OFFICE OF CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW

		Submission Dates:	2/29/00
NDA:	20-626/S004		6/28/00
Name of Drug:	Imitrex (Sumatriptan) Nasal Spray 5 mg/100 μL, and 20 mg/100 μL		
Indication of Drug:	Migraine		
Type of Submission:	Pediatric Supplement		
Sponsor:	Glaxo Wellcome, Research Triangle, NC		
Reviewer:	Hong Zhao, Ph.D.		

Introduction

Imitrex (sumatriptan) Nasal Spray was approved by the Agency on August 26, 1997 for the acute treatment of migraine in adults (NDA 20-626). This supplemental application provides information to include the acute treatment of migraine in adolescent patients, ages 12 to 17 years. Three clinical studies of sumatriptan nasal spray in adolescent patients have been conducted:

Protocol SUMB1006 - An open-label pharmacokinetic study of sumatriptan nasal spray 20 mg in adolescent patients (ages 12-17 years).

Protocol SUMA3005 - A double-blind, placebo-controlled study of the efficacy and tolerability of sumatriptan nasal spray 5 mg, 10 mg and 20 mg in adolescent patients (ages 12-17 years).

Protocol SUMA3006 - An open-label evaluation of the long-term (up to 12 months) safety and tolerability of sumatriptan nasal spray in adolescent patients (ages 12-17 years). This study is incorporated into the Four-Month Safety Update for this application.

One clinical trial of sumatriptan nasal spray in pediatric patients (Phase IV) is ongoing:

Protocol SUMA4025 - A single dose study to investigate pharmacokinetics of Sumatriptan Nasal Spray in pediatric subjects (6-11 years) outside of a migraine attack. Pediatric patients are given 5 mg, 10 mg or 20 mg sumatriptan nasal spray depending on their age and weight.

Pharmacokinetics Study Review

Study Design

Protocol SUMB1006 is a single dose, single center study in 21 male and female adolescent migraineurs to determine the pharmacokinetics and tolerability of 20 mg sumatriptan nasal spray administered outside of an attack. Blood samples were collected pre-dosing and at 15, 30, 45 minutes, 1, 2, 3, 4, 6 and 8 hours post-dosing for sumatriptan concentration determination.

Sumatriptan Concentration Determination
A validated HPLC method with electrochemical detection was used to determine serum sumatriptan concentrations. The limit of quantitation (LOQ) was 0.25 ng/ml. The assay covered the range of 0.25-20 ng/ml sumatriptan with coefficient of variation < 10%.

Pharmacokinetic Results
Of the twenty-one adolescent migraineurs (12 boys and 9 girls aged 12.3 to 17.5 years and weighing 45.0-59.5 kg) enrolled and treated in the study, 19 subjects completed the study and two subjects withdrew from the study due to not willing to continue blood sampling procedures. An apparatus failure led to a loss of a number of results, resulting in a population of 16 subjects with complete bioanalytical data. The pharmacokinetic results are shown below:

Single Dose (20 mg, Batch 7B12) Intranasal Spray in Adolescent Migraineurs

	C_{max} (ng/ml)	AUC_{∞} (ng.h/ml)	T_{max}	$t_{1/2}$ (h)
Adolescents	15 (43)	59 (30)	2.0 (0.5-3.0)	2.1 (24)

SUMB1006, N=16. Data reported as arithmetic means and (CV%). T_{max} reported as the median and range.

These Pharmacokinetic parameters show a large degree of variability (CV% 43% on C_{max}) due to a variety of factors such as deposition of intranasal solution in the nasal passages, the extent of the dose that is swallowed and perhaps variable presystemic metabolism. This inter-subject variability was also observed in adults:

Single Dose (20 mg) Intranasal Spray in Healthy Male Adults (C93-065, N=24)

	C_{max} (ng/ml)	AUC_{∞} (ng.h/ml)	T_{max}	$t_{1/2}$ (h)
Adults	14 (44)	50 (32)	1.5 (0.3-3.0)	1.9 (23)

Data reported as arithmetic means and (CV%). T_{max} reported as the median and range.

- These pharmacokinetic data show that after single dose of Imitrex nasal spray, systemic exposure to sumatriptan in adolescents and adults are comparable.

Population Pharmacokinetic Analysis
The exploration of the relationships between demographic covariates (i.e., age, weight, height and gender) and non-compartmental PK parameters (i.e., C_{max}, AUC, CL/F) did not reveal any significant effect. Population pharmacokinetic analysis (n=21) showed that clearance and volume of distribution increases with body size in the adolescent population [CL/F = 330(L/h) x BW(kg)/59.5; Vd/F=70.8 (L/yr) x Age].

Safety and Tolerability
Safety and tolerability were assessed using laboratory safety parameters, vital signs, ECG and adverse event monitoring. According to the sponsor, sumatriptan was well tolerated. All adverse events were mild to moderate in intensity and resolved spontaneously.

Sponsor's Proposed Changes to Labeling

The Clinical Pharmacology Section of the labeling has been changed to describe results from *Study SUMB 1006* as follows:

Comment 1
The results of the pharmacokinetics studies demonstrate that systemic exposure to sumatriptan in adolescents and adults are similar after administration of single dose of Imitrex nasal spray.

OCPB Suggested Labeling:
Pharmacokinetics: Replace the first sentence with the following one:
In a study of 20 adult female volunteers treated with 5 and 20 mg of intranasal sumatriptan, mean C_{max} was 5 and 14 ng/ml, and AUC_{∞} was 19 and 53 ng.hour/ml, respectively, and $t_{1/2}$ was 2.0 hours.

And add the following sentences to the end of the paragraph:
In 16 adolescent patients aged 12 to 17 years with migraine treated outside of an attack with 20 mg of intranasal sumatriptan, the pharmacokinetic parameters were not significantly different from adults. Mean C_{max} was 15 ng/ml; AUC_{∞} was 59 ng.hour/ml; and $t_{1/2}$ was 2.1 hours.

Add the following paragraph to Age factor under Special Populations subsection:
Special Populations
Age: *The pharmacokinetics of 20 mg of intranasal sumatriptan in 16 adolescent male and female patients (aged 12 to 17 years) suffering from migraine outside of a migraine attack were similar to that in healthy male adult subjects.*

Please convey Comments 1 & OCPB suggested labeling to Medical Review Officer.

Hong Zhao, Ph.D._____

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

cc: NDA 20-626/S-004 Imitrex (Sumatriptan) Nasal Spray, HFD-120, HFD-860 (Zhao, Baweja, Mehta), Central Documents Room (CDR-Biopharm)

APPEARS THIS WAY ON ORIGINAL

Attachment

Synopsis

Document Number: GM1998/00376/01 Protocol Number: SUMB1006.

NAME OF COMPANY: Glaxo Wellcome NAME OF FINISHED PRODUCT: [xx] NAME OF ACTIVE INGREDIENT(S): [xx]	INDIVIDUAL STUDY TABLE REFERRING TO PART IV OF DOSSIER Volume: [xx] Page: [xx]	(FOR NATIONAL AUTHORITY USE ONLY)
Title: An open, uncontrolled study to investigate the single dose pharmacokinetics of sumatriptan nasal spray in adolescent subjects with migraine outside of a migraine attack		
Investigator(s): Dr Michael Christensen		
Study center(s): University of Tennessee, College of Pharmacy, Memphis, TN, USA		
Publication(s): NA		
Study period: 7 July 1998, - 5 October 1998		Clinical phase: I
Objectives: To evaluate the pharmacokinetics and assess the safety of sumatriptan nasal spray (20mg) administered to adolescent migraineurs outside of a migraine attack		
Methodology: Single dose open study, no comparator, single centre		
Number of subjects: 21 subjects were enrolled in the study, two withdrew their consent		
Diagnosis and criteria for inclusion: male or female adolescents with migraine for at least 6 months; 12 to 17 years of age inclusive, healthy otherwise; suffering from at least 2 but no more than 8 moderate to severe migraines with or without aura per month over the last 2 months		
Test product, dose and mode of administration, batch no.: sumatriptan nasal spray 20mg		Batch 7B12
Duration of treatment: single dose study		
Reference therapy, dose and mode of administration, batch no.: none		
Criteria for evaluation: pharmacokinetics (non-compartmental analysis, PK modelling); safety (vital signs, ECG, laboratory safety, adverse events)		
Statistical methods: descriptive statistics only		
Summary and Conclusions: Twenty-one subjects were treated with single dose 20mg sumatriptan nasal spray; two subjects withdrew from the study; 19 completed the study. Sumatriptan was well tolerated. All adverse events were mild to moderate in intensity and resolved spontaneously. Non-compartmental pharmacokinetic parameters (n=16) of sumatriptan nasal spray were not significantly different from adults: C_{max} was 13.89(10.96, 17.60) ng/mL; AUC_{∞} was 57.32 (47.61, 69.02)ng/mL.hr and $t_{1/2}$ was 2.02(1.77, 2.32) hr. Population analysis showed that clearance and volume of distribution increase with age and body size.		

DRUG FORMULATION

Imitrex® Nasal Sprays are single dose units containing GR43175 nasal solution delivering 5 or 20mg GR43175. (b) (4)

The GR43175 is presented as a solution (b) (4)

(b) (4)

The formula for Imitrex® Nasal Sprays are summarized in the following table:

Nominal Strength	5mg (b) (4) 20mg
Name of Constituents	Quantities (mg/mL of solution)
GR43175X	(b) (4)
Monobasic Potassium Phosphate NF	
Dibasic Sodium Phosphate USP, anhydrous	
Sulfuric Acid NF*	
Sodium Hydroxide NF**	
Purified Water USP	

(b) (4)

IN VIVO STUDY DATA SUMMARY

Study (Report)	Route of Administration / Dosage Form	Dose	Regimen	Population Male/Female	C_{max} ng/mL	T_{max} hours	AUC_{∞} ng.h/mL	Half-life hours
GM1998/00376/01 Protocol SUMB1006	Intranasal/ Nasal spray	20mg	Single dose	Adolescent migraineurs 12/9	15 (43)	2 (0.50-3.00)	59 (30)	2.1 (24)
GCP/93/065 Protocol C93-065	Intranasal/ Nasal spray	20mg	Single dose	Adult healthy subjects * 24/0	14 (44)	1.5 (0.25-3.0)	50 (32)	1.9 (23)

Pharmacokinetic parameters are reported here as arithmetic means and (CV%); the geometric mean and 95% confidence intervals are reported in the text and individual study reports. T_{max} is reported as the median and range.

*Study C93-065

Figure 1. Median sumatriptan concentrations in adolescent after treatment with 20mg sumatriptan nasal spray: all subjects

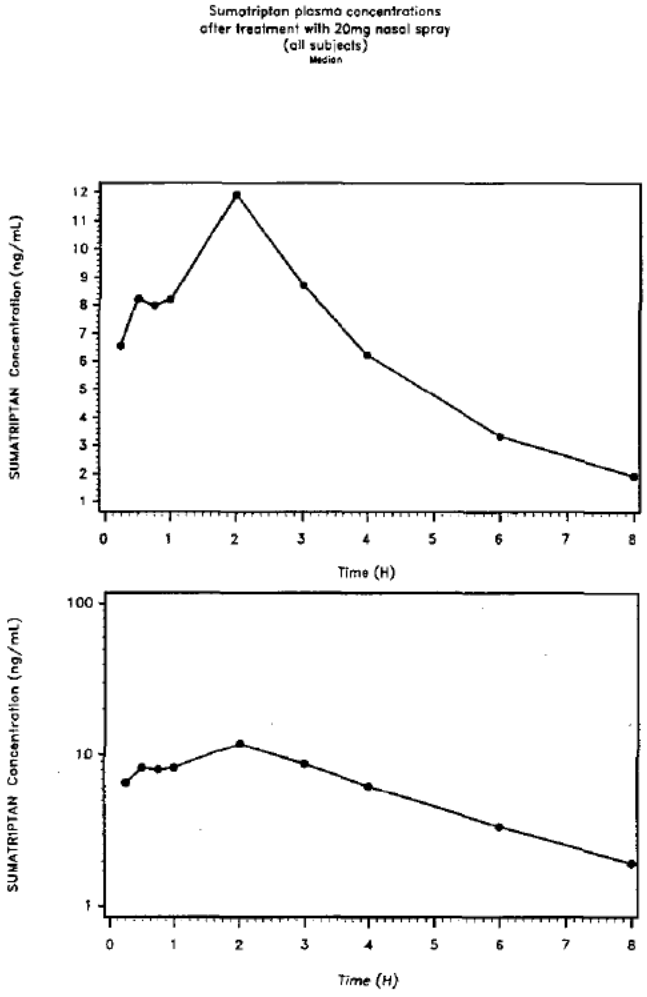

Table 7. Population estimates for derived Sumatriptan Pharmacokinetic Parameters (NONMEM analysis: final model)

Parameter		Estimate (Se)	unit
Apparent Clearance	Cl/F = THETA(1)*WTKG/59.5	330 (6%)	L/h
Apparent Volume of distribution	Vd/F = THETA(2)*AGE	70.8 (10%)	L/yr
Rate constant of absorption (first order abs)	Ka = THETA(3)	8.25 (90%)	h^{-1}
Duration of zero order absorpyion	D2 = THETA(4)	1.22 (15%)	h
Lag-time of zero order asborption	ALAG2= THETA(5)	0.416 (35%)	h
Fraction of the dose absorbed by first order	F1 = THETA(6)	0.423 (30%)	-
Between subject variability on Clearance	ETA(1)	24%	-
Between subject variability cn volume	ETA(2)	43%	-
Between subject variability on lag time	ETA(3)	61%	-
Between subject variability on fraction of dose absorbed by first order	ETA(4)	53%	-
Residual error	EPS	17%	-

/s/

Hong Zhao
11/28/00 01:59:19 PM
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Please sign off

Raman Baweja
11/28/00 02:28:20 PM
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