

**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 _____ 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 _____ . They state that _____ is the industry standard. At the present time this can not be confirmed. Literature for the _____ pump used in their studies recommend standard operating procedures for testing droplet size distribution (DSD) by _____ when using the _____ (the most common brand, at least in the US). _____ (for a unit dose system, and for two multidose pumps) _____ The problem is that the firm did not use an _____ 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 _____ of droplets below _____ are contained in the product.

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)

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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

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CLINICAL PHARMACOLOGY/BIPHARMACEUTICS 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:

<u>Test</u>	<u>Dose Size</u>
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

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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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2. Introduction and Background:

Zolmitriptan (ZOMIG®) is a selective 5-HT_{1B/1D} receptor agonist for the acute treatment of migraine. The efficacy and safety of the conventional oral tablet formulation of zolmitriptan has been demonstrated, and this formulation is indicated for the acute treatment of migraine with or without aura in adults (NDA 20-768, approved 25 November 1997). In addition, an orally disintegrating tablet (ZOMIG-ZMT®) has been developed, which dissolves rapidly in the mouth and is swallowed with the patient's saliva, obviating the need for access to water or other fluids (NDA 21-231, approved 13 February 2001).

The ongoing development of zolmitriptan has identified intranasal delivery as a clinically desirable additional method of drug administration for migraine sufferers. Drug absorption directly across the nasal mucosa allows rapid access into the systemic circulation, which would result in the intranasally absorbed proportion of a zolmitriptan dose initially avoiding the first-pass metabolism undergone by oral formulations of zolmitriptan. Consequently, compared to oral delivery, zolmitriptan nasal spray has the potential to provide faster onset of action and more rapid relief of migraine symptoms. Furthermore, intranasal administration offers effective delivery of zolmitriptan for patients affected by migraine-related gastric stasis, nausea or vomiting (any of which can limit or delay absorption of oral medication), and for patients with an aversion to swallowing tablets.

AstraZeneca has developed an alternative formulation, ZOMIG Nasal Spray, to provide a non-oral route of dosing that may be particularly useful in patients who experience nausea (a common symptom associated with migraine) or other difficulties with oral formulations. In addition, intranasal dosing offers the potential for rapid absorption of drug, and possibly faster onset of migraine relief, compared with oral dosing.

The clinical pharmacology of zolmitriptan after oral administration has been well characterized in the previous NDA submission for the conventional oral tablet formulation (NDA 20-768, approved 25 November 1997). Studies conducted for the nasal spray NDA were therefore complementary to previous studies with the oral tablet, and were designed to select an appropriate formulation of the nasal spray, define the absorption characteristics of zolmitriptan after intranasal dosing, and confirm the similarity of distribution, metabolism and elimination of zolmitriptan after oral and intranasal dosing. This document summarizes all available information on the pharmacokinetics of zolmitriptan nasal spray, and refers to relevant data on the pharmacokinetics of oral zolmitriptan. It was shown after the administration of single and multiple doses (0.5, 1, 2.5 and 5 mg) of the clinical intranasal formulation that the pharmacokinetics are dose proportional. A second study showed that zolmitriptan was primarily distributed to the nasopharynx region. A third study indicated that the absorption and distribution of zolmitriptan was identical after a single dose of either zolmitriptan 5 mg nasal spray 30 minutes after a single dose of intranasal xylometazoline (— weight/volume solution), or zolmitriptan 5 mg nasal spray alone. Together these data comprise the normal components of a new drug application (NDA).

Briefly, the pharmacokinetics, metabolism and elimination profiles of zolmitriptan when taken orally or intranasally are similar. This suggests that prescribing information relating to drug-drug interactions and drug-demographic interactions for ZOMIG oral tablet is equally relevant for ZOMIG Nasal Spray. The rapid intranasal absorption of zolmitriptan after intranasal administration indicates that ZOMIG Nasal Spray should have a faster onset of action with earlier relief of migraine symptoms than the ZOMIG oral tablet.

3.CURRENT SUBMISSION-

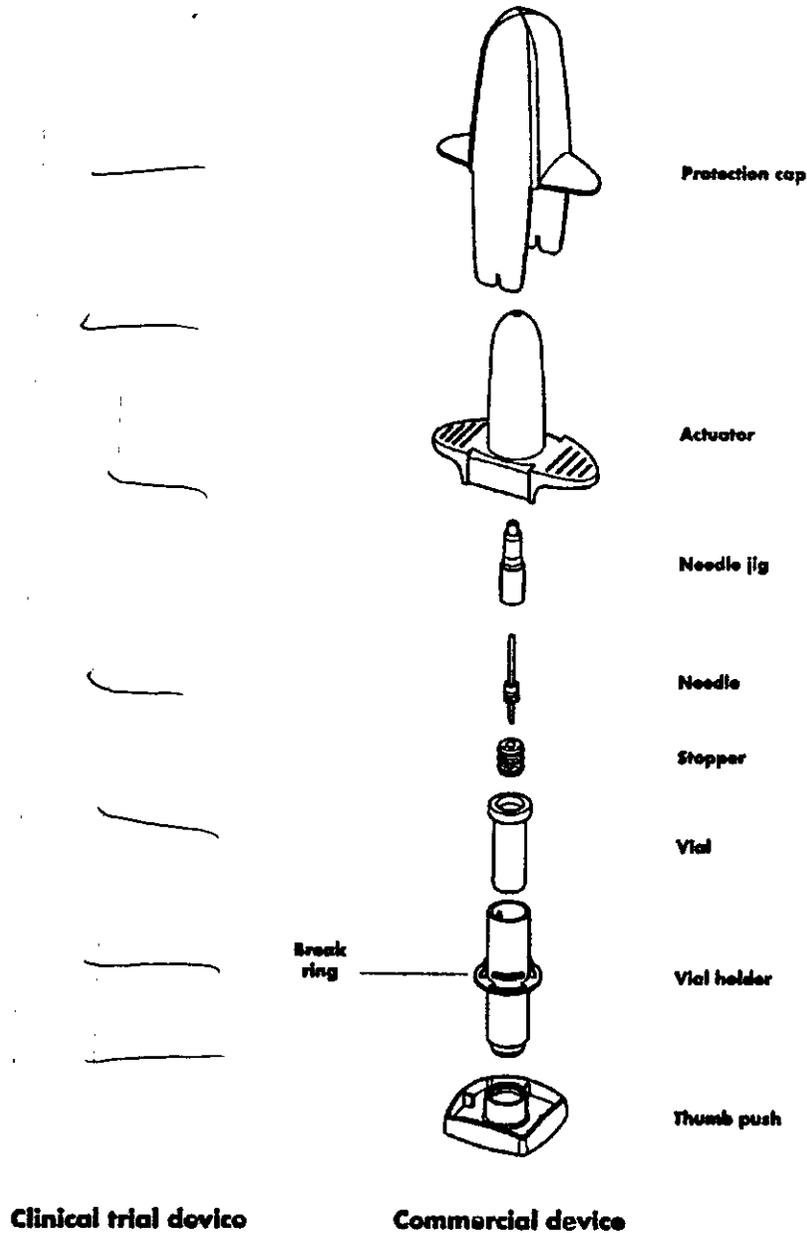
The objective of this study was to generate data to confirm the in vitro bioequivalence (BE) of ZOMIG Nasal Spray delivered via 2 nasal spray devices - the clinical trial device, used during the initial dose-finding efficacy study (Trial 311CIL/0077) for ZOMIG Nasal Spray, and the commercial device which is the device proposed for commercialization.

ZOMIG Nasal Spray is a unit dose system designed to deliver zolmitriptan to the nasal cavity. The device proposed for commercialization ('commercial' device) is comprised of a clear neutral USP Type I glass vial sealed with a ——— rubber stopper, assembled into a vial holder and an actuation device. The solution is contained within the glass vial. A protection cap is fitted over the device.

Both 'clinical trial' and 'commercial' devices are identical with respect to device firing mechanism and contact materials, however the appearance of the outer body of the 'commercial' device has been modified to incorporate a safety feature preventing removal of the filled vial. A thumb push has also been added to ease firing and the protection cap has been designed to prevent actuation of the device prior to patient use. An exploded diagram illustrating both devices is shown in Figure 1.

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Figure 1 Exploded view of clinical trial device and commercial device



In-vitro equivalence testing was performed according to the Center for Drug Evaluation and Research (CDER) document: Guidance for Industry, 'Bioavailability and Bioequivalence Studies for Nasal Aerosols and Nasal Sprays for Local Action', June 1999. ZOMIG Nasal Spray is a unit dose rather than a multi-dose system, and as such not all tests described in the guidance are

applicable. Testing on ZOMIG Nasal Spray 5 mg : _____
 _____ consistent with the CDER Draft Guidance, are described. _____
 [_____]

4. CLINICAL PHARMACOLOGY QUESTION BASED REVIEW

4.1 General Attributes

Equivalence of Clinical and Commercial Spray Devices

4.2 What were the formulations for the Clinical and Commercial Spray Devices?

The quantitative composition of the formulations for the clinical and commercial lots used in ZOMIG Nasal Spray 5, _____ mg are identical (see Table 1 to Table 3).

Table 1 Quantitative composition of ZOMIG Nasal Spray 5 mg used in clinical and commercial lots

Ingredient	Quantity (mg per nominal 100 µl dose)	Function
Zolmitriptan	5.0	Drug substance
Citric acid, anhydrous	[]	[]
Dibasic sodium phosphate	[]	[]
Purified water	[]	[]
Nitrogen	[]	[]

Table 2 Quantitative composition of Zomig Nasal Spray 2.5 mg used in clinical and commercial lots

Ingredient	Quantity (mg per nominal 100 µl dose)	Function
Zolmitriptan	2.5	Drug substance
Citric acid, anhydrous	[]	[]
Dibasic sodium phosphate	[]	[]
Purified water	[]	[]
Nitrogen	[]	[]

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Table 3 Quantitative composition of ZOMIG Nasal Spray 0.5 mg used in clinical and commercial lots

Ingredient	Quantity (mg per nominal 100 µl dose)	Function
Zolmitriptan	0.5	Drug substance
Citric acid, anhydrous		
Dibasic sodium phosphate		
Purified water		
Water for injection*		
Nitrogen		

Solvent used in batch PH/10828/95.

4.3 What were the specifications for the components for the Clinical and Commercial Spray Devices?

The specifications for all the internal components for the clinical and commercial devices are identical. Individual specifications for each of the components are shown (see Table 4 to Table 7).

Table 4 Specification for vial

Test	Specification
Appearance	Clear glass vial, free from any critical defects
Material	Clear Type I (USP) neutral glass
Height (mm)	19.5 ±0.5
Internal body diameter (mm)	5.0 ±0

The vial is regarded as the metered chamber volume for ZOMIG Nasal Spray

Table 5 Specification for rubber stopper

Test	Specification
Appearance	Black rubber stopper, free from any critical defects
Material	———— Type I (USP) ———— rubber
Rib diameter (mm)	5.300 ±0.075
Height (mm)	6.0 ±0.1
Diaphragm thickness (mm)	.0 ±0
Specific gravity	————
Hardness (Shore A)	————

Table 6 Specification for vial holder sub-assembly

Test	Specification
Appearance	Plastic vial holder with thumb push attached ² , free from any critical defects
Material	_____
Break ring diameter (mm)	14.0 ±0.1
Actuation force (N)	_____

The thumb push attachment is for the commercial device

Table 7 Specification for actuator sub-assembly

Test	Specification
Appearance	Plastic actuator sub-assembly, free from any critical defects
Material	Body/needle jig: _____ Needle: _____
Orifice diameter (mm)	0.31 ±0.05

Both clinical and commercial devices have the same specifications for the actuation force but it is highly likely that any combination of manual actuation differences and batch to batch variation of the break ring (which appears to be part of a pre-compression mechanism) could result in large variation in the median droplet size of particles delivered from study to study with different lots of the spray device.

4.4 Was a properly validated analytical method used for the analysis of the in vitro content uniformity and _____ data?

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Linearity

Linearity of zolmitriptan peak area response versus zolmitriptan content has been demonstrated over the range _____ (see Table 9).

Table 9 Droplet size by _____ - linearity of zolmitriptan

Zolmitriptan concentration (µg/ml)	Peak area
_____	_____
_____	_____
_____	_____
_____	_____

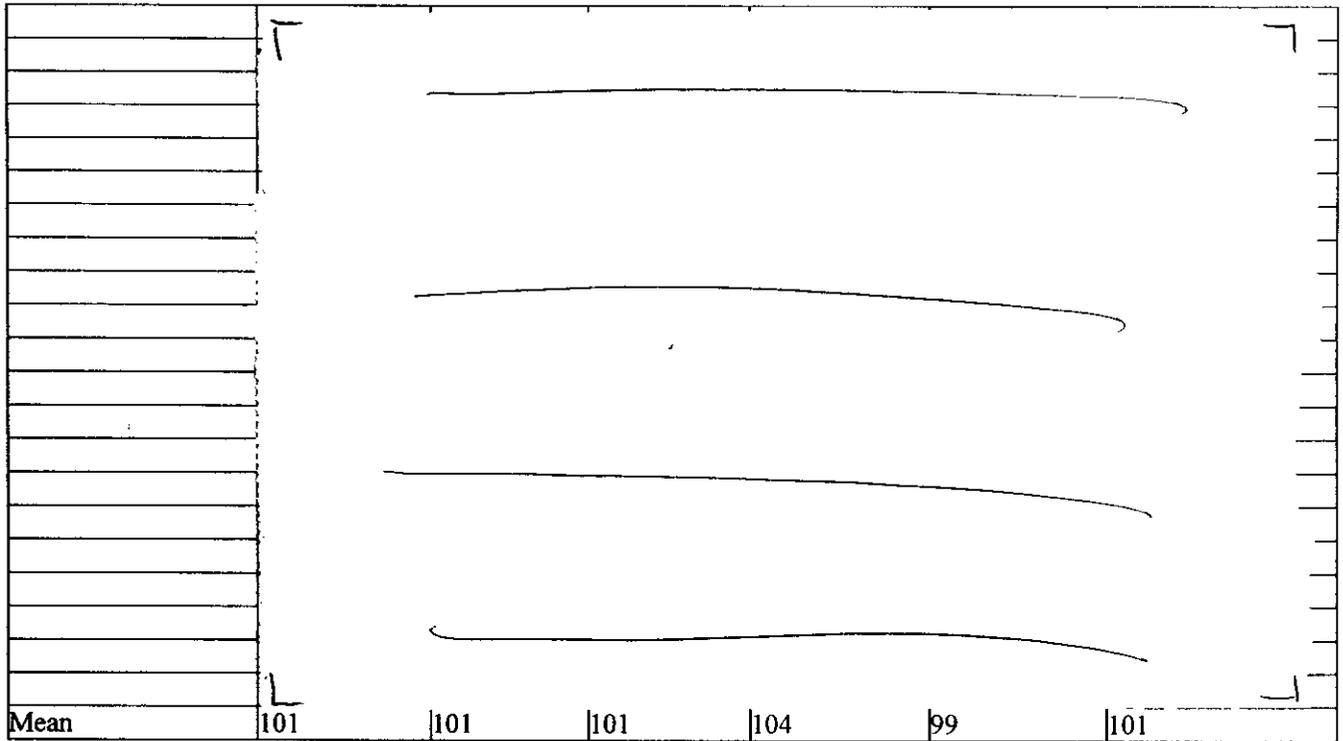
The linearity data was from _____ however, the firm claimed a sensitivity of _____ curve data / _____ needs to be supplied by the firm to support their claim. The current data submitted by the firm does not support the / _____ LOQ claimed by the firm for their assay.

4.5 Was the uniformity of the dosage units consistent with the % label claim for the clinical and commercial spray devices?

Dose content uniformity was performed as a single test per device; the firm did not conduct 'through container life' testing as described in the CDER Draft Guidance because ZOMIG Nasal Spray is a unit dose system.

Assay (mg/ml) and uniformity of dosage units (% label claim) for the reference and test batches of ZOMIG Nasal Spray 5 mg and ZOMIG Nasal Spray 0.5 mg are shown, see Table 6 and Table 7.

Table 6	Uniformity of dosage units (% label claim) for ZOMIG Nasal Spray 5 mg					
Batch number	P/1598/19	P/1598/20	P/2569/42	P/1598/31	P/1598/32	P/1598/36
Device type	Clinical	Clinical	Clinical	Commercial	Commercial	Commercial
Assay (mg/ml) of unit contents(100ul)	_____	_____	_____	_____	_____	_____
Uniformity of dosage units (% label claim)						



Ratio of Geometric mean (Test/Reference) for the — batches = 4.61/4.615=1.0

Table 7	Uniformity of dosage units (% label claim) for ZOMIG Nasal Spray					
	0.5 mg					
Batch number	PH10828/95	P/1598/16	P/1631/06	P/1598/14	P/1598/33	P/1598/15
Device type	Clinical	Clinical	Clinical	Commercial	Commercial	Commercial
Assay (mg/ml) of unit contents(100ul)						
Uniformity of dosage units (% label claim)						

Mean	103	100	102	102	103	101
------	-----	-----	-----	-----	-----	-----

Ratio of Geometric means (Test/Reference) for the 6 batches = $4.62/4.62=1.0$

CONCLUSION

The test and reference formulations both exhibit acceptable content uniformity. The ratios of geometric mean values for the 0.5 mg and 5 mg dose lots are within the acceptable ratio of _____

4.6 Do the summary parameters for the particle size distribution data collected with the _____, support bioequivalence between the clinical and commercial spray devices?

4.6.1 Median Droplet Size

Laser diffraction is a non-aerodynamic optical method of droplet sizing which measures the geometric size of droplets in flight. Laser instrumentation provides plots of obscuration(optical concentration) or per cent transmission and droplet size distribution over the entire life of a single spray.

Summary data for median droplet size for the 3 doses 5 mg, 2.5 mg and 0.5 mg are presented for the 3 distances from the Laser beam _____, which represent different stages of plume formation after actuation. Data is presented for between and within lot % CV for the 3 lots _____ devices per lot) at the different distances (N=30) that were tested. Summary statistics are presented for the ratio of geometric means and the F-test comparison of variances. The median diameter, _____ of the particles, referred to the volume, have a diameter \leq indicated value. Units are in um.) is presented in the following tables.

2.5 MG DROPLET SIZE BY LASER DIFFRACTION DATA

0.5))
data

Product	Distance (cm)	Mean n=30	Total % CV	Mean of log n=30	Between lot % CV
Ref		66.75	[]	1.8079	[]
		51.05		1.7001	
		45.12		1.6457	
Test		65.29	[]	1.8039	[]
		48.84		1.6783	
		39.81		1.5985	

Within lot % CV (n=10)

Product	Lot	Range	T/R ratios
Ref	[]	[]	[]
Test	[]	[]	[]
	[]	[]	[]

Distance (cm)	Arithmetic mean	Geometric mean
	0.9781	0.9908
	0.9567	0.9510
	0.8823	0.8970*

F-test comparison of variances

Distance (cm)	F-ratio	P-value
	1.22	0.298
	1.36	0.209
	8.73	4.8E-8

*T/R ratio outside []

0.5 MG DROPLET SIZE BY LASER DIFFRACTION DATA

data (0.5))

Product	Distance (cm)	Mean n=30	Total % CV	Mean of log n=30	Between lot % CV
Ref		84.71	┌───┐	1.8627	┌───┐
		60.86		1.7585	
		51.45		1.6877	
Test		70.09	┌───┐	1.8376	┌───┐
		54.24		1.7298	
		43.18		1.6335	

Within lot % CV (n=10)

Product	Lot	Range	T/R ratios
Ref	┌──┐	┌───┐	┌──┐
	┌──┐		
Test	┌──┐	┌───┐	┌──┐
	┌──┐		

Distance (cm)	Arithmetic mean	Geometric mean
	0.8274	0.9438
	0.8912	0.9361
	0.8393	0.8827*

F-test comparison of variances

Distance (cm)	F-ratio	P-value
	22.65	2.8E-13
	0.15	0.999
	22.35	3.3E-13

*T/R ratio outside ─

4.6.2 Span \

Summary data for particle size span for the 3 doses 5 mg, 2.5 mg and 0.5 mg are presented for the 3 distances from the Laser beam \ _____ which represent different stages of plume formation after actuation. Data is presented for between and within lot % CV for the 3 lots (— devices per lot) at the different distances (N=30) that were tested. Summary statistics are presented for the ratio of geometric means and the F-test comparison of variances. _____

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Span 2.5 mg Dose
Span data

Product	Distance (cm)	Mean n=30	Total % CV	Mean of log n=30	Between lot % CV
Ref	—	5.71	┌ ┐	0.7343	┌ ┐
	—	2.66	┌ ┐	0.3887	┌ ┐
	—	2.03	—	0.2444	—
Test	—	8.97	┌ ┐	0.9474	┌ ┐
	—	5.16	┌ ┐	0.6503	┌ ┐
	—	1.50	┌ ┐	0.1666	┌ ┐

Within lot % CV (n=10)

Product	Lot	Range	Range
Ref	—	┌ ┐	┌ ┐
	—	┌ ┐	┌ ┐
	—	┌ ┐	┌ ┐
Test	—	┌ ┐	┌ ┐
	—	┌ ┐	┌ ┐
	—	┌ ┐	┌ ┐

T/R ratios

Distance (cm)	Arithmetic mean	Geometric mean
—	1.5711	1.6334**
—	1.9424	1.8264*
—	0.7388	0.8360*

F-test comparison of variances

Distance (cm)	F-ratio	P-value
—	1.80	0.06
—	4.19	0.0001
—	16.99	1.2E-11

*T/R ratio outside —

**T/R ratio outside — but not considered pivotal due to the close — distance from the laser beam which does not give plume sufficient time to form and results in highly variable data

Span 0.5 mg Dose
Span data

Product	Distance (cm)	Mean n=30	Total % CV	Mean of log n=30	Between lot % CV
Ref		7.13	┌───┐	0.834	┌───┐
		2.17	───	0.32	───
		1.97	───	0.236	───
Test		8.37	───	0.917	───
		3.82	───	0.516	───
		1.75	└───┘	0.224	└───┘

Within lot % CV (n=10)

Product	Lot	Range	Range
Ref	┌──┐	┌───┐	───
	└──┘	└───┘	───
Test	┌──┐	┌───┐	───
	└──┘	└───┘	───

T/R ratios

Distance (cm)	Arithmetic mean	Geometric mean
	1.1733	1.2106**
	1.7632	1.5704*
	0.8884	0.9727

F-test comparison of variances

Distance (cm)	F-ratio	P-value
	2.18	0.02
	10.69	4.2E-9
	3.41	0.0007

*T/R ratio outside

**T/R ratio outside but not considered pivotal due to the close distance from the laser beam which does not give plume sufficient time to form and results in highly variable data

CONCLUSION

The following test/reference geometric mean ratios related to particle size exceeded _____

<u>Test</u>	<u>Dose Size</u>
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@ -
Span	2.5 mg droplet size@ -

Based upon these results, the firm has failed to demonstrate that the commercial product is bioequivalent to the clinical product based upon median particle size diameter and particle span.

4.7 Do the summary data for the _____ indicate that the clinical device and the commercial device result in the same deposition pattern within the _____ ?

The sizing of droplets or particles by _____ measures aerodynamic diameter based upon _____, an important factor in the deposition of drug in the nasal passage.

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5 MG DROPLET SIZE BY _____ DATA

_____ data

Product	Distance (micron)	Mean n=9	Total % cv	Mean of log n=9	Between lot % cv
Ref	_____	96.8	_____	1.986	_____
		2.55		0.404	
		0.34		-0.473	
		0.13		-0.904	
		0.13		-0.896	
		0.04		-1.38	
		0.02		-1.699	
	Test		96.83		1.986
		2.58		0.395	
		0.31		-0.518	
		0.11		-0.966	
		0.12		-0.956	
		0.03		-1.512	
		0.02		-1.699	

Within lot % cv (n=3)

Product	Lot	
Ref	_____	_____

	Range	_____
Test	_____	_____

	Range	_____

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(UNLESS OTHERWISE SPECIFIED)

T/R ratios

Size (micron)	Arithmetic mean	Geometric mean
7	1.0003	1.0002
	1.0118	0.9802
	0.9118	0.8999
	0.8462	0.8682
	0.9231	0.8706
	0.75	0.7688
1	1.0	1.0

F-test comparison of variances

Size (micron)	F-ratio	P-value
7	8.39	7.6E-8
	6.87	7.3E-7
	4.21	0.0001
	4.48	6.2E-5
	9.88	1.1E-8
	0	1.0
1	0	1.0

- The 0.76 ratio at 7 um is not considered pivotal since 7 of the applied dose was recovered in the 7 for the 7 for the clinical and commercial spray devices.

CONCLUSION

The data for the 5 mg spray indicates that for the 7 and particles 7 and larger, the commercial and clinical devices are bioequivalent. Recovery data indicated that 7 of the applied dose was recovered in the 7 for the 7 for the clinical and commercial spray devices

4.8 Does the comparative spray pattern summary data for the clinical device and the commercial device support the bioequivalence of the two products.

Spray pattern studies characterize the spray either during the spray prior to  or following  on an appropriate target such as thin-layer chromatography. The test is done at different distances from the TLC plate. Spray pattern analysis allows for comparison of shapes, measurement of area or maximum diameter (Dmax), minimum diameter (Dmin), and ovality (Dmax/Dmin).

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5 MG SPRAY PATTERN DATA

Ovality ratio

Ovality ratio data

Product	Distance (cm)	Mean n=30	Total % cv	Mean of log n=30	Between lot % cv
Ref	2	1.06	✓	0.025	✓
	3	1.067		0.028	
	4	1.083		0.034	
Test	2	1.07		0.029	
	3	1.07		0.029	
	4	1.07	✓	0.027	✓

Within lot % cv (n=10)

Product	Lot				
Ref	✓	✓	✓	✓	✓
	✓				
Test	✓				
	✓				

T/R ratios

Distance (cm)	Arithmetic mean	Geometric mean
✓	1.0094	1.0093
✓	1.0028	1.0021
	0.985	0.984

F-test comparison of variances

Distance (cm)	F-ratio	P-value
✓	1.08	0.416
✓	2.14	0.022
	1.37	0.201

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Dmax

D_{max} data

Product	Distance (cm)	Mean n=30	Total % cv	Mean of log n=30	Between lot % cv
Ref	7	3.17	7	0.498	7
		3.81		0.577	
		4.93		0.686	
Test		3.23	7	0.507	
		3.96		0.594	
		4.90		0.686	

Within lot % cv (n=10)

Product	Lot	←-----→					
Ref	7	7	7	7	7	7	7
		7					
	Range						
Test	7						
	Range	7	7	7	7	7	7

T/R ratios

Distance (cm)	Arithmetic mean	Geometric mean
	1.0189	1.0198
	1.0393	1.0399
	0.9951	0.9984

F-test comparison of variances

Distance (cm)	F-ratio	P-value
	1.08	0.416
	1.03	0.464
	1.39	0.191

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Dmin

D_{min} data

Product	Distance (cm)	Mean n=30	Total % cv	Mean of log n=30	Between lot % cv
Ref	7	2.99	7	0.473	7
		3.59		0.551	
		4.56		0.654	
Test	U	3.00	U	0.475	U
		3.72		0.566	
		4.58		0.656	

Within lot % cv (n=10)

Product	Lot			
Ref	7	7	7	7
		U		
Test	7	7		
		U	U	U

T/R ratios

Distance (cm)	Arithmetic mean	Geometric mean
7	1.0033	1.0065
	1.0362	1.0359
U	1.0044	1.0051

F-test comparison of variances

Distance (cm)	F-ratio	P-value
7	1.51	0.137
	1.06	0.438
U	1.14	0.360

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0.5 MG SPRAY PATTERN DATA

Ovality ratio

Ovality ratio

Product	Distance (cm)	Mean n=30	Total % cv	Mean of log n=30	Between lot % cv
Ref	7	1.06	7	0.0243	7
		1.04		0.0149	
		1.10		0.039	
Test	U	1.08	U	0.0338	U
		1.11		0.0438	
		1.08		0.0318	

Within lot % cv (n=10)

Product	Lot
Ref	7
Test	U
	U

T/R ratios

Distance (cm)	Arithmetic mean	Geometric mean
7	1.0217	1.0222
	1.0704	1.0687
U	0.9872	0.9837

F-test comparison of variances

Distance (cm)	F-ratio	P-value
7	0.94	0.566
	2.62	0.006
U	3.06	0.002

Dmax

Product	Distance (cm)	Mean n=30	Total % CV	Mean of log n=30	Between lot % CV
Ref		3.00	┌	0.4748	┌
		3.61		0.5527	
		4.19		0.6164	
Test		3.20		0.5043	
		4.09		0.6102	
		4.92	└	0.6896	└

Within lot % CV (n=10)

Product	Lot	Range	T/R ratios
Ref	┌		┌
	└		└
Test	┌		
	└		

Distance (cm) Arithmetic mean Geometric mean

	1.0666	1.0703
	1.1347	1.1416*
	1.1735	1.1836*

F-test comparison of variances

Distance (cm) F-ratio P-value

	1.90	0.045
	1.81	0.057
	2.08	0.027

*T/R ratio outside —

Dmin

Product	Distance (cm)	Mean n=30	Total % CV	Mean of log n=30	Between lot % CV
Ref		2.81		0.4457	
		3.41		0.5282	
		3.85		0.5788	
Test		2.96		0.4699	
		3.71		0.5667	
		4.54		0.6534	

Within lot % CV (n=10)**Product****Lot**

Ref

|

|

|

|

Range

Test

|

|

Range

|

|

T/R ratios**Distance (cm)****Arithmetic mean****Geometric mean**

1.0556

1.0573

1.0881

1.0927

1.1784

1.1874*

t-test comparison of variances**Distance (cm)****F-ratio****P-value**

0.79

0.732

0.67

0.859

0.65

0.870

T/R ratio outside*CONCLUSION**

The spray pattern data for the 5 mg dosage strength is acceptable. For the 0.5 mg dose, the Dmin and Dmax Test/Reference geometric means ratios exceed the $\frac{1}{2}$ limit at the $\frac{1}{2}$ distance. At the $\frac{1}{2}$ distance Dmin and Ovality were within the established limits.

4.9 Does the comparative plume geometry summary data for the 0° degree and 90° angles for the clinical device and the commercial device support the bioequivalence of the two products.

5 MG PLUME GEOMETRY DATA

Overall cv with raw data

Product	Degree	Position	Mean width	Total cv width	Mean length	Total cv length	Mean spray angle	Total cv spray angle
R	0	Begin	99.41	✓	167.93	✓	54.07	✓
R	0	Middle	113.32		231.27		48.67	
R	0	End	126.87		283.67		43.00	
T	0	Begin	97.38		137.13		60.40	
T	0	Middle	118.11		185.67		51.47	
T	0	End	119.73		208.27		28.27	
R	90	Begin	99.40		170.93		50.13	
R	90	Middle	106.07		228.60		45.80	
R	90	End	122.03		285.67		39.00	
T	90	Begin	97.48		144.00		58.13	
T	90	Middle	108.52		173.27		47.33	
T	90	End	115.13	✓	200.20	✓	29.40	✓

R Clinical.
T Commercial.

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Mean of log 10 of data

Product	Degree	Position	Mean of log width	Mean of log length	Mean of log spray angle
R	0	Begin	1.993	2.221	1.721
R	0	Middle	2.052	2.361	1.675
R	0	End	2.101	2.451	1.618
T	0	Begin	1.984	2.131	1.773
T	0	Middle	2.070	2.264	1.689
T	0	End	2.075	2.313	1.428
R	90	Begin	1.991	2.226	1.678
R	90	Middle	2.022	2.356	1.645
R	90	End	2.084	2.454	1.573
T	90	Begin	1.985	2.152	1.756
T	90	Middle	2.031	2.230	1.648
T	90	End	2.058	2.290	1.430

R Clinical.
T Commercial.

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T/R ratios raw mean

Degree	Position	T/R arithmetic mean width	T/R arithmetic mean length	T/R arithmetic mean spray angle
0	Begin	0.9795	0.8166	1.1171
0	Middle	1.0422	0.8028	1.0575
0	End	0.9437	0.7342	0.6574
90	Begin	0.9807	0.8424	1.1596
90	Middle	1.0231	0.7579	1.0335
90	End	0.9435	0.7008	0.7538

T/R ratios log data

Degree	Position	T/R geometric mean width	T/R geometric mean length	T/R geometric mean spray angle
0	Begin	0.9799	0.8140*	1.1285*
0	Middle	1.0420	0.7999*	1.0330
0	End	0.9419	0.7279*	0.6462*
90	Begin	0.9870	0.8442*	1.1946*
90	Middle	1.0208	0.7490*	1.0067
90	End	0.9434	0.6853*	0.7180*

*T/R ratio is less than or greater than _____

CONCLUSION

The plume geometry data for the 5 mg nasal spray indicates that the Test/Reference geometric means are outside of the acceptable limits. The firm should submit plume geometry data on the 0.5 mg dosage strength.

4.10.Overall Conclusions:

The in vitro results for the following tests comparing the commercial device to the clinical spray device were outside of the acceptable range of _____ for the ratio of geometric means:

1. Particle size

<u>Test</u>	<u>Dose Size</u>	<u>Value</u>
Median Diameter, 0.5 mg droplet size, _____	e	_____
Median Diameter, 2.5 mg droplet size, _____	e	_____
Span, 0.5 mg droplet size, _____	e	_____
Span, 2.5 mg droplet size, _____	e	_____

Span, 2.5 mg droplet size, _____

—

2. Spray Pattern 0.5 mg product

Parameter

Value

Dmin

—

Dmax

—

3. Plume Geometry 5.0 mg product

Parameter-Length

Value

0° Beginning

—

0° Middle

0° End

—

90° Beginning

90° Middle

—

90° End

Parameter-Spray Angle

Value

0° Beginning

—

0° End

90° Beginning

—

90° End

4. The to-be-marketed (_____ 5.0 mg) commercial nasal spray devices developed by the firm are not equivalent to the clinically studied nasal spray devices at the same strengths.

4. Comments to the Firm:

1. The ratio of geometric means results for the following in vitro tests were outside of the acceptable range of _____

a. Particle size

Test Dose Size

Parameter

Ratio geometric means

Median Diameter, 0.5 mg droplet size, _____

0.88

Median Diameter, 2.5 mg droplet size, _____

0.89

Span, 0.5 mg droplet size, _____

1.57

Span, 2.5 mg droplet size, _____

1.82

Span, 2.5 mg droplet size, _____

0.83

b. Spray Pattern 0.5 mg product

<u>Parameter</u>	<u>Value</u>
Dmin	
Dmax	

c. Plume Geometry 5.0mg product

<u>Parameter-Length</u>	<u>Value</u>
0° Beginning	
0° Middle	
0° End	
90° Beginning	
90° Middle	
90° End	

<u>Parameter-Spray Angle</u>	<u>Value</u>
0° Beginning	
0° End	
90° Beginning	
90° End	

2. You are requested for all new studies to always provide data on both the 0.5 mg strength and the 5 mg strength nasal sprays specifically for plume geometry and _____

3. You did not supply analytical data to support the LOQ of _____ for your HPLC assay.

4. Your to-be-marketed commercial (_____ 5.0 mg) nasal spray devices are not equivalent to your clinically studied nasal spray devices at the same strengths.

5. The Office of Clinical Pharmacology and Biopharmaceutics offers the following possible approaches to resolve the BE issues related to the commercial product:

- a. Repeat the in vitro study comparison of the clinical and commercial devices using either mechanical actuation or have the break-ring re-manufactured with more narrow specifications before repeating the study.
- b. Provide data showing that the particle size ranges observed for the commercial device are bioequivalent (i.e., Cmax and AUC) to the particle sizes reported for the clinical trial device.
- c. Provide efficacy data showing that the particle size ranges observed for the commercial devices are equivalent to the particle sizes reported for the clinical trial device.

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

Andre Jackson_____

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

OCPB Required Office Level Briefing on : November 4, 2002

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

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§ 552(b)(5) Deliberative Process

§ 552(b)(5) Draft Labeling

APPENDIX 2

THE FIRM CONDUCTED THREE PIVOTAL CLINICAL STUDIES TO CHARACTERIZE THE CLINICAL PRODUCT. RESULTS FROM THESE PIVOTAL STUDIES WILL BE PRESENTED IN APPENDIX 2.

A Phase I Trial to Investigate the Tolerability and Pharmacokinetics (Including Dose Proportionality) of Zolmitriptan (ZOMIG™) when Administered to Healthy Male and Female Volunteers as Single and Multiple Doses of an Intranasal Spray Formulation

OBJECTIVES

To investigate the tolerability of single and multiple doses of an intranasal spray formulation of zolmitriptan in healthy male and female volunteers.

To investigate the pharmacokinetics of single and multiple doses and assess the dose proportionality of the pharmacokinetics of zolmitriptan and its metabolite 183C91, when administered to healthy male and female volunteers as an intranasal spray formulation.

METHODS

Design: Randomized, double-blind, placebo-controlled, balanced, incomplete, 2-period crossover, single center trial.

Population: 30 healthy volunteers (10 male and 20 female).

Key inclusion criteria: Male or female aged between 18 and 62 years, normal medical examination.

Dosage: Five dose levels of zolmitriptan (0 [placebo], 0.5, 1, 2.5, and 5 mg) were supplied in 100 µl of buffered solution, pH 5.0 as single-use intranasal sprays. Each volunteer was randomized to receive 2 dose levels, 1 in each phase. In each phase the dosage was kept constant and consisted of a single dose on dosing day 1, and 2 doses (given 2 hours apart) on dosing days 2 to 4.

Key assessments

The primary endpoints were nasal tolerability and the maximum plasma concentration (C_{max}) of zolmitriptan.

The secondary endpoints were the area under the plasma concentration-time curve (AUC) for zolmitriptan, and C_{max} and AUC for the metabolite 183C91.

Pharmacokinetics: A summary of pharmacokinetic parameters on day 1 and day 4 is given in Table I for zolmitriptan and Table II for 183C91.

Table I Plasma pharmacokinetic parameters of zolmitriptan after intranasal administration of zolmitriptan as a single dose (day 1) and multiple doses (day 4)

Zolmitriptan dose (mg)	Day	C_{max} (ng/ml)			T_{max} (h)		AUC (ng·h/ml)			$t_{1/2}$ (h)		
		n	Mean ^a	CV	n	Median (range)	n	Mean ^a	CV	n	Mean	SD
0.5	1	12	0.91	34.8	12	1.50 (0.50 to 3.0)	10	5.30	28.4	10	2.81	0.80
	4	12	1.32	36.4	12	1.50 (0.50 to 2.5)	12	7.35	45.4	12	2.98	0.90
1.0	1	12	—	120.9	11	2.50 (0.75 to 4.0)	10	7.78	58.5	10	2.87	0.66
	4	12	2.61	52.2	12	1.50 (0.48 to 3.0)	12	15.00	55.5	12	3.53	0.74
2.5	1	12	3.63	39.8	12	2.00 (0.25 to 3.0)	12	22.10	41.9	12	2.98	0.57
	4	12	6.43	46.0	12	1.25 (0.25 to 3.0)	12	37.30	52.1	12	3.69	0.59
5.0	1	12	6.51	46.0	12	1.75 (0.25 to 5.0)	12	42.10	39.9	12	3.31	0.65
	4	12	10.70	48.4	12	1.25 (0.25 to 3.0)	12	59.80	49.2	12	3.48	0.43

^a Geometric mean

^b Limit of quantification substituted for missing value

C_{max} Maximum plasma concentration

T_{max} Time to maximum plasma concentration

AUC Area under the curve

$t_{1/2}$ Half life

CV Coefficient of variation

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Table II Plasma pharmacokinetic parameters of 183C91 after intranasal administration of zolmitriptan as a single dose (day 1) and multiple doses (day 4)

Zolmitriptan dose (mg)	Day	C _{max} (ng/ml)			T _{max} (h)		AUC (ng h/ml)			t _{1/2} (h)		
		n	Mean ^a	CV	n	Median (range)	n	Mean ^a	CV	n	Mean	SD
0.5	1	12	0.34	33.8	12	2.00 (0.75 to 3.0)	1	2.86	NC	1	3.50	NC
	4	12	0.67	25.1	12	2.50 (1.50 to 3.0)	10	3.97	25.0	10	2.40	0.49
1.0	1	12	— ^b	71.1	10	2.75 (1.50 to 4.0)	6	4.55	31.7	6	2.94	1.11
	4	12	1.06	43.3	12	3.00 (1.00 to 4.0)	11	6.45	38.9	11	2.91	1.05
2.5	1	12	1.47	85.2	11	3.00 (1.00 to 5.0)	11	11.40	25.1	11	2.94	0.70
	4	12	2.90	59.4	12	3.00 (1.50 to 5.0)	10	21.20	21.8	10	4.07	0.96
5.0	1	12	2.75	40.2	12	5.00 (2.00 to 5.0)	11	18.80	39.2	11	3.03	0.83
	4	12	5.14	71.3	12	3.00 (0.25 to 3.0)	11	31.40	64.7	11	4.02	0.85

^a Geometric mean

^b Limit of quantification substituted for missing value

C_{max} Maximum plasma concentration

T_{max} Time to maximum plasma concentration

AUC Area under the curve

t_{1/2} Half life

CV Coefficient of variation

Zolmitriptan was rapidly absorbed and was detectable in the plasma within 15 minutes of intranasal dosing. The time at which maximum plasma concentrations were observed was similar after single (day 1) or multiple (day 4) dosing (range 0.25 to 5 hours).

The appearance of 183C91 in the plasma was delayed suggesting that initial absorption takes place intranasally with reduced first pass metabolism. Generally, 183C91 was not detected in the plasma samples obtained at 15 minutes after dosing and in some cases was not detectable until 2.5 or 3 hours after dosing. The median T_{max} for 183C91 observed for both single and multiple dosing at all dose levels was higher than that observed for zolmitriptan.

The mean elimination half-life for both zolmitriptan and 183C91 was approximately 3 hours and plasma concentrations were low or non-detectable prior to the first dose on subsequent days.

Consequently, there was no accumulation of zolmitriptan during the multiple dose phase, although some increase in pre-dose concentrations of 183C91 between days 2 and 4 was observed.

As expected, C_{max} and AUC for zolmitriptan and 183C91 increased when a second dose was administered 2 hours after the first. For zolmitriptan the ratios of geometric mean C_{max} after the second dose on day 4 compared to day 1 ranged from 1.5 to 2.6 and for AUC ranged from 1.4 to 1.9. For 183C91 the geometric mean C_{max} after the second dose on day 4 compared to day 1 showed an approximately 2-fold increase. The increase in 183C91 AUC between day 1 and the second dose on day 4 ranged from 1.4-fold to 1.9-fold.

The AUC values for 183C91 were on average 43% of those for zolmitriptan following single intranasal doses, and 51% after the second dose on day 4.

Dose proportionality was demonstrated for the C_{max} and AUC of both zolmitriptan and 183C91 after single and multiple intranasal doses of 0.5, 1, 2.5 and 5 mg.

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

§ 552(b)(5) Deliberative Process

§ 552(b)(5) Draft Labeling

A Phase I, Open, Randomized, Two-period Crossover Trial to Evaluate the Effect of a Nasally Administered Decongestant (Xylometazoline) on the Absorption of the Intranasal Formulation of Zolmitriptan When Given to Healthy Male Volunteers

OBJECTIVES

The primary objective of this trial was to compare the absorption and pharmacokinetics of the intranasal formulation of zolmitriptan when given alone and after dosing with an intranasal sympathomimetic vasoconstrictor to healthy male volunteers.

The safety of all volunteers was ensured by clinical monitoring.

METHODS

Design: Open, randomized, 2-period crossover, single-dose, single-center trial.

Population: 18 healthy male volunteers.

Dosage: Volunteers received, in random order and separated by a wash-out period of at least 48 hours, a single dose of either zolmitriptan 5 mg nasal spray (batch number 35618G97) 30 minutes after a single dose of intranasal xylometazoline (weight/volume solution; batch number 98006), or zolmitriptan 5 mg nasal spray alone.

Key assessments

Pharmacokinetic: Blood samples were taken pre-dose and then at predetermined intervals up to 15 hours post-dose for the measurement of plasma concentrations of zolmitriptan and its active metabolite, 183C91. The following pharmacokinetic parameters were determined for zolmitriptan and 183C91: area under the plasma concentration-time curve (AUC), maximum plasma concentration (C_{max}), time of maximum plasma concentration (T_{max}) and terminal elimination half-life (t_{1/2}). In addition, AUC during the first hour post-dose (AUC₀₋₁) was determined for zolmitriptan. The pharmacokinetic parameters for the 2 treatments were summarized. AUC, AUC₀₋₁ and C_{max} were analyzed using an analysis of variance model allowing for the effect of volunteer, period and treatment. The primary endpoints were the pharmacokinetic parameters AUC and C_{max} for zolmitriptan. Secondary endpoints were AUC₀₋₁ and T_{max} for zolmitriptan and AUC, C_{max} and T_{max} for 183C91.

RESULTS

Pharmacokinetics: Zolmitriptan was rapidly absorbed when dosed intranasally. The geometric mean plasma concentration-time profiles for zolmitriptan were similar when zolmitriptan was

dosed alone or after pre-treatment with xylometazoline. Geometric mean plasma AUC, AUC₀₋₁ and C_{max} for zolmitriptan were slightly higher when zolmitriptan was dosed alone compared with dosing after pre-treatment with xylometazoline. Differences in AUC, AUC₀₋₁ and C_{max} of 5, 11, and 7%, respectively, were observed. Statistical analyses (Table I) showed that the 90% confidence intervals were within the predetermined limits of _____ for both AUC and C_{max}. The time at which C_{max} for zolmitriptan was observed (T_{max}) was the same whether zolmitriptan was dosed alone or after previous treatment with xylometazoline (0.25 to 5.00 hours). Delayed appearance of 183C91 in the systemic circulation provided evidence of intranasal absorption which was not affected by prior treatment with xylometazoline. The geometric mean plasma concentration-time profiles for 183C91 were the same for both treatments and there were no differences observed for C_{max} and AUC. The observed T_{max} for 183C91 was the same for both treatments (2.00 to 5.00 hours). The elimination of zolmitriptan and 183C91 were unaffected by prior treatment with xylometazoline. Summary statistical data for zolmitriptan is presented in Table 1 while the statistical data for 183C91 is presented in Table 6.

Table I Statistical comparison of AUC, AUC₀₋₁ and C_{max} of zolmitriptan with and without previous treatment with xylometazoline

Comparison Parameter	n	Zolmitriptan gmean	n	Zolmitriptan following xylometazoline gmean	Ratio of gmeans	90% CI for ratio
Zolmitriptan						
AUC (ng.h/ml)	18	37.1	18	35.3	1.05	0.95 to 1.17
AUC ₀₋₁ (ng.h/ml)	18	2.71	18	2.43	1.11	0.94 to 1.32
C _{max} (ng/ml)	18	5.86	18	5.46	1.07	0.94 to 1.23
183C91						
AUC (ng.h/ml)	18	17.8	18	17.3	1.03	0.92 to 1.16
C _{max} (ng/ml)	18	2.77	18	2.72	1.02	0.90 to 1.15

AUC Area under the plasma concentration time curve from zero to infinity

AUC₀₋₁ Area under the plasma concentration time curve over the first hour post-dose

CI Confidence interval

C_{max} Maximum plasma concentration

gmean Geometric mean

n Number of volunteers

Ratio of gmean is the ratio of zolmitriptan:zolmitriptan following xylometazoline

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Table 6 Statistical comparison of AUC and C_{max} for 183C91 after treatment with zolmitriptan alone and after prior treatment with xylometazoline

Parameter	n	Zolmitriptan gmean	n	Zolmitriptan following xylometazoline gmean	Ratio of gmeans	90% CI for ratio
AUC (ng.h/ml)	18	17.8	18	17.3	1.03	0.92 to 1.16
C _{max} (ng/ml)	18	2.77	18	2.72	1.02	0.90 to 1.15

AUC Area under the plasma concentration time curve from zero to infinity

CI Confidence interval

C_{max} Maximum plasma concentration

gmean Geometric mean

n Number of volunteers

Ratio of gmeans is the ratio of zolmitriptan : zolmitriptan following xylometazoline

OVERALL CONCLUSIONS

Zolmitriptan was rapidly absorbed when dosed by the intranasal route. The absorption was not affected by prior treatment with xylometazoline.

The results of the pharmacokinetic analyses of zolmitriptan and 183C91 fell within the acceptable limits of — for AUC(0-inf) and C_{max}.

Zolmitriptan administered intranasally was well tolerated both when administered alone and following xylometazoline.

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Office of Clinical Pharmacology and Biopharmaceutics			
New Drug Application Filing and Review Form			
General Information About the Submission			
Information		Information	
NDA Number	21-450	Brand Name	Zomig Nasal Spray
OCPB Division (I, II, III)		Generic Name	Zolmitriptan
Medical Division	Neuropharmacology	Drug Class	Triptans
OCPB Reviewer	Andre Jackson, Ph.D.	Indication(s)	Migraine with or without aura in adults.
OCPB Team Leader	Raman Baweja, Ph.D.	Dosage Form	5 mg unit dose Nasal Spray
		Dosing Regimen	5 mg in 100 µl into one nostril
Date of Submission	2/27/02	Route of Administration	Intranasal
Estimated Due Date of OCPB Review	10/1/02	Sponsor	Astra Zeneca
PDUFA Due Date	12/27/02	Priority Classification	Standard
Division Due Date	11/1/02		
Clin. Pharm. and Biopharm. Information			
	"X" if included	Number of	Number of
	at filing	studies submitted	studies reviewed
			Critical Comments if any
STUDY TYPE			
Table of Contents present and sufficient to locate reports, tables, data, etc.	X		
Tabular Listing of All Human Studies	X		
HPK Summary	X		
Labeling	X		
Reference Bioanalytical and Analytical Methods	X		
I. Clinical Pharmacology			
Mass balance:			
Isozyme characterization:			
Blood/plasma ratio:			
Plasma protein binding:			
Pharmacokinetics (e.g., Phase I) -			
Healthy Volunteers-			
single dose:	X	1	1
multiple dose:	X	1	1
Patients-			
single dose:			
multiple dose:			
Dose proportionality -			

fasting / non-fasting single dose:					
fasting / non-fasting multiple dose:					
Drug-drug interaction studies -					
In-vivo effects on primary drug:	X	1	1		Concomitant administration
					with vasoconstrictive
					decongestant to compare
					Bioavailability.
In-vivo effects of primary drug:					
	In-vitro:				
Subpopulation studies -					
	ethnicity:				
	gender:				

pediatrics:					
geriatrics:					
renal impairment:					
hepatic impairment:					
PD:					
Phase 2:					
Phase 3:	X	3	1		Clinical Safety and Efficacy Trials
PK/PD:					
Phase 1 and/or 2, proof of concept:					
Phase 3 clinical trial:					
Population Analyses -					
Data rich:					
Data sparse:					
II. Biopharmaceutics					
Absolute bioavailability:					
Relative bioavailability -					
solution as reference:					
alternate formulation as reference:	X	1			Tablet as a reference for nasal spray
Bioequivalence studies -					
traditional design; single / multi dose:					
replicate design; single / multi dose:					
Food-drug interaction studies:					
Dissolution:					
(MIVC):					
Bio-waiver request	X	1	1		Bio waiver based on in vitro
					BE data of Nasal Spray
III. Other CPB Studies					
Site of Absorption	X	1	1		

Genotype/phenotype studies:				
Chronopharmacokinetics				
Pediatric development plan				
Literature References				
Total Number of Studies		9	5	

Background:

Zomig[®] is currently indicated for the treatment of migraine with or without auras in adults. The present formulations consist of a tablet and an orally disintegrating tablet. Following the onset of a migraine, several GI effects exist, such as nausea and vomiting, which could influence the absorption and onset of action of the tablet formulation. Thus, the sponsor has developed a Nasal spray solution for zolmitriptan in order to maximize the bioavailability of the drug through a different route of administration, with the belief that the onset of pharmacological action will be faster.

In the current submission, the sponsor has performed 3 pharmacokinetic studies (# 79, 102, and 104) to assess dose proportionality, single and multiple dose administration, the effect of pH on the absorption process through the nasal cavity, site of nasal absorption, and concomitant administration with a vasoconstrictive decongestant (Xylometazoline). Studies 79 and 102 used the _____ (pivotal studies). To assess efficacy and safety by the intranasal route, the sponsor has conducted three clinical trials, which utilized the same formulation and device _____ as in pivotal PK studies #79 and #102. The sponsor has changed the delivery device that is to be marketed compared with the device that was used in the clinical trials. Thus, the sponsor has conducted *in vitro* equivalence testing of the delivery device using _____ 5 mg strengths of zolmitriptan to support all dose strengths for marketing.

		Filability and QBR comments
		"X" if yes Comments
Application filable ?	X	
Comments sent to firm ?		1. We are requesting that the sponsor provide <i>in vitro</i> data that evaluates equivalence of the clinical and to be marketed product for all intermediate strengths. Only data for the _____ 75 mg strengths have been submitted in the NDA. Abbreviated <i>in vitro</i> testing for the intermediate strengths is reasonable.
QBR questions (key issues to be considered)		1. Are the clinical and to be marketed Nasal Spray products bioequivalent? 2. Can the sponsor be granted a blowaver for the to be marketed device based on <i>in vitro</i> testing of the nasal spray? 3. Does a dose-response relationship exist for Zomig nasal spray? 4. Is the bioavailability of the nasal formulation similar to the tablet formulation?
Other comments or information not included above		
Primary reviewer Signature and Date		
Secondary reviewer Signature and Date		
CC: NDA 21-450, HFD-850(Lee), HFD-120 (Chen), HFD-860 (Jackson, Baweja, Sahajwalla, Mehta), CDR (Clin. Pharm./Biopharm.)		

**This is a representation of an electronic record that was signed electronically and
this page is the manifestation of the electronic signature.**

/s/

Andre Jackson
11/7/02 10:49:26 AM
BIOPHARMACEUTICS

Raman Baweja
11/7/02 11:22:21 AM
BIOPHARMACEUTICS

APPEARS THIS WAY
ON ORIGINAL