CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-450

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

CLINICAL PHARMACOLOGY/BIOPHARMACEUTICS REVIEW

DRUG: Zomig ® (Zolmitriptan)
NDA: 21-450
FORMULATION: Nasal Spray
APPLICANT: Astra Zeneca

PRIMARY REVIEWER: Andre Jackson
TYPE: NDA Amendment
STRENGTH: **0.5** , 2.5 , 5.0 mg
SUBMISSION DATE: Nov 11, 2002

INDICATION: **Migraine Headache**
Generic Name: Zolmitriptan

STUDY AMENDMENT

The firm has submitted an amendment to their NDA 21-450 to address deficiencies in the in vitro data for their [redacted] 5.0 mg nasal sprays. There was no new data in the submission only the firm's re-interpretation of the previously submitted data.

The major points made were:

1. The firm takes exception to the particle size distribution data at the [redacted]. They state that [redacted] is the industry standard. At the present time this can not be confirmed. Literature for the [redacted] pump used in their studies recommend standard operating procedures for testing droplet size distribution (DSD) by [redacted] when using the [redacted] (the most common brand, at least in the US). [redacted] (for a unit dose system, and for two multidose pumps) [redacted] The problem is that the firm did not use an [redacted] so it is difficult to validate their argument.

2. The firm also contends that differences in span measurements would not effect the delivery of the spray since they maintain a routine specification that not more than [redacted] of droplets below [redacted] are contained in the product.

[redacted]

3. The firm also argues that plume geometry and spray pattern are also not meaningful since the limited volume of the nasal cavity does not allow the plume to fully develop. This may also be true, but spray pattern and plume geometry analysis are current in vitro requirements for nasal sprays.

Therefore the arguments presented by the firm provide no compelling new evidence to support the in vitro equivalence of the commercial device to the clinical device.

Andre Jackson

RD/FT Initialed by Raman Baweja, Ph.D.

CcNDA 21450, HFD-120, HFD-860(Jackson,Baweja,Mehta), Central Documents Room (Biopharm-CDR)

APPEARS THIS WAY
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/s/

Andre Jackson
12/2/02 12:22:43 PM
BIOPHARMACEUTICS

Raman Baweja
12/2/02 02:31:12 PM
BIOPHARMACEUTICS

APPEARS THIS WAY
ON ORIGINAL

CLINICAL PHARMACOLOGY/BIOPHARMACEUTICS REVIEW

DRUG: Zomig ® (Zolmitriptan)
NDA: 21-450
FORMULATION: Nasal Spray
APPLICANT: Astra Zeneca

PRIMARY REVIEWER: Andre Jackson
TYPE: NDA Amendment
STRENGTH: ——— , 5.0 mg
SUBMISSION DATES: 2-27-02
9-26-02
10-9-02

INDICATION: Migraine Headache
Generic Name: Zolmitriptan

1.EXECUTIVE SUMMARY

The firm conducted a double-blind placebo, double-dummy parallel group multi-center trial to compare the efficacy and two open-label safety studies with Zomig nasal spray in subjects with migraine headaches.

Zomig nasal spray is a unit dose system designed to deliver zolmitriptan to the nasal cavity.

The sponsor changed the outer body of the clinical trial nasal spray device used to deliver zolmitriptan to the nasal cavity. These changes included a safety feature to prevent removal of the filled vial and a thumb push was added to ease firing. The bioequivalence of the clinical device and commercial device will be determined based upon in vitro performance of these two devices.

This Clinical Pharmacology/Biopharmaceutics review will evaluate whether the applicant has adequately demonstrated in vitro that the commercial device is bioequivalent to the clinical device.

In vitro product performance data was determined based upon the following in vitro tests:
1.Dose or spray content uniformity
2.Droplet size distribution, ———
3.Particle size distribution
4.Drug and aggregate particle size density
5.Spray pattern(Dmax, Dmin, Ovality)
6.Plume geometry

Bioequivalence was based upon the ratio of geometric means (Test/Reference) being within the interval of ——— The following in vitro tests had ratios for geometric means that exceeded the limits of ——— These were:

Test	Dose Size
Median Diameter	0.5 mg droplet size
Median Diameter	2.5 mg droplet size
Span	0.5 mg droplet size
Span	2.5 mg droplet size
Dmin	0.5 mg spray pattern
Dmax	0.5 mg spray pattern
Plume Geometry-Length	5.0 mg

Plume Geometry-Spray Angle 5.0 mg

Based upon these findings the Office of Clinical Pharmacology and Biopharmaceutics (OCPB) recommends that the clinical and commercial devices are deemed not to be bioequivalent.

1.1 Recommendation: The in vitro product performance studies provided in this study amendment to the Division of Neuropharmacological Drug Products does not provide in vitro evidence supporting the bioequivalence of the to be marketed commercial nasal spray device to the clinical Zomig nasal spray device. This submission is not acceptable from the OCPB perspective.

Please see comments to the firm on pages 33 and 34 and forward these to the sponsor.

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