmitriptan nasal spray NDA 21-450 was submitted on February 27, 2002. In the action letter dated December 19, 2002, FDA classified the submission as 'approvable'. Additional information was requested from AstraZeneca to address concerns regarding the clinical efficacy of the commercial zolmitriptan nasal spray device. At a teleconference (February 11, 2003), FDA agreed that the provision of efficacy data from an ongoing, placebo-controlled clinical trial using the commercial zolmitriptan nasal spray device (311CUS/0022) was an acceptable approach.

This interim analysis consists of results from a subset of the Study 311CUS/0022 in 210 adult patients who treated the first headache attack with study medication and provided efficacy assessments. This sample size provided adequate power (for 2-hour headache response) to show superiority over placebo and confirm the clinical efficacy of the zolmitriptan 5-mg commercial nasal spray device.

The primary objective for this interim analysis is to evaluate the efficacy (as assessed by the 2 hour headache response) of zolmitriptan 5-mg nasal spray compared to placebo in the acute treatment of adult patients with migraine, using

first attack analysis. The primary endpoint is the 2-hour headache response of the first treated attack.

The sponsor planned an adjustment for Type I error for both the interim and final full studies. The alpha spending function methodology based on Hwang, Shih, and deCani (1990) γ-family approach was used to control the overall two-sided type I error rate at 5% for both the interim and final analyses. The 2-sided significance boundaries for the p-values were calculated and pre-specified to be 0.0027 and 0.0479 (based on $\gamma = -2$ and information fraction of t=15%) for the interim and the final analyses, respectively. That is, the statistical significance of the analysis results for the primary efficacy parameter of 2-hour headache response was tested against significance level of 0.0027 for the interim and 0.0479 for the final analyses, respectively.

The first 210 adult men and women who treated the first migraine attack with study medication, and who had an established diagnosis of migraine headache, with or without aura, as defined by IHS criteria were included in this analysis. This sample size provided approximately 90% power of showing a difference (at 0.27% two-sided level of significance) in headache response rate between the zolmitriptan 5-mg nasal spray dose and placebo at 2 hours after treatment. Calculations were based on the assumption that the headache response rate at 2 hours would be 39% for placebo and 69% for zolmitriptan 5-mg nasal spray.

Reviewer's Comments:

This statistical reviewer used EaSt 2000 statistical software to verify α adjustment for the interim and final analyses and summarized the results in Table 1. The calculation was based on the overall significance level = 0.05, power = 90%, proportion response of control = 6%, and proportion response of treatment = 11% which were used by the sponsor for sample size determination of the full study.

Table 1. α Adjustment for Interim and Final Analyses — FDA Analysis

Boundary to Reject H_0 (Δ)	Maximum Subjects (n)	For Interim Analysis (α)	For Final Analysis (α)
0.0	1307	0.0000	0.0500
0.1	1316	0.0000	0.0500
0.2	1331	0.0003	0.0498
0.3	1354	0.0014	0.0489
0.4	1386	0.0055	0.0454
0.5	1427	0.0144	0.0374

This statistical reviewer has the following comments.

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