CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: 20626

STATISTICAL REVIEW(S)

Statistical Review and Evaluation

NDA#: 20-626

APR 26 1996

Sponsor: Glaxo Wellcome Inc.

Name of Drug: Imitrex Nasal Spray

Document Reviewed: Vol 79 (clinical)

Medical Officer: Randy Levin, M.D., HFD-120

This submission consists of eight (8) studies which evaluate the efficacy of Imitrex using a new route of administration (nasal). The primary endpoint in 7 of the 8 studies was the proportion of patients who experienced "relief" (improvement from moderate or severe pain to mild or none) at 2 hours. The sponsor's tables below summarize the results from the trials. The first displays results of active doses vs placebo, whereas the second displays those for active-active comparisons. On the basis of the predominance of very low p-values in these tables, we have concluded that all three doses are effective and that 20mg is more effective than 10mg or 5 mg.

Headache Severity: Relief Rates at 120 Minutes Postdose

Study	Placebo	Sumatriptan 5mg	Sumatriptan 10mg	Sumatriptan 20mg
Dose-Ranging Studies				
S2B-T35	35%	67%**	67%**	78%***
S2B-T39	42%	45%	66%*	74%**
S2B-T47	25%	49%**	46%*	64%***
Single-Attack Studies				
S2B-T05	32%	—	—	75%***
S2B-T50	25%	—	44%***	55%***
S2B-340	35%	—	54%**	63%***
S2B-341	29%	—	43%	62%***
Multiple-Attack Study				
S2B-342#	32%	44%***	54%***	60%***

* p≤0.05 vs. placebo; **p<0.01 vs. placebo; ***p<0.001 vs. placebo.
# Rates for S2B-342 are for all attacks combined.
Note: A "—" indicates that a particular dose and/or efficacy parameter was not evaluated.

Headache Severity: Relief Rates at 120 Minutes Postdose
Comparison of Active Doses

Study	Sumatriptan 5mg	Sumatriptan 10mg	Sumatriptan 20mg
Dose-Ranging Study			
S2B-T47	49%	46%	64%**†
Single-Attack Studies			
S2B-T50	—	44%	55%**
S2B-340	—	54%	63%
S2B-341	—	43%	62%**
Multiple-Attack Study			
S2B-342#	44%	54%	60%*†††

* p≤0.05 vs. 10mg; **p<0.01 vs. 10mg; ***p<0.001 vs. 10mg.
† p≤0.05 vs. 5mg; †† p<0.01 vs. 5mg; ††† p<0.001 vs. 5mg.
# Rates for S2B-342 are for all attacks combined.
Note: A "—" indicates that a particular dose was not evaluated

Dr. Levin and I have concluded that there are no substantial statistical issues which warrant a separate review.

David Hoberman, Ph.D.
Mathematical Statistician

Concur: Dr. Sahlroot JTS 4-26-96

Dr. Chi Chi 4/26/96

cc:
NDA# 20-644
~~HFD-701/Dr. Anello~~
HFD-120/Dr. Leber
HFD-120/Dr. Levin
HFD-120/Dr. Katz
HFD-120/Mr. Purvis
HFD-120/Mr. Grilley
HFD-344/Dr. Lisook
HFD-710/Dr. Chi
HFD-710/Dr. Sahlroot
✓HFD-710/Dr. Hoberman
HFD-710/chron

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: 20626

BIOEQUIVALENCE REVIEW(S)

Imitrex^R Nasal Spray (Sumatriptan) — Glaxo Wellcome Inc.
5, 10, and 20 mg (per 100 µl unit dose) — Moore Drive
Reviewers: Iftekhar Mahmood, Ph. D. — Research Triangle Park, NC 27709.
Vijay K. Tammara, Ph. D.

NDA 20-626 — Submission Dates: August 29, 1995 and October 27, 1995
Submission Dates: October 28, 1994; December 19, 1994; February 23, 1995 and December 18, 1995.

INTRODUCTION

Sumatriptan is a potent agonist for a vascular 5-hydoxytryptamine$_{1D}$ receptor subtype. Sumatriptan is used to relieve migraine attacks. The antimigrainous effect of sumatriptan is believed to be due to vasoconstriction of cranial arteries which are dilated during a migraine attack. Commercially available Imitrex^R Injection and Imitrex^R Tablets have been shown to be effective for the treatment of migraine. Imitrex^R Nasal Spray has been formulated for those patients who are unable to tolerate or unwilling to use Imitrex^R Injection and Imitrex^R Tablets. A clinical program comprising 97 healthy subjects and 3,635 patients exposed to sumatriptan nasal spray has been submitted to the Clinical Division to support the safety and efficacy of Imitrex nasal spray.

Following intranasal administration sumatriptan is rapidly absorbed. The mean C_{max} after a 5, 10, and 20 mg dose was 5, 9 and 16 ng/mL, respectively, and the time to reach peak varies from 1 to 1.5 hours. The terminal half-life of sumatriptan is about two hours. The clearance following a dose of 20 mg intranasally is about 7 Liters/minute, whereas the renal clearance is about 0.21 Liters/minute. The relative bioavailability following intranasal administration was 16.7% as compared to subcutaneous administration. Mean values of C_{max} and AUC increased with dose indicating that sumatriptan is linear over the single dose range of 2.5 to 20 mg. Pretreatment with a nasal decongestant (xylometazoline), 15 minutes before intranasal administration of sumatriptan produced no effect on the pharmacokinetics of sumatriptan.

The Sponsor has submitted 10 pharmacokinetic studies. Four studies were found to be pivotal and reviewed. The other 6 studies were not the focus of this application (due to unrelated dosage form and formulation, and small sample size (n = 2 or 4) and therefore, were not reviewed.

Table of Contents

SUMMARY

I. BIOAVAILABILITY:

A. Relative Bioavailability:

The relative bioavailability for the suppository was slightly higher (22%; CV = 33%) than that of oral (15%; CV = 48%) or intranasal (16.7%; CV=30%) administration, as compared to subcutaneous administration (Study 1). The relative bioavailability of sumatriptan for the tablets and intranasal spray were similar.

B. Bioequivalence:

Bioequivalence studies for the intranasal formulation were not performed since the proposed market formulation (formulation D) was used in the pivotal clinical trials

II. PHARMACOKINETICS:

A. Absorption:

Pharmacokinetic parameters (AUC and C_{max}) show a large degree of variability (%CV = 20-50%) due to a variety of factors such as deposition of intranasal solution in the nasal passage, the extent of dose that is swallowed and variable presystemic metabolism.

Sumatriptan is rapidly absorbed following intranasal administration. The mean C_{max} after a 5, 10, and 20 mg dose was 5.0 (CV = 31%), 8.9 (CV = 28.6%) and 16.1 (CV = 48.9%) ng/mL, respectively, and the time to reach peak varied from 1 to 1.5 hours (Study 2a).

B. Metabolism:

Sumatriptan is metabolized by monoamine oxidase (MAO) , predominantly the A isozyme to the inactive indole acetic acid analogu

C. Elimination:

The terminal elimination half-life of sumatriptan following intranasal administration is about 2 hours and is consistent with that observed after oral and subcutaneous administration. The clearance following a 20 mg dose of sumatriptan intranasally was about 7 L/min and the renal clearance was 0.21 L/min. Following intranasal sumatriptan administration, approximately 42% of the administered dose is excreted in the urine as indole acetic acid and 3% as unchanged drug (Study 1).

D. Dose Proportionality:

Mean values of C_{max} and AUC increased with dose, demonstrating dose proportionality over the single dose range of 2.5 to 20 mg (Studies 2a and 2b).

E. Multiple Dosing:

Multiple administration (3 times daily for 10 doses) of intranasal sumatriptan (20 mg) produced a 22% accumulation of the parent and metabolite in plasma (Study 3). Serum metabolite concentrations were 4-5 fold higher than corresponding sumatriptan concentrations.

III. SPECIAL POPULATIONS:

The pharmacokinetics of intranasal sumatriptan has not been evaluated in special populations. However, such information is available following oral and subcutaneous administration of sumatriptan.

A. Age:

The pharmacokinetics of sumatriptan in healthy elderly subjects (mean age 71.1 years) was similar to young healthy volunteers.

B. Gender:

Following 100 mg oral administration of sumatriptan in males and females, the AUC was 21% higher in females compared to males. Adjusted for body weight the difference was statistically not significant.

C. Hepatic Impairment:

In the hepatically impaired patients, no difference in the pharmacokinetics of sumatriptan was found after subcutaneous administration. However, after oral administration, the C_{max} and AUC were about 70% higher in the hepatically impaired patients compared to controls.

D. Renal Impairment:

The effect of renal impairment on the pharmacokinetics of sumatriptan has not been evaluated, since renal excretion is not a primary route of elimination for sumatriptan, the primary metabolite (indole acetic acid) is inactive, and the drug is indicated for acute therapy only.

IV. DRUG INTERACTION:

The pharmacokinetic drug interaction study between sumatriptan nasal spray and a nasal decongestant, xylometazoline (3 drops, 0.1% w/v) indicated that xylometazoline when administered 15 minutes prior to a 20 mg nasal dose of sumatriptan does not alter the pharmacokinetics of sumatriptan (Study 4).

V. ANALYTICAL METHODS:

detection.

VI. BIOWAIVER:

The sponsor under the provisions of 21 CFR 320.22 has submitted a waiver request for additional study(ies) evaluating the bioequivalence and substitutability of two separate 5 mg sprays (one in each nostril) of sumatriptan nasal spray compared to a single 10 mg spray.

The clinical and pharmacokinetic data demonstrated that a single 10 mg dose given in one nostril ( ) is comparable to the administration of two 5 mg sumatriptan nasal sprays (one spray in each nostril,) using preserved, unbuffered formulations. Efficacy following a 10 mg dose was observed to be similar across studies regardless of the formulations [preserved, unbuffered ( ) vs. unpreserved, buffered (to-be-marketed, ___)], and there was no difference in efficacy when 10 mg dose was administered as one 10 mg spray in one nostril vs. two 5 mg sprays, one in each nostril. In addition, based on the known dose proportionality over the dosing range of 2.5-20 mg, and a wide therapeutic window, the Agency agrees with the sponsor's request for a biowaiver.

COMMENTS TO THE CLINICAL DIVISION (HFD-120):

1. The Sponsor has provided pharmacokinetic data to support substitution of two 5 mg nasal sprays (one in each nostril) compared to a single 10 mg nasal spray in one nostril. Based on similar efficacy and pharmacokinetic results, the following information could be included under the "Dosage and Administrations" section of the labeling:
"Clinical and pharmacokinetic data support the administration of a 10 mg dose as two 5 mg applications (one in each nostril)".

2. The reviewing Chemist is requested to note and make appropriate revisions in Line 15 of the sponsor's proposed labeling, where the unit dose volume for each strength of the nasal spray has not been mentioned.

APPEARS THIS WAY
ON ORIGINAL

LABELING COMMENTS

The Sponsor is requested to perform the following revisions on the submitted annotated draft labeling:

Comment 1:

The following information should be deleted under the **"Pharmacokinetics: Absorption and Elimination"** section of the proposed labeling:

Comment 2:

The following information should be deleted under the **"Pharmacokinetics: Absorption and Elimination"** section of the proposed labeling:

Comment 3:

The Sponsor is requested to incorporate the following information under the **"Drug Interaction"** section of the proposed labeling:

"The pharmacokinetic drug interaction study between sumatriptan nasal spray and a nasal decongestant, xylometazoline indicated that 3 drops of xylometazoline (0.1% w/v) when administered 15 minutes prior to a 20 mg nasal dose of sumatriptan does not alter the pharmacokinetics of sumatriptan".

Comment 4:

The sponsor is requested to revise all pharmacokinetic parameter values reported in the proposed labeling using arithmetic means rather than geometric means.

Recommendations:

From a pharmacokinetic point of view this NDA is acceptable to the Office of Clinical Pharmacology and Biopharmaceutics. The Sponsor is requested to incorporate all the labeling changes as outlined in Comments 1-4.

The waiver for additional study(ies) to evaluate the bioequivalence of two separate 5 mg sprays (one in each nostril) of sumatriptan nasal spray compared to a single 10 mg spray is granted to the sponsor under the provisions of 21 CFR 320.22.

Please, forward this Recommendation and Labeling Comments to the Sponsor.

Iftekhar Mahmood, Ph.D. _____ 12/29/95

Vijay K. Tammara, Ph. D. _____ 12/29/95

RD/FT initialed by Mohammad Hossain, Ph.D. _____ 12/29/95

Division of Pharmaceutical Evaluation I

Biopharm Day: December 27, 1995 (attendees: Fleischer, Mehta, Hossain, Tammara and Mahmood).

CC: NDA 20-626, HFD-120, HFD-860 (Mahmood, Tammara, Hossain, Mehta, Malinowski), HFD-870 (Chen Me), HFD-880 (Fleischer), HFD-340 (Viswanathan), Chron, Drug, Reviewer and FOI (HFD-19) files.

STUDY #1

SUMMARY OF REPORT

TITLE

A study to estimate the bioavailability of single dose oral, suppository and intranasal sumatriptan and to compare the pharmacokinetic profiles following these routes and subcutaneous sumatriptan.

OBJECTIVES

To estimate the bioavailability of sumatriptan administered as an oral tablet, suppository and intranasal spray.

To directly compare the pharmacokinetic profile of sumatriptan administered as a subcutaneous injection, oral tablet, suppository and as an intranasal spray.

DESIGN

This was an open, randomised, four-way cross-over study. Each subject received sumatriptan as a subcutaneous injection (6mg), oral tablet (25mg), suppository (25mg) and intranasal spray (20mg). Treatments were administered on separate occasions at least three days apart.

SETTING/STUDY DATES

The study was performed at the Clinical Pharmacology and Dynamics Department, Glaxo Research and Development Limited, Ware between 21 December 1993 and 28 March 1994.

SUBJECTS

Twenty-four healthy male subjects aged 22-49 years (mean age 35.9 years), and weighing 70.8-97.3kg (mean weight 82.1kg) completed the study.

TREATMENTS

Each subject received sumatriptan as a:

a) 6mg subcutaneous injection
b) 25mg oral tablet
c) 25mg suppository*
d) 20mg intranasal spray –TBM–1D4

on four separate study days, at approximately 08.30-09.00 hours.

* a 4g glycerol suppository was self-administered the night before treatment with sumatriptan suppository, in order to assist evacuation of the bowels.

MEASUREMENTS

Pharmacodynamics

Not applicable.

Pharmacokinetics

Blood samples (5mL) to measure serum sumatriptan concentrations were taken pre-treatment and at: 10, 20, 30, 45 minutes, 1, 1.5, 2, 3, 4, 6 and 8 hours post oral and suppository treatments.

Blood samples were taken pre-treatment and at: 2, 5, 10, 15, 20, 30, 45 minutes, 1, 1.5, 2, 3, 4, 6, 8 hours post subcutaneous and intranasal treatments.
All urine voided was collected at 0-2, 2-4, 4-6, 6-12 and 12-24 hours post-treatment and recorded as weight. A pre-treatment sample was also collected. Aliquots were stored pending analysis for sumatriptan (20mL) and concentrations (100mL).

Safety

Safety was assessed by recording adverse events during the monitoring period and performing routine clinical chemistry, haematology and urinalysis screening pre-study (within 3 weeks of the first treatment) and 6-8 days post study. Any values outside the reference ranges were repeated if considered clinically significant.

Conclusion:

The results of this study indicated that the relative bioavailability for the suppository was slightly higher (22%) than that of oral (15%) or intranasal (16.7%) administration, when compared to the subcutaneous route of administration. Though the renal clearance of sumatriptan was almost similar across all four routes of administration, the oral clearance was almost 7 fold higher for oral tablet than the subcutaneous administration, indicating a substantial metabolism of sumatriptan in the gut and/or the liver. This can also be demonstrated from the urinary recovery of the , which was 4 fold higher after oral dosing than subcutaneous administration of sumatriptan. The pharmacokinetics of sumatriptan following oral and intranasal routes were similar.

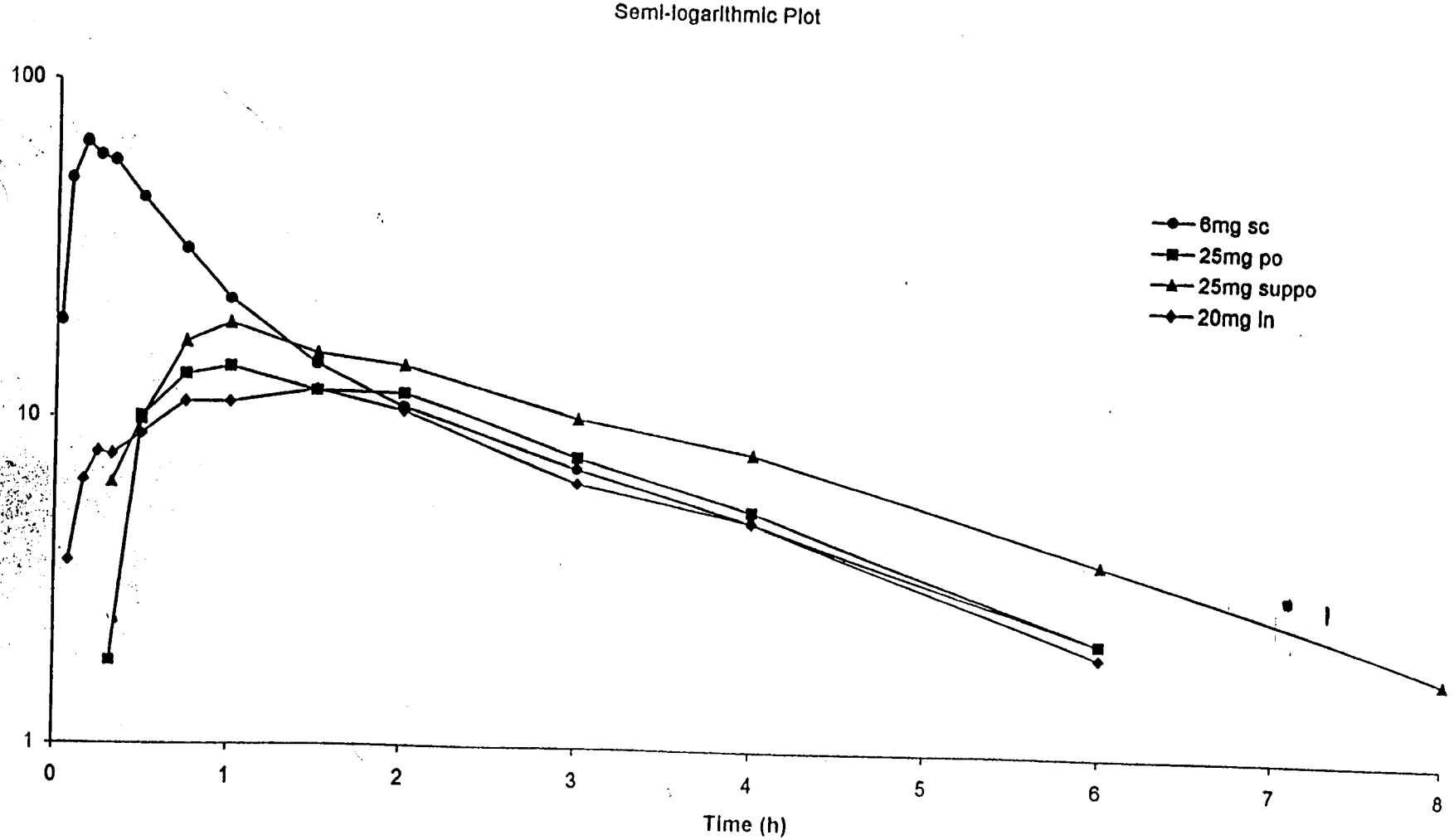
TABLE 2. SUMMARY OF PHARMACOKINETIC AND ASSOCIATED STATISTICAL ANALYSIS

Parameter		Route of administration			
		Subcutaneous 6mg	Oral 25mg	Suppository 25mg	Intranasal 20mg
F (/sc) (%)	Geo LSMean	-	14.3	19.2	15.8
	95%CI	-	11.4 - 17.9	15.3 - 24.1	12.6 - 19.8
	Ari Mean	-	15.0	21.8	16.7
	CV %		32.8	48.6	29.9
F (/po) (%)	Geo LSMean	-	-	134.7	111.0
	95%CI	-	-	107.5 - 168.9	88.6 - 139.2
	Ari Mean	-	-	168.2	121.7
	CV %		-	63.9	44.3
AUC_{∞} (h.ng/mL)	Geo Mean	89.7	53.3	72.1	47.7
	95%CI	84.5 - 95.3	45.2 - 62.9	57.4 - 90.4	41.1 - 55.3
	Arith Mean	90.6	57.5	82.1	50.3
	CV %	14.0	43.9	53.8	32.4
AUC_{last} (h.ng/mL)	Geo Mean	82.9	47.0	64.2	41.9
	95%CI	77.7 - 88.4	39.5 - 56.1	51.2 - 80.3	35.6 - 49.2
	Arith Mean	83.8	51.2	72.7	44.7
	CV %	15.5	47.8	50.5	36.0
C_{max} (h.ng/mL)	Geo Mean	69.5	16.5	22.9	12.9
	95%CI	62.8 - 76.8	13.5 - 20.1	18.4 - 28.6	10.5 - 15.9
	Arith Mean	71.3	18.3	26.0	14.3
	CV %	24.3	49.7	53.9	43.7
t_{max} (h)	Median	0.17	1.50	1.00	1.50
	Range	0			
	Arith Mean	0.21	1.25	1.34	1.15
	CV %	31.2	45.9	42.8	62.8
C_{max}/AUC_{∞} (1/h)	Geo Mean	0.77	0.31	0.32	0.27
	95% CI	0.71-0.84	0.27-0.35	0.26-0.39	0.24-0.30
	Arith Mean	0.79	0.32	0.35	0.28
	CV%	18.2	27.1	42.2	21.5
λ_z (1/h)	Geo Mean	0.368	0.417	0.378	0.377
	95%CI	0.342 - 0.396	0.359 - 0.485	0.320 - 0.445	0.342 - 0.414
	Arith Mean	0.374	0.442	0.403	0.385
	CV %	17.4	35.2	34.4	21.1
$t_{½}$ (h)	Geo Mean	1.9	1.7	1.8	1.8
	95%CI	1.7 - 2.0	1.4 - 1.9	1.6 - 2.2	1.7 - 2.0
	Arith Mean	1.9	1.8	2.0	1.9
	CV %	16.9	37.4	44.7	23.3

TABLE 2. SUMMARY OF PHARMACOKINETIC AND ASSOCIATED STATISTICAL ANALYSIS (CONTINUED)

Parameter		Route of administration			
		Subcutaneous 6mg	Oral 25mg	Suppository 25mg	Intranasal 20mg
Cl/F (L/min)	Geo Mean	1.11	7.81	5.78	7.00
	95%CI	1.05 - 1.18	6.62 - 9.21	4.61 - 7.25	6.03 - 8.12
	Arith Mean	1.12	8.35	6.58	7.42
	CV %	13.6	37.0	53.1	36.6
(mg)	Geo Mean	1.02	0.45	0.70	0.44
	95%CI	0.88 - 1.18	0.32 - 0.63	0.53 - 0.93	0.33 - 0.57
	Arith Mean	1.07	0.56	0.84	0.51
	CV %	30.8	54.2	56.7	48.2
Clr (L/min)	Geo Mean	0.22	0.17	0.17	0.21
	95%CI	0.19 - 0.25	0.14 - 0.21	0.14 - 0.21	0.18 - 0.25
	Arith Mean	0.23	0.18	0.20	0.23
	CV %	31.2	35.9	77.6	50.0
(mg)	Geo Mean	3.08	12.74	6.59	7.63
	95%CI	2.59 - 3.67	10.89 - 14.90	5.12 - 8.48	6.45 - 9.03
	Arith Mean	3.33	13.65	7.67	8.19
	CV %	38.1	41.2	51.7	36.3

FIGURE 2. MEDIAN CONCENTRATIONS OF SUMATRIPTAN IN SERUM FOR EACH ROUTE OF ADMINISTRATION (N=23)



APPEARS THIS WAY
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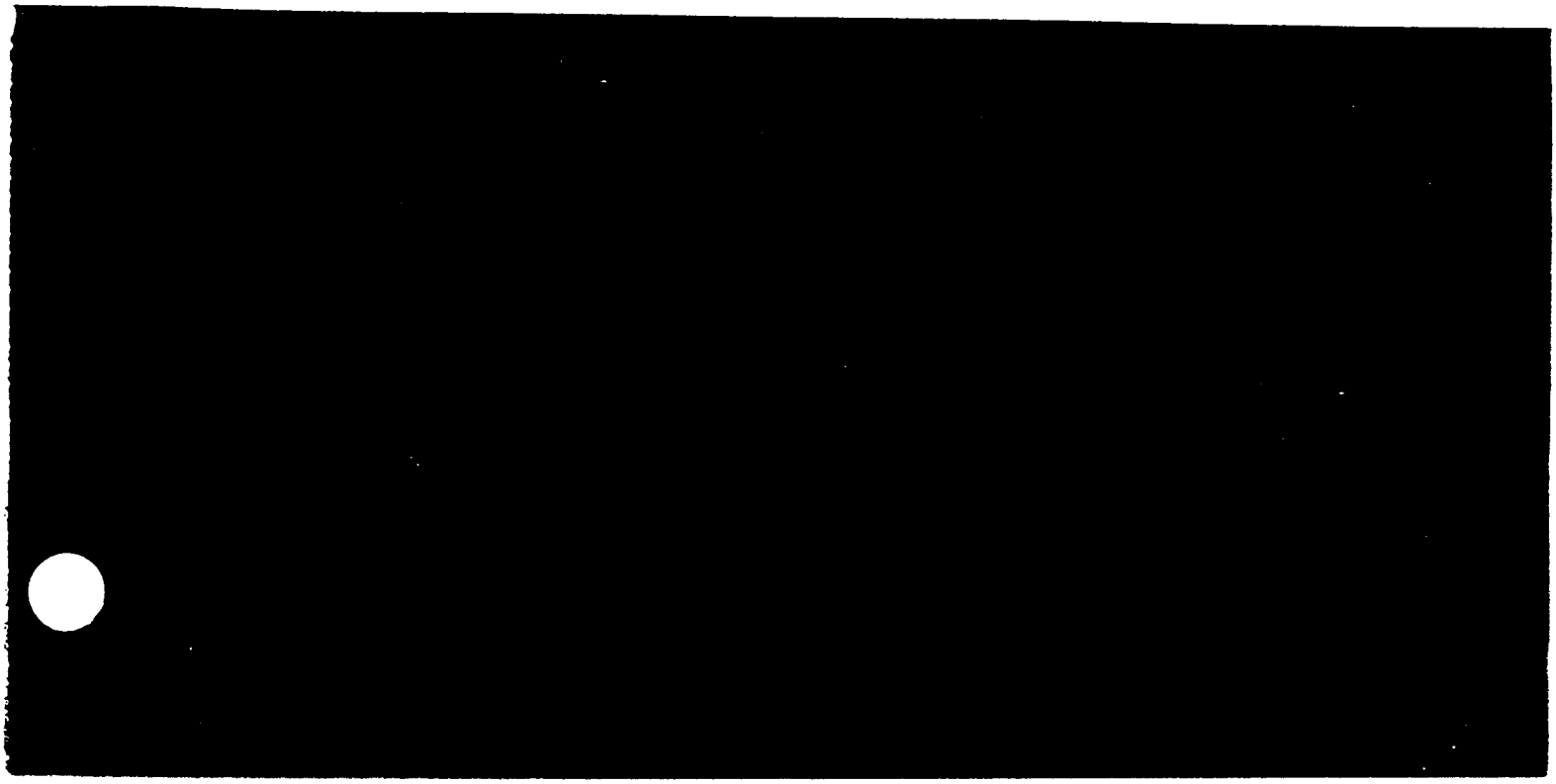
The structures of sumatriptan and the indole acetic acid metabolite are depicted below.



Metabolism: Sumatriptan is metabolized by monoamine oxidase (MAO), predominantly the A isoenzyme to the indole acetic acid analogue, (Report WBP/92/060, NDA 20-132, April 18, 1994). Following intranasal sumatriptan administration, approximately 42% of the administered dose is excreted in the urine as (Protoc . In the serum, is present at concentrations 4 times greater relative to sumatriptan (Protocol

The following summarizes the pharmacokinetic and pharmacodynamic profile of sumatriptan and its metabolites:

Compound Metabolite	Percent (range) radioactivity in Plasma/Urine mean (range)	Half Life (hours) mean	Ratio of Met/Parent AUC/Cmax	Relevant Pharmacologic Activity	Protein Type and % Bound	Toxicity	Enzyme/ Isoenzyme Reponsible
Total Radio-activity[1]	UR=50-65% Feces 38% Total 89-99%	oral 2.4					
	Plasma 5.7% (3.8-7.8) Urine 3.3% (2.6-4.8)	Oral 1.5 Supp 1.8 IN 2.1		5 HT_1 agonist	14-21%		
	Plasma 67.8 Urine 35%	Oral 2.3 Supp 2.7 IN 1.8	Oral 11/9 Subc 1.5/0.5 Supp 2.3/1.2 IN 5.2/4.8	no activity[2]	N/A	none known	MAO-A[3]
ester glucuronide		8					

[1] oral administration (Protocol WHP:89:01, Original NDA-080, Vol. 62, p. 001)
[2] Report WNP/90/012 (Original NDA 20-080, June 29, 1990)
[3] Report WBP/92/060 (NDA 20-132, April 18, 1994)

STUDY #2a

SUMMARY OF REPORT GCP/93/053

TITLE

A study to assess the pharmacokinetic and pharmacodynamic profile of intranasal sumatriptan at doses of 5mg, 10mg and 20mg (Protocol number

OBJECTIVES

The aim of this study was to assess the pharmacokinetic profile following intranasal sumatriptan at doses of 5mg, 10mg and 20mg.

To monitor blood pressure effects following intranasal sumatriptan at doses of 5mg, 10mg and 20mg.

DESIGN

This was a double-blind, placebo controlled, four-way crossover study in which each subject received three doses of intranasal sumatriptan and placebo on four separate occasions. There was an interval of at least four days between each treatment.

LOCATION/STUDY DATES

The study was carried out in the
between 16 September 1993 and 24 November 1993.

PARTICIPANTS

Twenty healthy female volunteers, aged between 22 and 45 years (mean age 31 years), weighing between 50.4 and 76.9kg, (mean weight 60.7kg) and height between 153 and 168cm (mean height 162.4cm) completed this study.

TREATMENTS

Unit dose nasal sprays containing base as the hemisulphate salt were supplied.

Subjects received one of the following treatments as a 100µL shot on separate occasions, in a randomised order.

1. 5mg sumatriptan (
2. 10mg sumatriptan (
3. 20mg sumatriptan (
4. Placebo

} TBM-"D"

~~17~~ 16

MEASUREMENTS

Pharmacokinetics

Blood samples (5mL) for sumatriptan levels were taken pre-treatment and at 5, 10, 15, 20, 30, 45 minutes 1, 1.5, 2, 3, 4, 6 and 8 hours after treatment.

Pharmacodynamics

Blood pressure measurements were taken pre-treatment and at 5, 10, 15, 20, 30, 45 minutes, 1, 1.5, 2, 3 and 4 hours after treatment.

RESULTS

Pharmacokinetics

The results of the non-compartmental pharmacokinetic analysis are summarised below:

Parameter	Dose	5mg	10mg	20mg
C_{max} (ng/mL)	Geo LSMean	4.7	8.5	14.4
	95%CI	3.9-5.7	7.4-9.8	11.3-18.2
	Arith Mean	5.0	8.9	16.1
	CV%	31.0	28.6	48.9
t_{max} (h)	Median	1.00	1.50	1.00
	Range			
	Arith Mean	1.17	1.45	1.42
	CV%	59.9	60.1	77.5
t½ (h)	Geo LSMean	2.0	2.0	2.0
	95%CI	1.6-2.4	1.6-2.5	1.7-2.4
	Arith Mean	2.1	2.1	2.1
	CV%	38.2	43.1	46.1
AUC_{∞} (ng.h/mL)	Geo LSMean	18.5	30.7	53.5
	95%CI	15.8-21.5	26.8-39.2	41.7-68.8
	Arith Mean	19.0	33.0	60.2
	CV%	22.1	32.0	50.3

CI =confidence interval, Geo LSMean:geometric least square mean, CV:coefficient of variation.

The statistical results of dose normalised parameter comparison are summarised below:

	Dose comparison	Estimate of the ratio	90% CI of the ratio	ANOVA p-value
C_{max}	10 vs 5mg	0.90	0.74 - 1.11	0.416
	20 vs 5mg	0.76	0.62 - 0.94	0.033
	20 vs 10mg	0.84	0.69 - 1.04	0.171
AUC_{∞}	10 vs 5mg	0.82	0.64 - 1.06	0.194
	20 vs 5mg	0.79	0.62 - 1.00	0.099
	20 vs 10mg	0.96	0.78 - 1.20	0.770

Proportionality was demonstrated between 5 and 10mg but not across the dose range 5-20mg. In the opinion of this reviewer, Sumatriptan is proportional over the dose range of 5-20 mg.

Pharmacodynamics

There was no statistically significant difference in systolic blood pressure or pulse rate following any dose of sumatriptan compared to placebo.

For diastolic blood pressure the weighted mean difference from baseline over the period 0-4h after dosing was 3mmHg greater following 5mg of sumatriptan than following placebo (95% CI: 0 to 5 p=0.019). No other statistically significant differences were found.

SAFETY

Adverse Events and Subject Withdrawal

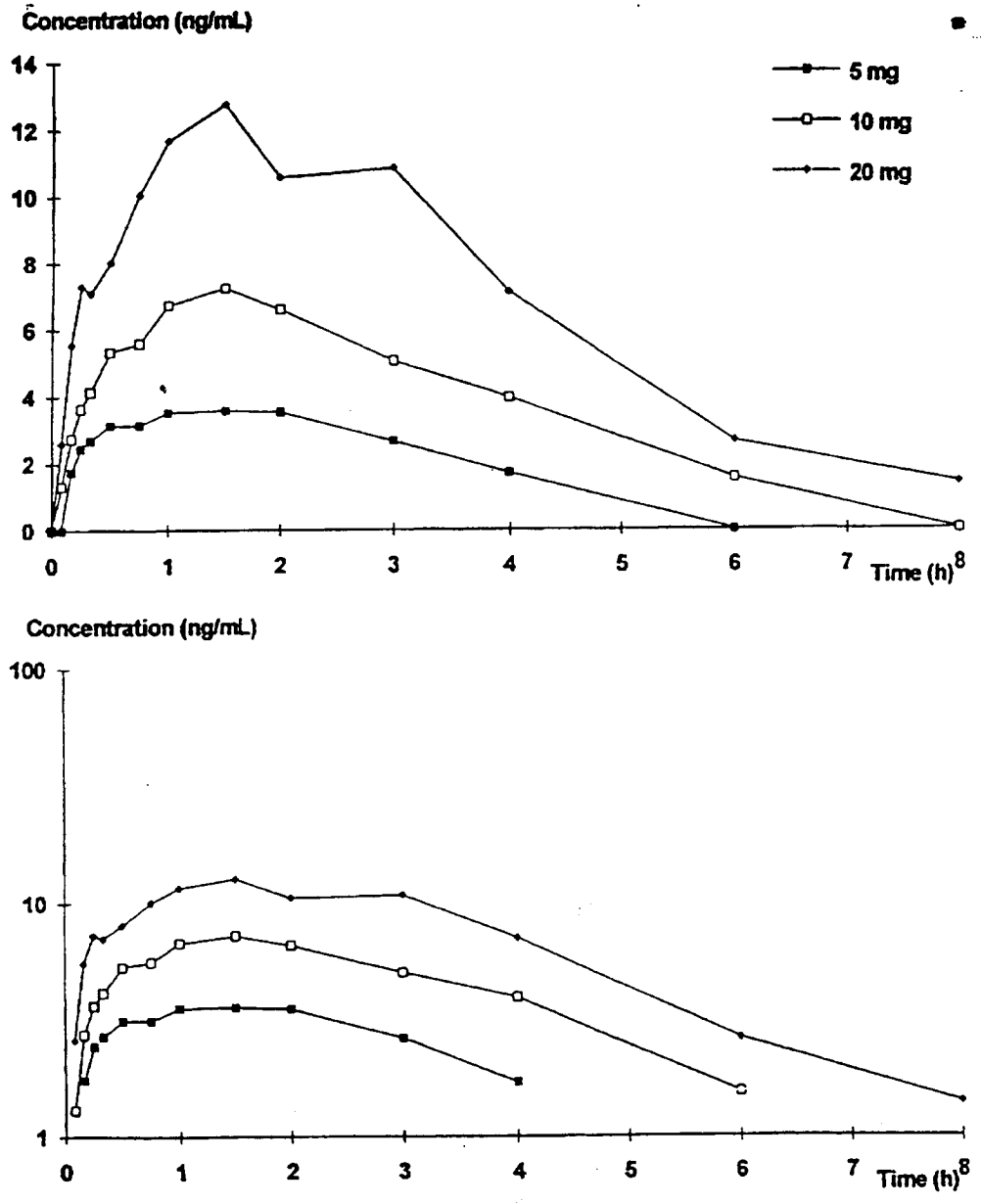
No subjects withdrew from the study. Adverse events mainly consisted of reports of bitter taste at back of throat, which were considered drug related. One subject experienced stomach cramps and loss of appetite on all four study days.

All other adverse events were typical of those seen previously following administration of sumatriptan which included headache, lightheadedness and tingling.

LABORATORY SAFETY SCREENING

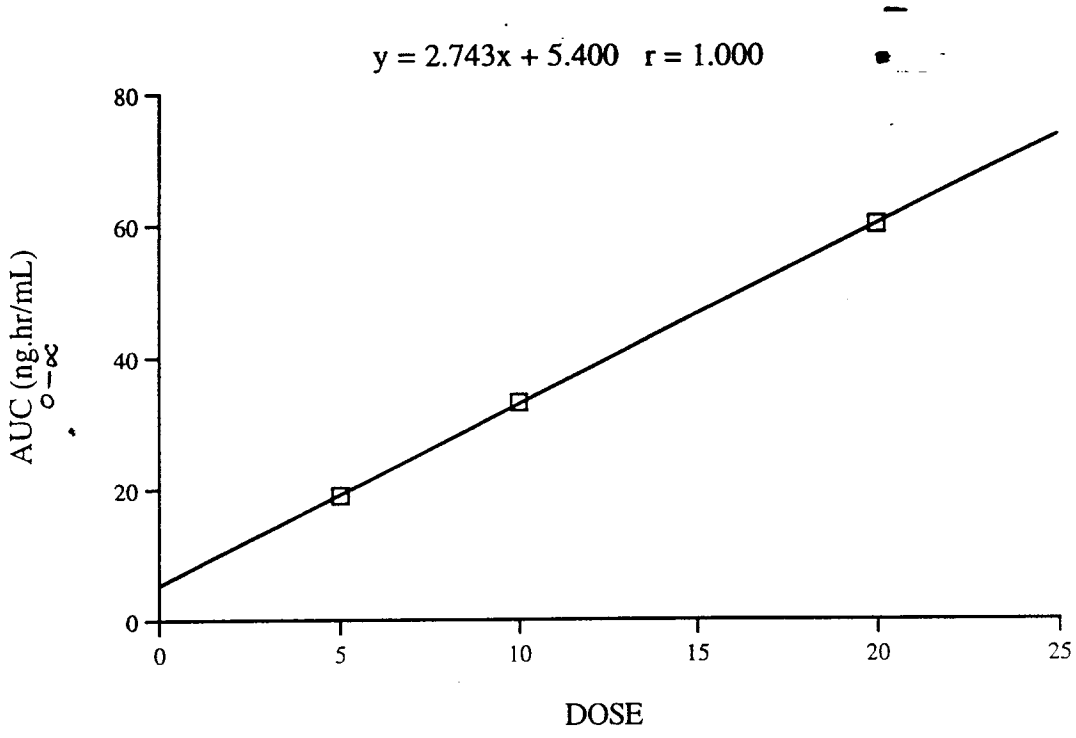
Laboratory safety screening (clinical chemistry, haematology and urinalysis) were carried out pre-study, and 6-8 days post study. In the opinion of the Medically Qualified person responsible there were no clinically significant changes attributable to drug administration.

Figure 1 Median plasma concentration-time profiles following intranasal administration of 5, 10 and 20mg of sumatriptan to 20 healthy female subjects.



(Analysis Performed by the Reviewer)

AUC vs Dose
$0-\infty$



Cmax vs Dose

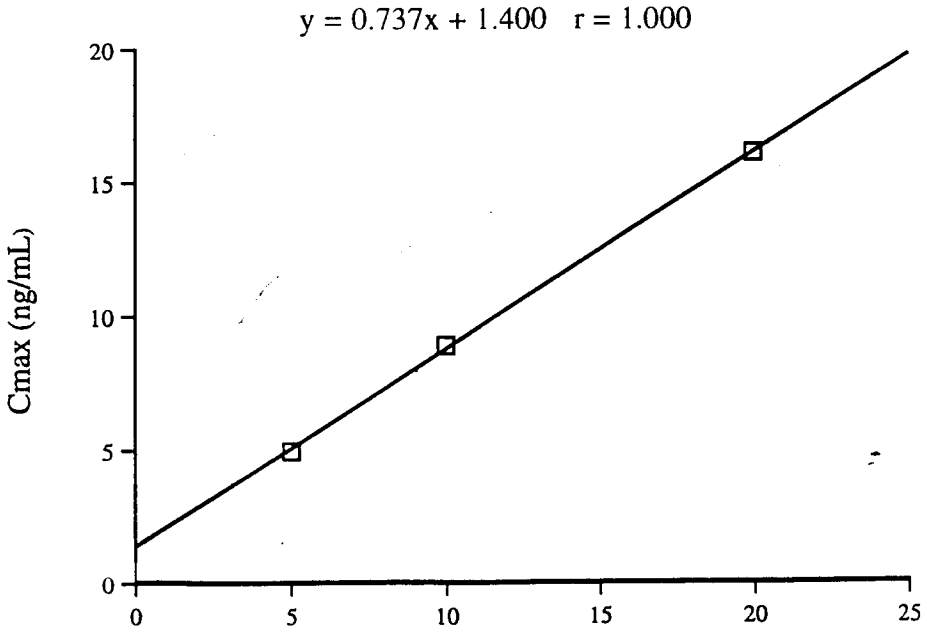


Figure 2 **Mean C_{max} (ng/mL) following intranasal administration of 5, 10 and 20mg of sumatriptan to 20 healthy female subjects.**

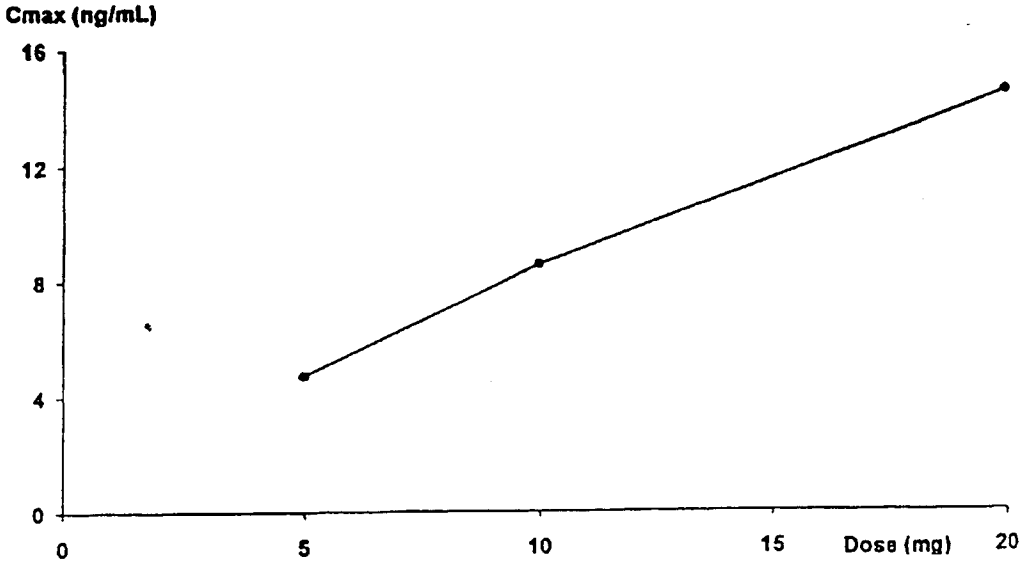
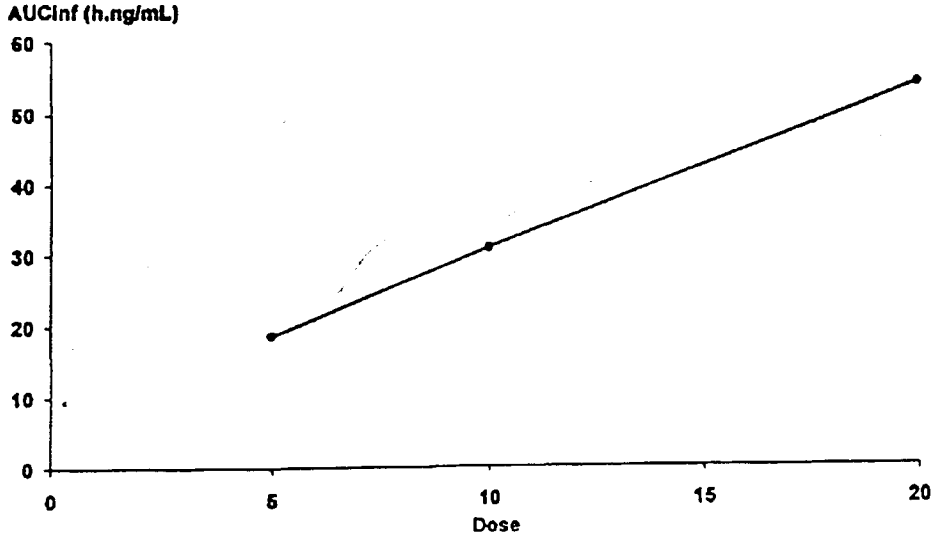


Figure 4 **Mean AUC_{∞} (h.ng/mL) following intranasal administration of 5, 10 and 20mg of sumatriptan to 20 healthy female subjects.**



STUDY #2b

SUMMARY OF REPORT GCV/94/007

TITLE

PROTOCOL S2BT47 (Re-issued): A double-blind, placebo-controlled, parallel group study to evaluate four dose levels of intranasal sumatriptan (2.5, 5, 10 and 20mg) in the acute treatment of migraine.

OBJECTIVES

The primary objective of the study was: TBM — 'D'

- to compare the efficacy of intranasal sumatriptan (GR43175N 2.5, 5, 10 and 20mg) with that of placebo in the acute treatment of migraine in terms of headache relief and resultant headache severity grades post-dosing.

The secondary objectives were:

a) to compare the efficacy of intranasal sumatriptan with placebo in terms of:

- resolution of nausea, vomiting, photophobia and/or phonophobia
- reduction of patients clinical disability scores
- the time to meaningful relief of headache pain

b) to assess the safety and tolerability of intranasal sumatriptan

c) to compare the pharmacokinetics of the different doses of intranasal sumatriptan

DESIGN

This was a double-blind, randomised placebo-controlled, multicentre, multinational, parallel group, dose-ranging study. Each patient treated a single migraine attack.

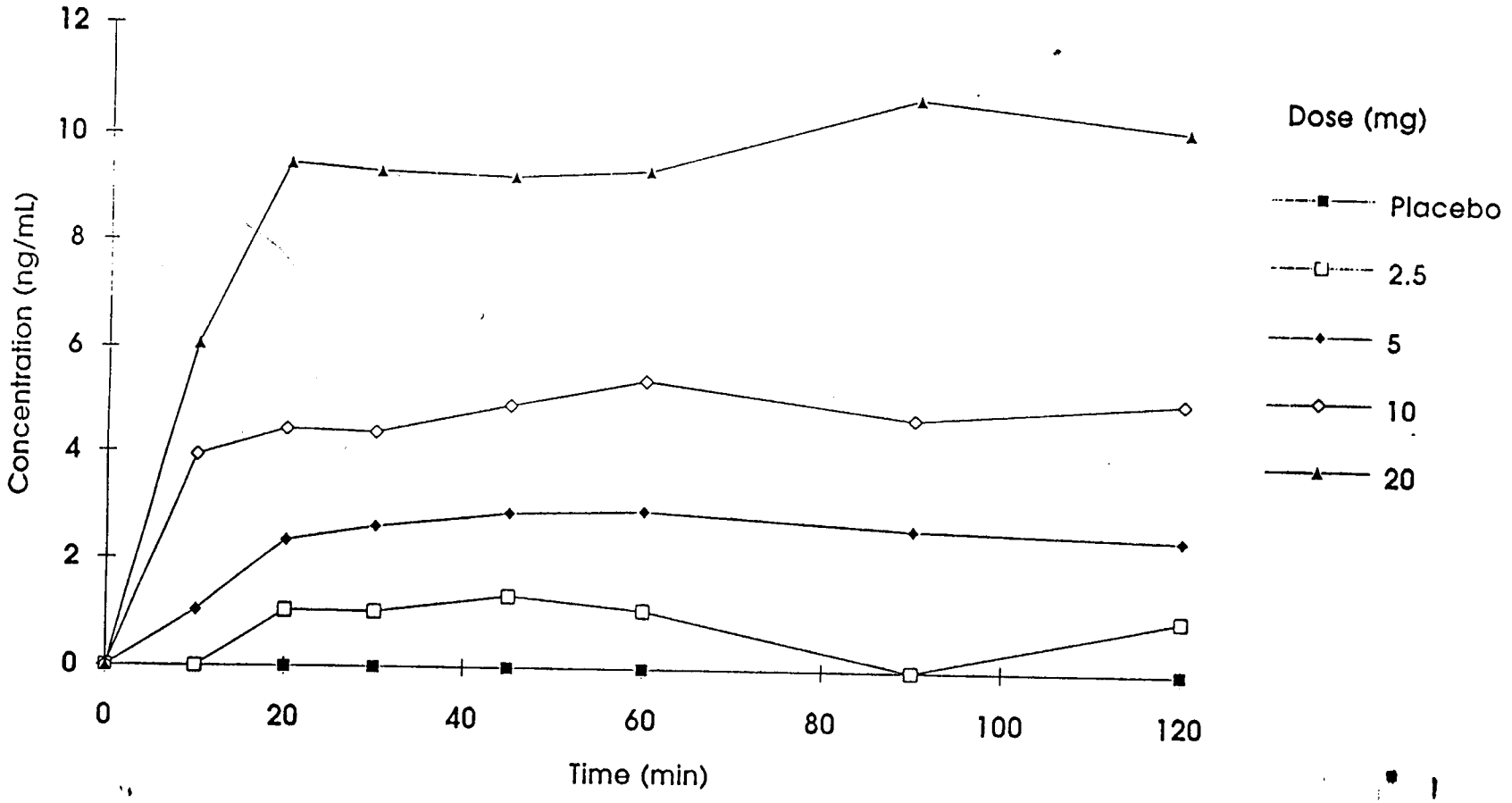
SETTING

The study was conducted at 68 centres in eight countries (Canada, Finland, France, Germany, Holland, Israel, Norway and Sweden). Patients were treated in the clinic where they remained for the first 2 hours post dosing; they then continued to record details of their attack on a diary card on an out-patient basis for the next 22 hours.

PATIENTS

A total of 855 patients were enrolled into the study; 544 patients (placebo 64, sumatriptan 2.5mg 123, 5mg 122, 10mg 115 and 20mg 120) went on to treat an attack with study medication.

Figure 3. Median serum concentration vs time during migraine attack after intranasal administration



jure 4: Dose proportionality of Cmax

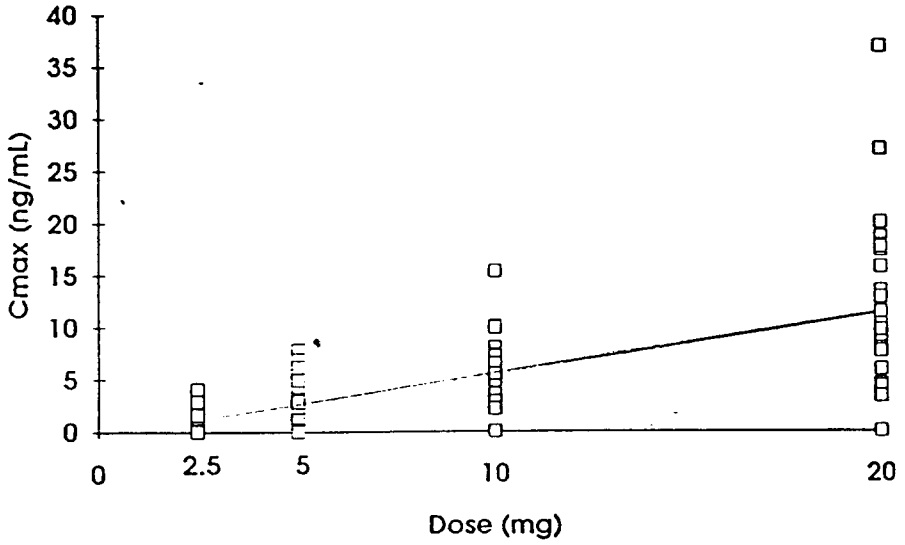
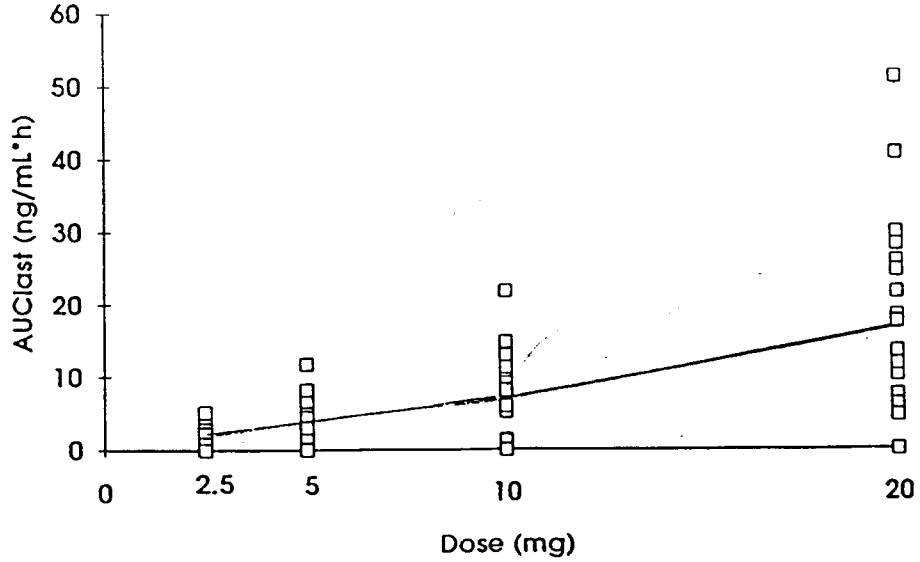


Figure 5: Dose proportionality of AUC



STUDY #3

SUMMARY

TITLE

PROTOCOL A Study to Evaluate the Safety, Tolerability, and Pharmacokinetics of Sumatriptan Following Repeat Administration Intranasally

OBJECTIVES

The objectives of this study were: 1) to investigate the safety and tolerability of sumatriptan 20mg administered intranasally three times daily (at four hour intervals) for 4 days and 2) to investigate the steady state pharmacokinetics of sumatriptan 20mg administered intranasally three times daily (at four hour intervals) for 4 days.

DESIGN

This was a randomized, placebo controlled, double-blind, two period, repeat dose crossover study in 12 evaluable adult healthy volunteers.

SETTING

This study was conducted at
Subjects were admitted and received treatments as in-patients. Subjects were dosed between 27 June 1994 and 15 July 1994.

SUBJECTS

Twelve (12) evaluable adult volunteers who were healthy and between the ages of 18-45 years of age were enrolled in the study.

TREATMENTS

TBM-"D"

Each volunteer received A) Sumatriptan 20mg intranasally (hemisulphate salt as aqueous nasal spray containing 20mg base equivalent/100µL administered via a one shot nasal applicator and B) placebo.

ASSAY

MEASUREMENTS

Pharmacokinetic

Serum and urine samples were collected during the 8 hours following the 4 p.m. intranasal dose on Day 1 and 4 for determination of sumatriptan and its indole acetic metabolite concentrations. Day 1 and Day 4 pharmacokinetic parameters including peak serum concentration (C_{max}), time of peak serum concentration (T_{max}), area under the curve (AUC), the elimination rate constant (λ_z), half-life ($t_{1/2}$), renal clearance (Cl_r), and the amount (Ae) and fraction of the dose (fe) excreted in the urine were calculated and compared to determine the effect of multiple dosing.

Safety

Safety and tolerability were evaluated by monitoring:

- physical examination at screening, and at the end of each treatment phase;
- clinical adverse events, vital signs, 12-Lead ECG (also at screening);
- evaluation of the nasal mucosa by nare speculum at screening, prior the 4 p.m. dose and one hour after this dose on Days 1 and 4;
- olfaction evaluated prior to first dose (Day 1) and one hour after the last dose (Day 4);
- clinical laboratory tests at screening and post-study.

RESULTS

Pharmacokinetic

Twelve subjects completed the study.

Pharmacokinetic parameters for the 12 subjects are summarized below:

	Day 1 Sumatriptan	Day 4 Sumatriptan	Ratio Day 4 / Day 1	Day 1 Metabolite	Day 4 Metabolite	Ratio Day 4 / Day 1
AUC* (ng*h/mL)						
Geo. LS mean	55.1	61.2		288.2	316.3	
95% CI	(44.4 - 68.4)	(49.3 - 75.9)		(215.7 - 385.2)	(236.6 - 422.7)	
Mean ratio			1.11			1.10
90% CI			(0.87 - 1.42)			(0.79 - 1.53)
p value			0.4654			0.6253
Arithmetic Mean	56.8	69.4		303.6	360.1	
%CV	23.6	42.9		32.4	50.6	
C_{max} (ng/mL)						
Geo. LS mean	13.1	16.9		63.3	72.0	
95% CI	(11.0 - 15.7)	(14.2 - 20.1)		(46.1 - 86.8)	(52.4 - 98.8)	
Mean ratio			1.28			1.14
90% CI			(1.05 - 1.57)			(0.79 - 1.64)
p value			0.0491			0.5339
Arithmetic Mean	13.9	18.8		68.1	83.4	
%CV	32.7	39.4		37.0	54.3	
$t_{½}$ (h)						
Geo. LS mean	1.93	2.18		1.74	2.06	
95% CI	(1.82 - 2.05)	(2.05 - 2.31)		(1.49 - 2.03)	(1.76 - 2.39)	
Mean ratio			1.13			1.18
90% CI			(1.05 - 1.21)			(0.99 - 1.41)
p value			0.0094			0.1148
Arithmetic Mean	1.97	2.21		1.77	2.10	
%CV	22.2	20.4		19.5	23.0	
t_{max} (h)						
Median	1.75	0.88		3.00	2.00	
Range						
95% CI	(1.25 - 2.00)	(0.63 - 1.25)		(2.00 - 3.50)	(1.50 - 2.50)	
Est. diff.			-0.75			-0.75
90% CI			(-1.0 - -0.38)			(-1.50 - 0.00)
p value			0.0039			0.1016
Arithmetic Mean	1.63	0.94		2.82	2.14	
%CV	29.7	42.7		31.0	33.3	

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	Day 1 Sumatriptan	Day 4 Sumatriptan	Ratio Day 4 / Day 1	Day 1 Metabolite	Day 4 Metabolite	Ratio Day 4 / Day 1
f_e						
Geo. LS mean	3.6	6.2		25.5	41.3	
95% CI	(2.7 - 4.5)	(4.8 - 8.4)		(17.9 - 36.1)	(29.1 - 58.7)	
Mean ratio			1.72			1.62
90% CI			(1.22 - 2.43)			(1.08 - 2.43)
p value			0.1680			0.0543
Arithmetic Mean	3.8	6.9		29.2	57.9	
%CV	33.7	59.2		39.8	59.5	
Clr (L/hr)						
Geo. LS mean	14.2	19.0		23.0	32.5	
95% CI	(12.2 - 16.6)	(16.1 - 22.6)		(19.9 - 26.5)	(28.2 - 37.5)	
Mean ratio			1.34			1.42
90% CI			(1.11 - 1.61)			(1.20 - 1.67)
p value			0.0186			0.0032
Arithmetic Mean	14.8	17.9		24.0	33.4	
%CV	30.2	38.3		29.4	23.9	

* Day 1 AUC_∞ and Day 4 AUC_8

Geo. LS mean = Geometric least square mean; Est. diff. = Estimated difference

Considerable intersubject variability (%CV >30%) was observed in most pharmacokinetic parameters. Some accumulation (~22%) occurred following multiple dosing. Serum metabolite concentrations were 4-5 fold higher than corresponding sumatriptan concentrations. Following the first dose, less than 4% of the dose was renally excreted as sumatriptan compared with approximately 25% as the indole acetic metabolite; following repeat administration, 7% of the dose was renally excreted as sumatriptan and 41% as the metabolite.

Safety

No deaths or serious adverse events were reported for subjects enrolled in this study. No patients were withdrawn due to adverse events.

- All subjects (100%) reported mild adverse events following administration of intranasal sumatriptan compared to 3 subjects (25%) receiving placebo. Disturbance of taste was reported by all subjects following intranasal sumatriptan and by one subject following placebo (these events were considered to drug-related by the investigator). Headache was reported by 1 subject following intranasal sumatriptan and 2 subjects following placebo.
- No clinically significant abnormal laboratory values were observed however an elevated potassium was observed post-dosing in one subject.
- Clinically significant changes in systolic blood pressure (decrease by 20mmHg to 80mmHg) and diastolic blood pressure (decrease by 20mmHg to 50mmHg) occurred in

1 subject following intranasal sumatriptan. One subject had a decrease in systolic blood pressure (decrease by 24mmHg to 90mmHg) following placebo administration.

- Eight subjects did not recognize all scents on Day 1 compared to 5 subjects on Day 4 following placebo; 4 subjects did not recognize all scents on Day 1 compared to 6 subjects on Day 4 following intranasal sumatriptan.
- Nasal exams by nare speculum were normal.
- No changes in physical examination findings occurred during the study.

CONCLUSIONS

- Some accumulation (~22%) of sumatriptan occurred following multiple dosing (every 4 hours for a total of three daily doses) via the intranasal route.

- Repeat administration of intranasal sumatriptan was safe and well tolerated.

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10. DISCUSSION

Pharmacokinetic Data

Intersubject variability of sumatriptan pharmacokinetic parameters was generally high (%CV > 30%) following single and repeat intranasal administration of sumatriptan 20mg as a nasal spray. Accumulation (~22%) between Days 1 and 4 was observed for most parameters and is consistent with the dosing interval (every 4 hours for a total of 3 daily doses) and the $t_{1/2}$ (~2 hours). The sumatriptan serum concentrations achieved following repeat administration are within the range of concentrations achieved by other routes of sumatriptan administration and as was observed in this study, are not likely to be associated with significant adverse events.

Serum metabolite concentrations were generally 4 fold higher than corresponding sumatriptan concentrations. Following oral administration, metabolite levels were 6-7 fold higher than sumatriptan levels . Thus, the degree of presystemic metabolism appears to be less following intranasal administration which is consistent with a portion of the dose being swallowed and absorbed from the gastrointestinal tract while a portion of the dose is absorbed from the nasal mucosa and may bypass presystemic metabolism. Similarily, 25% of the dose was excreted in the urine as (the indole acetic acid metabolite); 4% of the dose was excreted as sumatriptan following the first dose (Day 1). The fractions of the dose excreted as metabolite and sumatriptan were higher on Day 4 (41 and 7%, respectively) than on Day 1 and are consistent with accumulation.

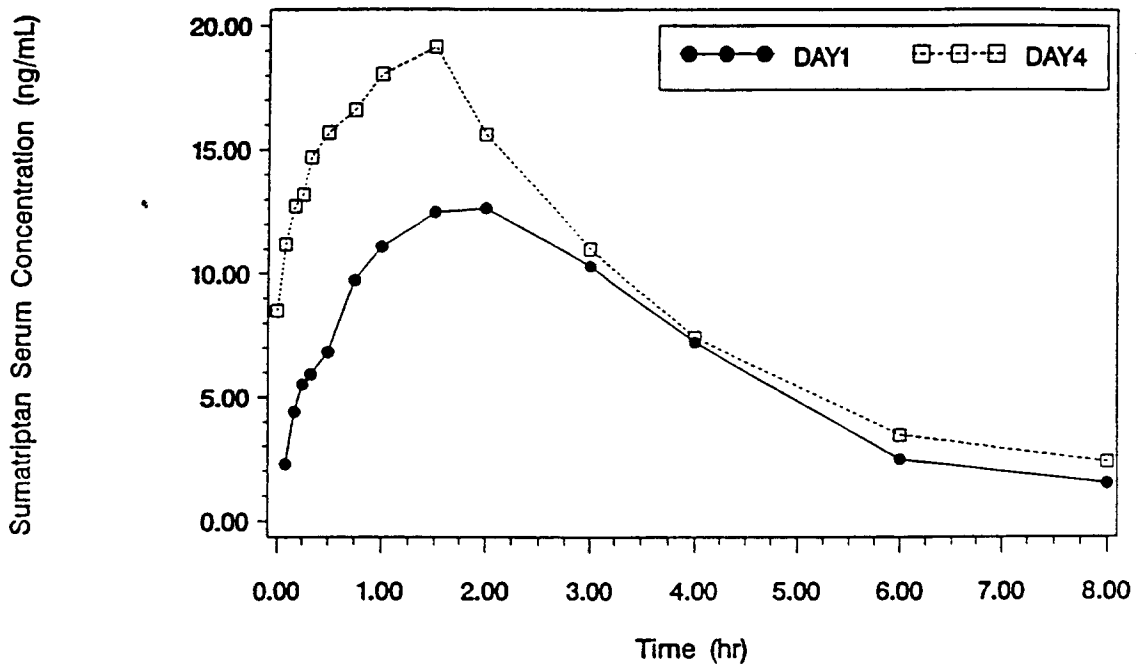
Terminal half-live estimates for sumatriptan and its principal metabolite were slightly longer following multiple dosing compared to the first dose; this difference was statistically significant for sumatriptan. Sumatriptan half-life estimates were also increased following multiple oral dosing . Sumatriptan half-life estimates following intranasal administration however are similar to those observed following subcutaneous and oral administration . Metabolite half-life values were consistent with the sumatriptan half-life and consistent with the metabolite half-life observed following oral dosing . Consistent with other routes of sumatriptan administration, the terminal half-life of the metabolite appears to be formation rate dependent.

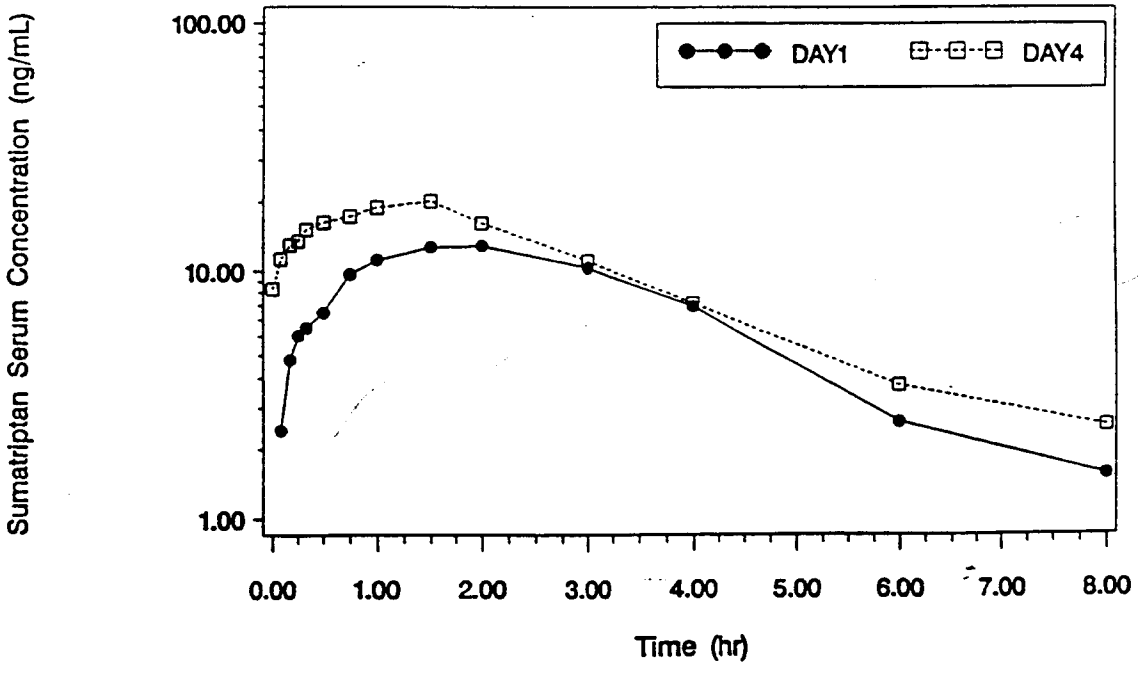
Less than 5% of the dose was renally excreted as sumatriptan compared with approximately 25% as the indole acetic metabolite. Thus, approximately 30% of the dose can be accounted for by measuring the urinary elimination of these two compounds. Following subcutaneous administration, 25% and 38% of the dose can be accounted for in the urine as sumatriptan and its metabolite. After oral dosing, however, only 2% and 35% of the dose can be accounded for as sumatriptan and its metabolite. These data are consistent with the bioavailability of intranasally administration sumatriptan compared to the subcutaneous (15.8%) and oral (111.0%) routes.

Safety Data

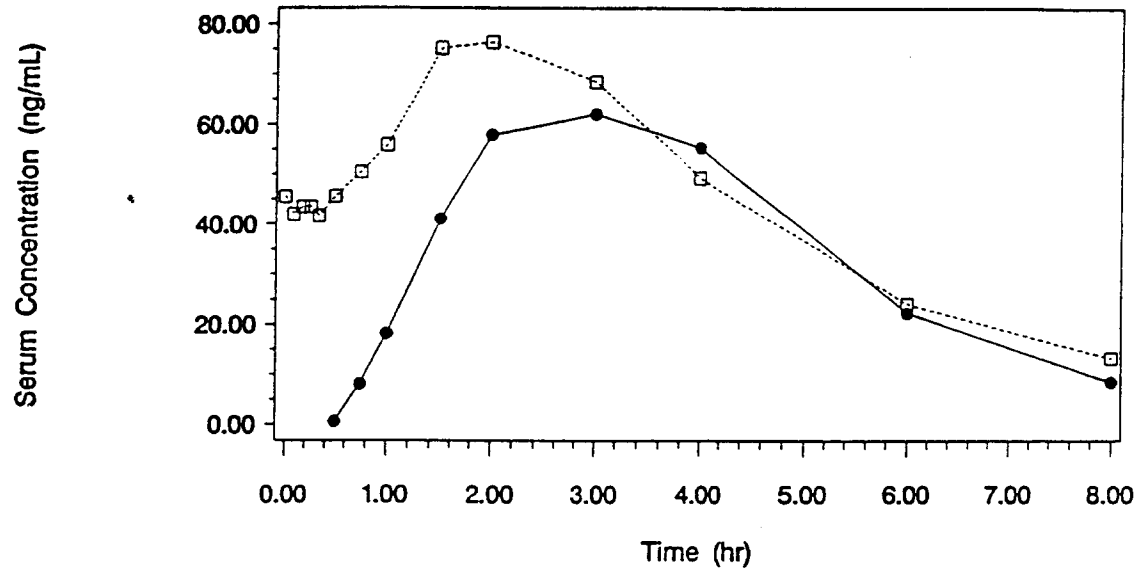
Intranasal sumatriptan was well tolerated. No serious adverse events, deaths, or withdrawals due to adverse events occurred. Disturbances in taste was the most frequently reported adverse event. Clinically significant decreases in systolic and diastolic blood pressures occurred in 1 subject following sumatriptan administration on only one occasion. A significant decrease in systolic blood pressure was also observed in one subject during placebo administration. Olfaction and nasal examination results were all negative. No changes in physical examination findings occurred during the study.

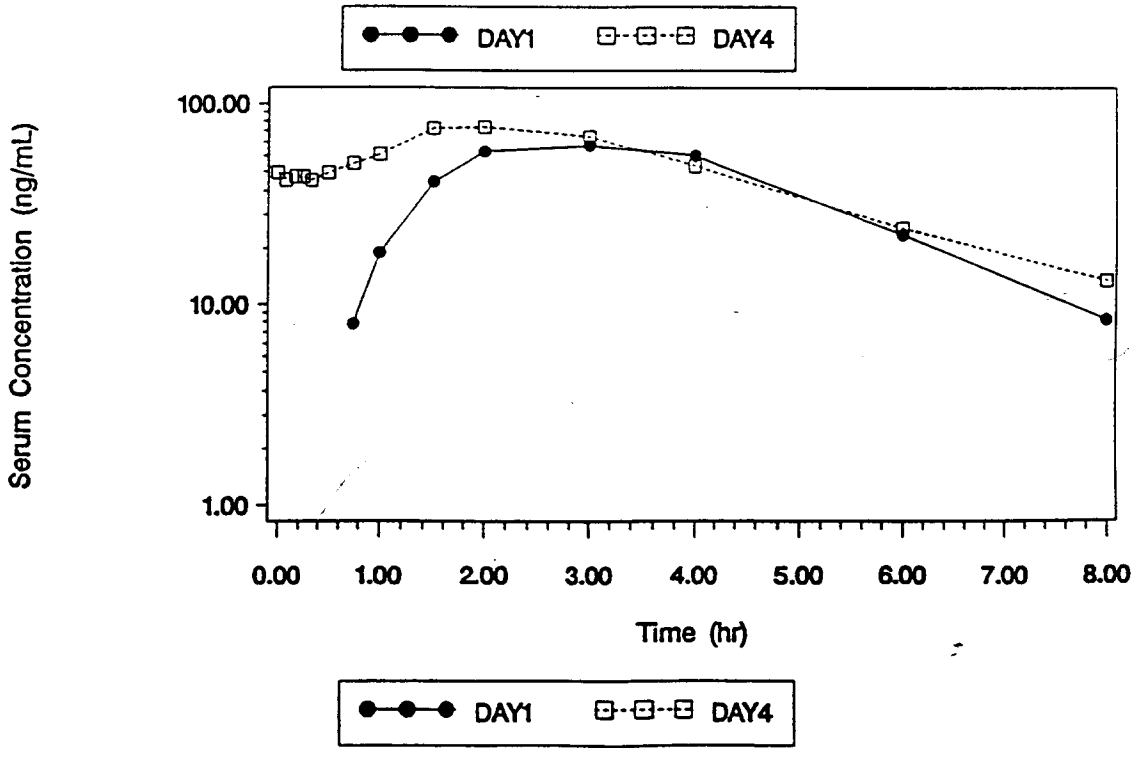
Sumatriptan Serum Concentration Versus Time
Median





Serum Concentration Versus Time
Sumatriptan Metabolite
Mean





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STUDY #4

SUMMARY OF REPORT

TITLE

A study to investigate the effect of xylometazoline administration on the pharmacokinetics, safety and tolerability of nasal sumatriptan

OBJECTIVES

Nasal administration of sumatriptan offers advantages over other routes of administration, especially in patients who are nauseated or dislike injections. It is possible that some patients may use nasal sumatriptan whilst using a nasal decongestant such as xylometazoline (Otrivine®), and this may lead to an altered pharmacokinetic or safety profile of sumatriptan. The aim of this study is to define the extent, if any, of an interaction between nasal sumatriptan and xylometazoline.

To assess the pharmacokinetic profile of nasal sumatriptan (20mg) administered 15 minutes after xylometazoline (3 drops).

To monitor blood pressure and pulse rate effects of nasal sumatriptan (20mg) administered 15 minutes after xylometazoline (3 drops).

To assess nasal irritancy following nasal sumatriptan (20mg) administered 15 minutes after xylometazoline (3 drops).

DESIGN

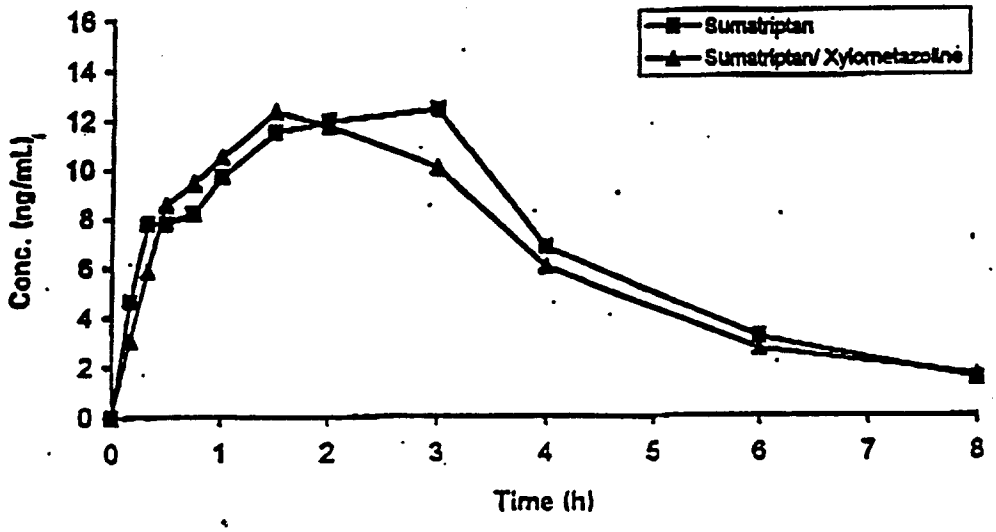
This will be a double-blind, randomised, placebo controlled, two-way, crossover study.

Subjects will receive one of the following treatments on each of the study days:-

1. 3 drops xylometazoline (0.1% w/v) followed 15 minutes later by 20mg nasal sumatriptan in the same nostril.

2. 3 drops placebo (0.9% normal saline) followed 15 minutes later by 20mg nasal sumatriptan in the same nostril.

RESULTS:



The sumatriptan Nasal Spray pharmacokinetic parameters are shown below:

Treatment	B 20mg sumatriptan after placebo	A 20mg sumatriptan after xylometazoline
C_{max} (ng/mL) (95%CI)	10.57 (5.18 - 21.55)	10.24 (4.71 - 22.27)
t_{max}(h) (range)	1.5 (0.33 - 6)	1.51 (0.17 - 3)
$t_{½}$(h) (95%CI)	1.95 (1.67 - 2.27)	2.02 (1.72 - .37)
AUC_{∞}(h.ng/mL) (95%CI)	58.91 (47.42 - 73.19)	58.54 (46.97 - 72.95)
Cl/F(L/min) (95%CI)		

The pharmacokinetic of sumatriptan is not changed by pre-treatment with nasal decongestant xylometazoline .

Adverse Events and Subject Withdrawals:

No subjects were withdrawn from the study as a result of adverse events. Adverse events characteristic of sumatriptan were reported. The intranasal spray produced sensations involving the nose or throat and an unpleasant taste. In general, adverse events were mild to moderate in severity with no serious adverse events experienced by any of the subjects. There was no significant change in any laboratory safety parameter.

Laboratory Safety Screening:

CONCLUSIONS

- Pre-treatment with a nasal decongestant single clinical dose followed 15 minutes later by 20mg nasal spray sumatriptan did not change the pharmacokinetics of sumatriptan
- Sumatriptan administered 15minutes after nasal decongestant xylometazoline was well tolerated.

BIOWAIVER REQUEST

APPENDIX II

Request for waiver of Bioequivalence Study

The sponsor under the provisions of 21 CFR 320.22 has submitted a waiver request for additional studies evaluating bioequivalence and substitutability of two separate 5 mg sprays (one in each nostril) of sumatriptan nasal spray compared to a single 10 mg spray.

The sponsor is evaluating three doses of sumatriptan nasal spray 5 mg, 10 mg, and 20 mg in phase III studies to accommodate dose individualization. The sponsor submitted an NDA providing for marketing of 5 mg and 20 mg doses and allow for an alternative 10 mg dose that can be achieved by administration of two 5 mg sprays.

The sponsor is intending to market buffered, unpreserved formulation of sumatriptan as nasal spray , even though some pilot studies were performed using unbuffered, preserved formulation (Attachment 1).

In the present submission, the sponsor provided justification for waiver request based on: similar pharmacokinetic parameters between formulations, demonstrated dose proportionality between 5, 10, and 20 mg doses, and wide therapeutic window for sumatriptan.

It was observed that administration of sumatriptan nasal spray in a clinical studies , using either as a single 10 mg dose in one nostril or a 5 mg dose in each nostril, resulted in similar pharmacokinetic parameters (Table 1; Attachment 2).

In another efficacy study, the to be marketed formulation (buffered, unpreserved) was evaluated as a 10 mg dose in one nostril. It was observed that efficacy rates following 10 mg administered into two nostrils as the unbuffered, preserved formulation compared to a 10 mg single spray (buffered, unpreserved formulation) were similar i.e., 18% vs 21%. Dose proportionality was observed across the doses 5 - 20 mg (Table 2 and Figures 1-2; Attachment 2). Further, the sponsor proposed to use 5, 10, and 20 mg doses in clinical trials to evaluate safety and efficacy.

Based on the pharmacokinetic data provided, the Agency had a teleconference with the sponsor on February 6, 1995 and agreed with the sponsor's request for a waiver of additional studies to demonstrate that two administrations of the 5 mg sumatriptan nasal spray (one 5 mg dose in each nostril) are comparable to a single 10 mg sumatriptan nasal spray administration in one nostril (Attachment 3).

1 page

PURGED

TRADE

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Information

ATTACHMENT 2

Table 1.

Pharmacokinetic parameters are summarized below for

10mg Sumatriptan Nasal Spray	1x10mg "B"	nostrils) 2x5mg "B"	1x10mg "D" - TBM
Formulation	preserved, unbuffered	preserved, unbuffered	unpreserved, buffered
C_{max} (ng/mL) Mean (range)	8.7 (4.0-21.5)	7.8 (4.1-19.2)	6.3 (0-15.3)
t_{max} (hr) Median (range)	0.8 (0.5-2.5)	0.5 (0.5-1.5)	0.75 (0.17-2.0)
AUC (ng.hr/mL) Mean (range)	13.3 (1.0-33.4)	14.8 (5.7-38.0)	9.1 (0-21.9)
N	12	12	18

AUC collected over 3 hours for S2BT35 and S2BT39 and over 2 hours for S2BT47.

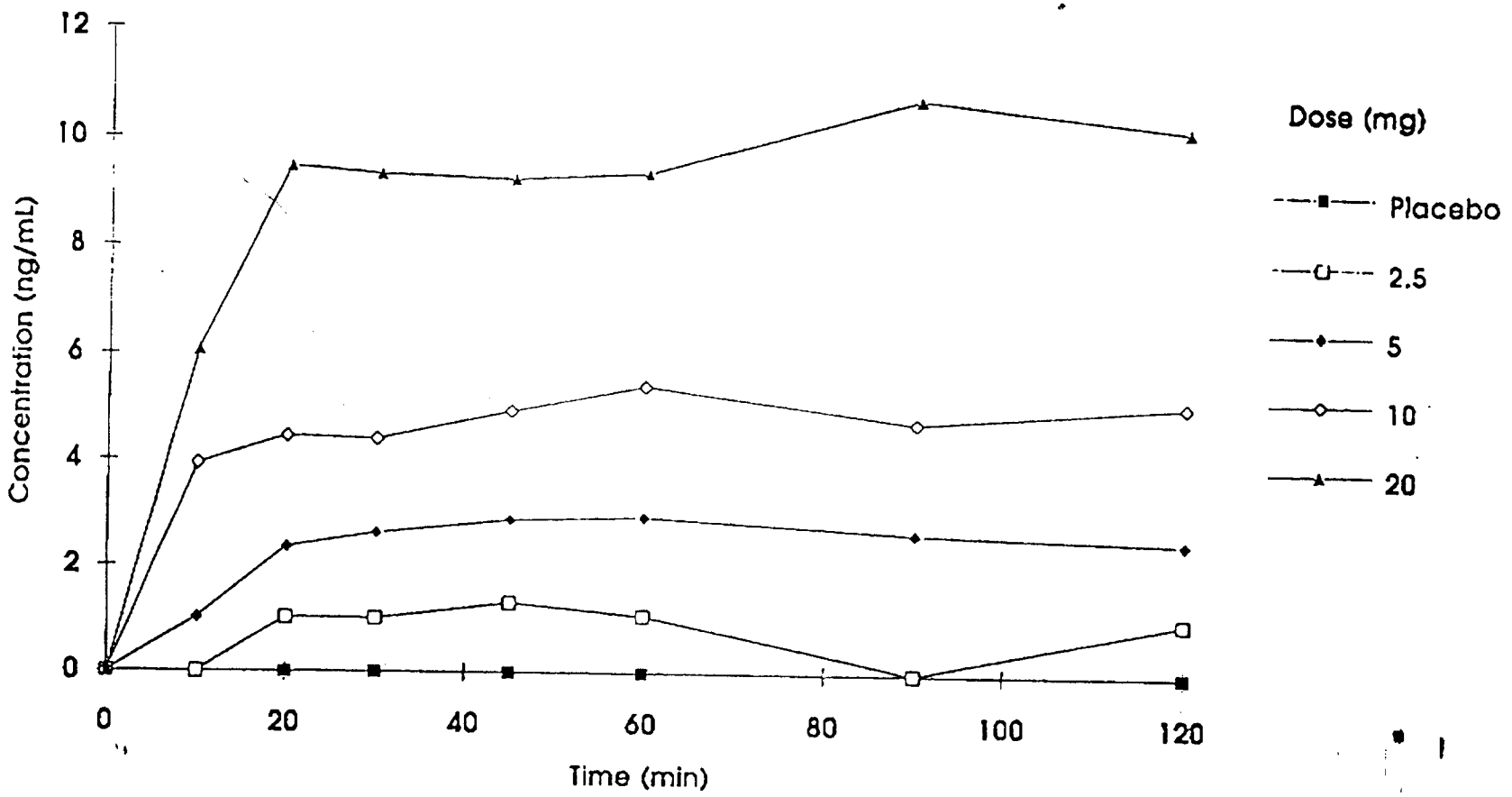
Table 2. SUMMARY OF PHARMACOKINETIC PARAMETERS

Parameter		Sumatriptan 2.5mg	5mg	10mg	20mg
Cmax (ng/mL)	Mean	1.6	3.4	6.3	13.7
	SD	1.4	2.3	3.4	8.4
	CV%	88	69	54	61
	G. Mean	1.3	2.9	5.5	11.4
	Range	0-4.1	0-7.8	0-15.3	4.5-36.9
	n	13	19	18	19
t_{max} (min)	Median	45	60	45	45
	Mean	48	70	51	62
	SD	34	43	37	39
	CV%	76	62	73	62
	Range	10-120	20-120	10-120	10-120
	n	9	16	17	19
AUC_{last} (ng.hr/mL)	Mean	2.1	4.8	9.1	20.4
	SD	1.9	3.0	5.4	12.6
	CV%	92	63	59	61
	G.Mean	1.9	4.0	6.9	16.8
	Range	0-5.2	0-11.8	0-21.9	4.5-51.2
	n	13	15	17	17

Mean :arithmetic mean, G.M: geometric mean, SD: standard deviation,
CV: coefficient of variation
AUC_{last} estimated when samples results available up to 120 minutes post dose.

ATTACHMENT 2

Figure 1. Median serum concentration vs time during migraine attack after intranasal administration



ATTACHMENT 2

Figure 4: Dose proportionality of Cmax

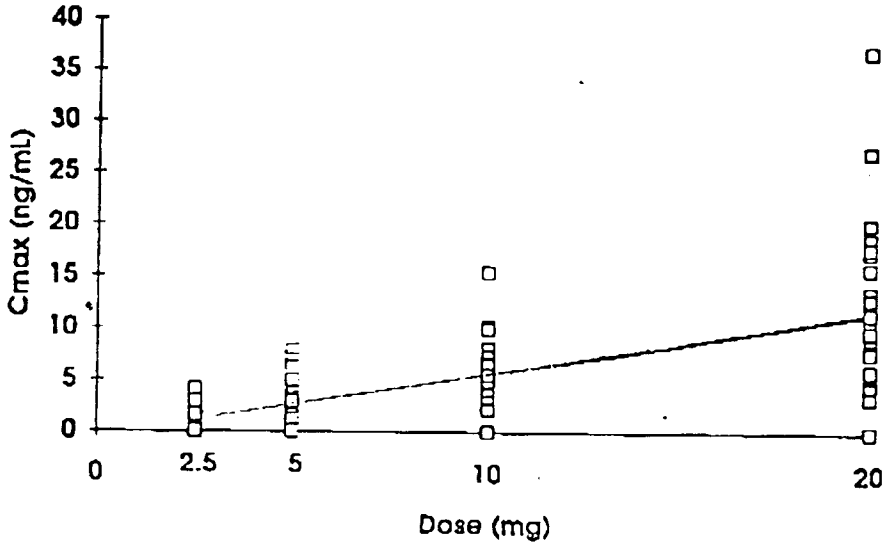
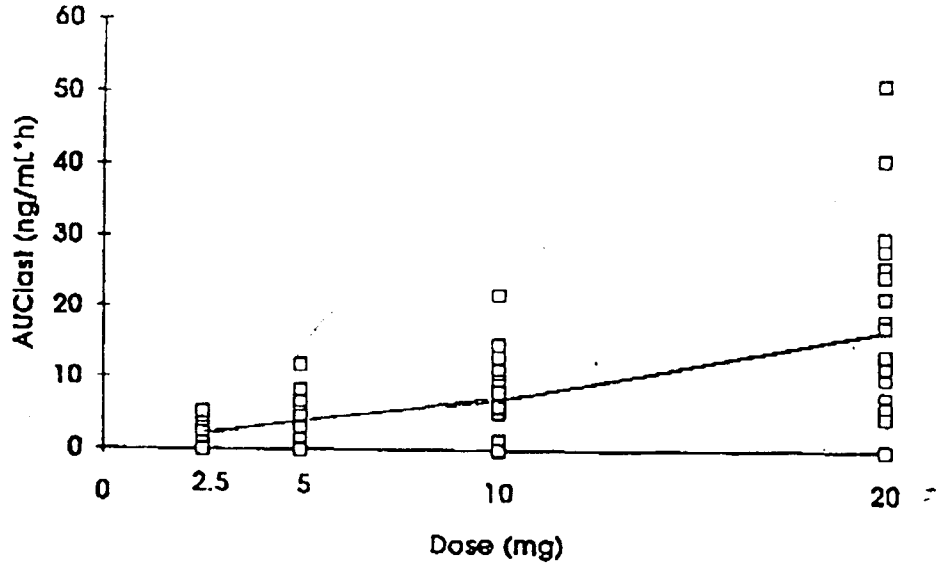


Figure 5: Dose proportionality of AUC



CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: 20626

ADMINISTRATIVE DOCUMENTS

Memorandum **Department of Health and Human Services**
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research

DATE: August 15, 1997

FROM: Paul Leber, M.D.
Director,
Division of Neuropharmacological Drug Products
HFD-120

SUBJECT: Imitrex [sumatriptan] Intranasal Spray.

TO: File NDA 20-626

This memorandum conveys more formal recommendation to the file that NDA 20-626 for Imitrex Intranasal Spray be approved.

My views on the substantive issues affecting approval of the application are provided in my approvable action recommendation memorandum of April 4, 1997.

The sponsor replied formally to the agency's April 23, 1997 approvable action by letter on 5/7/97. That submission provided 1) a draft annotated labeling counter-proposal to the draft labeling proposed in the agency's approval action, 2) a safety update, 3) a World Literature update, 4) a report on
5) a commitment to conduct a phase 4 and 6) copies of introductory promotional material.

Post approvable action Review Team activities:

1) Assessment of the adequacy of the firm's proposed phase 4

Upon review, (5/21/97), Dr. Powell identified a number of deficiencies in the sponsor's proposal. She and Dr. Fitzgerald have discussed these with the firm (circa 6/3/97).

2) Safety Update, published literature and regulatory action review.

Dr. Armando Oliva conducted the review on behalf of the review team. No deaths or serious AEs were reported for the interval of interest 81/96 to 4/30/97. A review of the probable causes for premature discontinuations of subjects in ongoing trials identified no new or unexpected adverse clinical event. The archival literature in Dr. Oliva judgment contains no report that would cause us to revise our conclusions about the product's safety for use.

3) Labeling

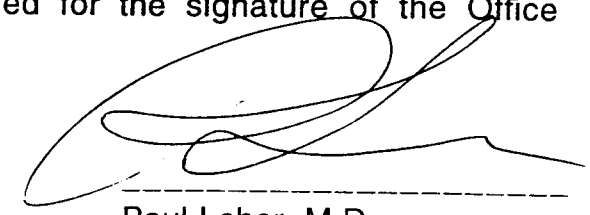
As is always the case, the details of the final text of labeling have been the focus of much of the review team's attention.

In his memorandum of 7/1/97, amended on 8/5/97, Dr. Levin provides his analysis and resolutions of labeling issues that at one time or another were a matter of disagreement either among the review team or between the review team and the firm. Dr. Fitzgerald, the supervisory pharmacologist, provides a memorandum (7/31/97) detailing how (and why) labeling suggested by the firm was modified.

Upon review, I am satisfied that the final labeling developed by the review team under Dr. Levin's guidance not only reflects a reasonable and acceptable synthesis of the views of the review team and those sponsor, but is accurate and informative as to the benefits, risks, and conditions of use of Imitrex intranasal spray.

Conclusion and Recommendation.

The approval action letter prepared for the signature of the Office Director should issue.



Paul Leber, M.D.
August 15, 1997

cc:
NDA 20-626
HFD-101
Temple
HFD-100
Katz
Levin
Fitzgerald
Oliva
Powell
Chen

MEMORANDUM

DEPARTMENT OF HEALTH & HUMAN SERVICES
Public Health Service
Food and Drug Administration

Division of Neuropharmacological Drug Products (HFD-120)
Center for Drug Evaluation and Research

Date: 8/25/97
From: Randy Levin, M.D., Neurology Team Leader
Subject: NDA 20-626 (Imitrex Nasal Spray)
To: File

Background:

The division's recommendations for the approval letter and labeling were referred to Dr. Temple. He agreed with and signed the approval letter with some changes to the division's labeling. The following are the more substantial changes:

• Dr. Temple removed the statement '
Dr. Temple noted that he was inclined to believe that the differences in studies will affect the percent responders but not the time shape of the curve. While I do not necessarily agree that this is correct, I agree with Dr. Temple that the initial sentence, " Note that in general, comparisons of results obtained in studies conducted under different conditions by different investigators with different samples of patients are ordinarily unreliable for purposes of quantitative comparison" addresses the division's point.

• Dr. Temple removed the statement describing
because he felt that it did not provide any additional useful information.

• Dr. Temple requested that the labeling more clearly state that only a small number of patients had serious cardiac events without CAD risk factors. Currently, the labeling states that the
with serious cardiac events within 1 hour of dosing had risk factors of CAD. I have changed the labeling to state that "almost all of the patients" had risk factors as suggested by Dr. Temple. I have added a similar statement in the Adverse Events section describing that most of the serious cardiac events have been reported in patients with risk factors predictive of CAD.

Recommendations:

I recommend approval with the labeling as changed by Dr. Temple.

Randy Levin, M.D.
Neurology Team Leader

cc:
HFD-120/Leber/Chen
rl/August 25, 1997

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION

APPLICATION MARKET A NEW DRUG FOR HUMAN USE OR AN ANTIBIOTIC DRUG FOR HUMAN USE

(Title 21, Code of Federal Regulations, 314)

Form Approved: OMB no. 0910-0001
Expiration Date: April 30, 1994
See OMB Statement on Page 3

FOR FDA USE ONLY

DATE RECEIVED	DATE FILED
DIVISION ASSIGNED	**NDA/ANDA NO. ASS.**

NOTE: No application may be filed unless a completed application form has been received (*21 CFR Part 314*).

NAME OF APPLICANT	DATE OF SUBMISSION
Glaxo Wellcome Inc.	05/07/97
	TELEPHONE NO (*Include Area Code*) (919) 483-2100
ADDRESS (*Number, Street, City, State, and Zip Code*) Five Moore Drive Research Triangle Park, N.C. 27709	NEW DRUG OR ANTIBIOTIC APPLICATION NUMBER (If previously issued) NDA 20-626

DRUG PRODUCT

ESTABLISHED NAME (*e.g. USP/USAN*)	PROPRIETARY NAME (*If any*)
USAN Sumatriptan	Imitrex® Nasal Spray

CODE NAME (*If any*)	CHEMICAL NAME
GR43175C Nasal Spray	3 - [Dimethylamino ethyl [-N-methyl-1H-indole-5-methane sulfonamide, butane-1, 4 dioate (1:1)

DOSAGE FORM	ROUTE OF ADMINISTRATION	STRENGTH(S)
Nasal Spray	Intranasal	5mg, 10mg, 20mg

PROPOSED INDICATIONS FOR USE

Acute Treatment of Migraine

LIST NUMBERS OF ALL INVESTIGATIONAL NEW DRUG APPLICATIONS (*21 CFR Part 312*), NEW DRUG OR ANTIBIOTIC APPLICATIONS (*21 CFR Part 314*), AND DRUG MASTER FILES (*21 CFR 314.420*) REFERRED TO IN THIS APPLICATION:

NDA 20-080 Imitrex (sumatriptan succinate) Injection

NDA 20-132 Imitrex (sumatriptan succinate) Tablets

INFORMATION ON APPLICATION

TYPE OF APPLICATION (*Check one*)

☐ THIS SUBMISSION IS A FULL APPLICATION (*21 CFR 314.50*) ☐ THIS SUBMISSION IS AN ABBREVIATED APPLICATION (ANDA) (21 CFR 314.55)

IF AN ANDA, IDENTIFY THE APPROVED DRUG PRODUCT THAT IS THE BASIS FOR THE SUBMISSION

NAME OF DRUG	HOLDER OF APPROVED APPLICATION

TYPE SUBMISSION (*Check One*)

☐ PRESUBMISSION ☒ AN AMENDMENT TO A PENDING APPLICATION ☐ SUPPLEMENTAL APPLICATION

☐ ORIGINAL APPLICATION ☐ RESUBMISSION

SPECIFIC REGULATION(S) TO SUPPORT CHANGE OF APPLICATION (e.g. Part 314.70(b)(2)(iv)) _____

PROPOSED MARKETING STATUS (*Check one*)

☒ APPLICATION FOR A PRESCRIPTION DRUG PRODUCT (*Rx*) ☐ APPLICATION FOR AN OVER-THE-COUNTER PRODUCT (*OTC*)

CONTENTS OF APPLICATION	
This application contains the following items: (Check all that apply)	
	1. Index
	2. Summary (21 CFR 314.50 (c))
	3. Chemistry, manufacturing, and control section (21 CFR 314.5 (d) (1))
	4. a. Samples (21 CFR 314.50 (e) (1)) (Submit only upon FDA's request)
	b. Methods Validation Package (21 CFR 314.50 (e) (2) (i))
	c. Labeling (21 CFR 314.50 (e) (2) (ii))
	i. draft labeling (*4 copies*)
X	ii. final printed labeling (12 copies)
	5. Nonclinical pharmacology and toxicology section (21 CFR 314.50 (d) (2))
	6. Human pharmacokinetics and bioavailability section (21 CFR 314.50 (d) (3))
	7. Microbiology section (21 CFR 314.50 (d) (4))
X	8. Clinical data section (21 CFR 314.50 (d) (5))
	9. Safety update report (21 CFR 314.50 (d) (5) (vi) (b))
	10. Statistical section (21 CFR 314.50 (d) (6))
	11. Case report tabulations (21 CFR 314.50 (f) (1))
	12. Case reports forms (21 CFR 314.50 (f) (1))
	13. Patent information on any patent which claims the drug (21 U.S.C. 355 (b) or (c))
	14. A patent certification with respect to any patent which claims the drug (21 U.S.C. 355 (b) (2) or (j) (2) (A))
X	15. OTHER (*Specify*) **Response to Approvable Letter**

I agree to update this application with new safety information about the drug that may reasonably affect the statement of contraindications, warnings, precautions, or adverse reactions in the draft labeling. I agree to submit these safety update reports as follows: (1) 4 months after the initial submission, (2) following receipt of an approvable letter and (3) at other times as requested by FDA. If this application is approved, I agree to comply with all laws and regulations that apply to approved applications, including the following:

1. Good manufacturing practice regulations in 21 CFR 210 and 211.
2. Labeling regulations in 21 CFR 201.
3. In the case of a prescription drug product, prescription drug advertising regulations in 21 CFR 202.
4. Regulations on making changes in application in 21 CFR 314.70, 314.71 and 314.72.
5. Regulations on reports in 21 CFR 314.80 and 314.81.
6. Local, state and Federal environmental impact laws.

If this application applies to a drug product that FDA has proposed for scheduling under the controlled substances Act I agree not to market the product until the Drug Enforcement Administration makes a final scheduling decision.

NAME OF RESPONSIBLE OFFICIAL OR AGENT	SIGNATURE OF RESPONSIBLE OFFICIAL OR AGENT	DATE
James E. Murray, Director, Regulatory Affairs	James E. Murray	05/07/97

ADDRESS (*Street, City, State, Zip Code*)	TELEPHONE NO. (*Include Area Code*)
Glaxo Wellcome Inc. Five Moore Drive Research Trinagle Park, N.C. 27709	(919) 483-5119

(**WARNING**: A willfully false statement is a criminal offense. U.S.C. Title 18, Sec. 1001.)

DRUG STUDIES IN PEDIATRIC PATIENTS
(To be completed for all NME's recommended for approval)

NDA # 20-626 Trade (generic) names/dosage form: Imitrex (sumatriptan) Nasal Spray

Check any of the following that apply and explain, as necessary, on the next page:

____ 1. A proposed claim in the draft labeling is directed toward a specific pediatric illness. The application contains adequate and well-controlled studies in pediatric patients to support that claim.

____ 2. The draft labeling includes pediatric dosing information that is not based on adequate and well-controlled studies in children. The application contains a request under 21 CFR 210.58 or 314.126© for waiver of the requirement at 21 CFR 201.57(f) for A&WC studies in children.

____ a. The application contains data showing that the course of the disease and the effects of the drug are sufficiently similar in adults and children to permit extrapolation of the data from adults to children. The waiver request should be granted and a statement to that effect is included in the action letter.

____ b. The information included in the application does not adequately support the waiver request. The request should not be granted and a statement to that effect is included in the action letter. (Complete #3 and #4 below as appropriate.)

____ 3. Pediatric studies (e.g., dose-finding, pharmacokinetic, adverse reaction, adequate and well-controlled for safety and efficacy) should be done after approval. The drug product has some potential for use in children, but there is no reason to expect early widespread pediatric use (because, for example, alternative drugs are available or the condition is uncommon in children).

____ a. The applicant has committed to doing such studies as will be required.

____ (1) Studies are ongoing.
____ (2) Protocols have been submitted and approved.
____ (3) Protocols have been submitted and are under review.
____ (4) If no protocol has been submitted, on the next page explain the status of discussions.

____ b. If the sponsor is not willing to do pediatric studies, attach copies of FDA's written request that such studies be done and of the sponsor's written response to that request.

___ 4. Pediatric studies do not need to be encouraged because the drug product has little potential for use in children.

✓ 5. If none of the above apply, explain.

Explain, as necessary, the foregoing items:

The labeling does not contain a claim or dosing directed to the pediatric population. The sponsor has performed studies in the pediatric age group that does not support the use of the drug in this group. These studies are described in labeling.

Signature of Preparer

8/25/97.
Date

cc:
Orig NDA
HFD-120 Division File
NDA Action Package

Amendment to ITEM 13

Patent Information Pursuant to 21 U.S.C. §355
for
IMITREX® (sumatriptan) Nasal Spray

NDA 20-626

The following is provided in accord with the Drug Price Competition and Patent Term Restoration Act of 1984:

Trade Name:	IMITREX® Nasal Spray
Active Ingredient(s):	sumatriptan
Strength(s):	5mg, 10mg and 20mg
Dosage Form:	Intranasal Spray
NDA Number:	20-626
Approval Date:	Pending

U.S. Patent 5,554,639

Expiration Date:	September 10, 2013
Type of Patent:	Drug Product • Formulation / Composition Method of Use • Method of treating migraine
Name of Patent Owner:	Glaxo Group Limited
U.S. Agent:	David J. Levy, Ph.D. Patent Counsel Glaxo Wellcome Inc. Five Moore Drive Research Triangle Park, North Carolina 27709 (919) 483-2723

The undersigned declares that U.S. Patent 5,554,639 covers the formulation, composition and/or method of use of IMITREX® (sumatriptan) Nasal Spray and should be included in Item 13 of NDA 20-626. This product is the subject of NDA 20-626.

18 Sept 96

Date

Robert H. Brink

Robert H. Brink, Ph.D.
Registered Patent Attorney
Registration No. 36,094

EXCLUSIVITY SUMMARY

NDA # 20-626

Trade Name: **IMITREX**
Generic Name: **sumatriptan**
Applicant Name: **GlaxoWellcome**
Division: **HFD-120**
RMO: **Merril J. Mille, R. Ph.**
Approval Date: AUGUST 26, 1997

PART I IS AN EXCLUSIVITY DETERMINATION NEEDED?

1. An exclusivity determination will be made for all original applications, but only for certain supplements. Complete Parts II and III of this Exclusivity Summary only if you answer "yes" to one or more of the following questions about the submission.

   a) Is it an original NDA? **YES**

   b) Is it an effectiveness supplement? **NO**

   If yes, what type? (SE1, SE2, etc.)

   c) Did it require the review of clinical data other than to support a safety claim or change in labeling related to safety? (If it required review only of bioavailability or bioequivalence data, answer "no.")

   YES

   If your answer is "no" because you believe the study is a bioavailability study and, therefore, not eligible for exclusivity, EXPLAIN why it is a bioavailability study, including your reasons for disagreeing with any arguments made by the applicant that the study was not simply a bioavailability study.

   If it is a supplement requiring the review of clinical data but it is not an effectiveness supplement, describe the change or claim that is supported by the clinical data: _____

   d) Did the applicant request exclusivity? **YES**

   If the answer to (d) is "yes," how many years of exclusivity did the applicant request? **THREE**

IF YOU HAVE ANSWERED "NO" TO ALL OF THE ABOVE QUESTIONS, GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

2. Has a product with the same active ingredient(s), dosage form, strength, route of administration, and dosing schedule previously been approved by FDA for the same use?
   NO

IF THE ANSWER TO QUESTION 2 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

cc: Original NDA Division File HFD-85 Mary Ann Holovac

3. Is this drug product or indication a DESI upgrade? **NO**

IF THE ANSWER TO QUESTION 3 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8 (even if a study was required for the upgrade).

PART II FIVE-YEAR EXCLUSIVITY FOR NEW CHEMICAL ENTITIES
(Answer either #1 or #2, as appropriate)

1. Single active ingredient product.

Has FDA previously approved under section 505 of the Act any drug product containing the same active moiety as the drug under consideration? Answer "yes" if the active moiety (including other esterified forms, salts, complexes, chelates or clathrates) has been previously approved, but this particular form of the active moiety, e.g., this particular ester or salt (including salts with hydrogen or coordination bonding) or other non-covalent derivative (such as a complex, chelate, or clathrate) has not been approved. Answer "no" if the compound requires metabolic conversion (other than deesterification of an esterified form of the drug) to produce an already approved active moiety.

YES

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA # 20-080/Imitrex Injection
NDA # 20-132/Imitrex Tablets

2. Combination product.

If the product contains more than one active moiety (as defined in Part II, #1), has FDA previously approved an application under section 505 containing any one of the active moieties in the drug product? If, for example, the combination contains one never-before-approved active moiety and one previously approved active moiety, answer "yes." (An active moiety that is marketed under an OTC monograph, but that was never approved under an NDA, is considered not previously approved.)

NO

IF THE ANSWER TO QUESTION 1 OR 2 UNDER PART II IS "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8. IF "YES," GO TO PART III.

PART III THREE-YEAR EXCLUSIVITY FOR NDA'S AND SUPPLEMENTS

To qualify for three years of exclusivity, an application or supplement must contain "reports of new clinical investigations (other than bioavailability studies) essential to the approval of the application and conducted or sponsored by the applicant." This section should be completed only if the answer to PART II, Question 1 or 2, was "yes."

1. Does the application contain reports of clinical investigations? (The Ageney interprets "clinical investigations" to mean investigations conducted on humans other than bioavailability studies.) If the application contains clinical investigations only by virtue of a right of reference to clinical investigations in another application, answer "yes," then skip to question 3(a). If the answer to 3(a) is "yes" for any investigation referred to in another application, do not complete remainder of summary for that investigation.

YES

IF "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

2. A clinical investigation is "essential to the approval" if the Agency could not have approved the application or supplement without relying on that investigation. Thus, the investigation is not essential to the approval if 1) no clinical investigation is necessary to support the supplement or application in light of previously approved applications (i.e., information other than clinical trials, such as bioavailability data, would be sufficient to provide a basis for approval as an ANDA or 505(b)(2) application because of what is already known about a previously approved product), or 2) there are published reports of studies (other than those conducted or sponsored by the applicant) or other publicly available data that independently would have been sufficient to support approval of the application, without reference to the clinical investigation submitted in the application.

   For the purposes of this section, studies comparing two products with the same ingredient(s) are considered to be bioavailability studies.

   (a) In light of previously approved applications, is a clinical investigation (either conducted by the applicant or available from some other source, including the published literature) necessary to support approval of the application or supplement?

   YES

   If "no," state the basis for your conclusion that a clinical trial is not necessary for approval **AND GO DIRECTLY TO SIGNATURE BLOCK ON PAGE 8:**

   _____

   (b) Did the applicant submit a list of published studies relevant to the safety and effectiveness of this drug product and a statement that the publicly available data would not independently support approval of the application?

   NO

   (1) If the answer to 2(b) is "yes," do you personally know of any reason to disagree with the applicant's conclusion? If not applicable, answer NO.

   NO

   If yes, explain: _____

(2) If the answer to 2(b) is "no," are you aware of published studies not conducted or sponsored by the applicant or other publicly available data that could independently demonstrate the safety and effectiveness of this drug product? **NO**

If yes, explain: _____

(c) If the answers to (b)(1) and (b)(2) were both "no," identify the clinical investigations submitted in the application that are essential to the approval:

Investigation #1, Study # S2B-T47
Investigation #2, Study # S2B-T50
Investigation #3, Study # 340
Investigation #4, Study # 341
Investigation #5, Study # 342

3. In addition to being essential, investigations must be "new" to support exclusivity. The agency interprets "new clinical investigation" to mean an investigation that 1) has not been relied on by the agency to demonstrate the effectiveness of a previously approved drug for any indication and 2) does not duplicate the results of another investigation that was relied on by the agency to demonstrate the effectiveness of a previously approved drug product, i.e., does not redemonstrate something the agency considers to have been demonstrated in an already approved application.

a) For each investigation identified as "essential to the approval," has the investigation been relied on by the agency to demonstrate the effectiveness of a previously approved drug product? (If the investigation was relied on only to support the safety of a previously approved drug, answer "no.")

Investigation #1 **NO** Investigation #2 **NO**

If you have answered "yes" for one or more investigations, identify each such investigation and the NDA in which each was relied upon:
NDA # _____ Study #_____

b) For each investigation identified as "essential to the approval," does the investigation duplicate the results of another investigation that was relied on by the agency to support the effectiveness of a previously approved drug product?

Investigation #1 **NO** Investigation #2 **NO**

If you have answered "yes" for one or more investigations, identify the NDA in which a similar investigation was relied on:
NDA # _____ Study #_____

c) If the answers to 3(a) and 3(b) are no, identify each "new" investigation in the application or supplement that is essential to the approval (i.e., the investigations listed in #2(c), less any that are not "new"):

Investigation #1, Study # S2B-T47
Investigation #2, Study # S2B-T50
Investigation #3, Study # 340
Investigation #4, Study # 341
Investigation #5, Study # 342

4. To be eligible for exclusivity, a new investigation that is essential to approval must also have been conducted or sponsored by the applicant. An investigation was "conducted or sponsored by" the applicant if, before or during the conduct of the investigation, 1) the applicant was the sponsor of the IND named in the form FDA 1571 filed with the Agency, or 2) the applicant (or its predecessor in interest) provided substantial support for the study. Ordinarily, substantial support will mean providing 50 percent or more of the cost of the study.

a) For each investigation identified in response to question 3(c): if the investigation was carried out under an IND, was the applicant identified on the FDA 1571 as the sponsor?

(b) For each investigation not carried out under an IND or for which the applicant was not identified as the sponsor, did the applicant certify that it or the applicant's predecessor in interest provided substantial support for the study?

NOT APPLICABLE

(c) Notwithstanding an answer of "yes" to (a) or (b), are there other reasons to believe that the applicant should not be credited with having "conducted or sponsored" the study? (Purchased studies may not be used as the basis for exclusivity. However, if all rights to the drug are purchased (not just studies on the drug), the applicant may be considered to have sponsored or conducted the studies sponsored or conducted by its predecessor in interest.)

NO

Merril J. Mille 3/21/97

Merril J. Mille, R. Ph. Date
Senior Regulatory Management Officer

3/21/97

Division Director Date

cc: Original NDA Division File HFD-85 Mary Ann Holovac

NDA 20-626

Imitrex® (sumatriptan) Nasal Spray 5mg, 10mg, and 20mg

Request for Marketing Exclusivity

Under Sections 505(c)(3)(D)(iii) and 505(j)(4)(D)(iii) of the Federal Food, Drug, and Cosmetic Act, Glaxo Wellcome requests three years of exclusivity from the date of approval of Imitrex® (sumatriptan) Nasal Spray 5mg, 10mg, and 20mg for the acute treatment of migraine with and without aura.

Glaxo Wellcome is entitled to such exclusivity as this application contains reports of new clinical investigations (other than bioavailability studies) essential to the approval of the application and conducted or sponsored by Glaxo Wellcome. These investigations are "essential to the approval of the application" in that the application could not be approved by FDA without the following investigations:

S2B-340	A Double-Blind, Placebo-Controlled, Parallel Group Study to Evaluate Two Dose Levels (10mg and 20mg) of Intranasal Sumatriptan in the AcuteTreatment of a Migraine Attack
S2B-341	A Double-Blind, Placebo-Controlled, Parallel Group Study to Evaluate Two Dose Levels (10mg and 20mg) of Intranasal Sumatriptan in the Acute Treatment of a Migraine Attack
S2B-342	A Randomized, Double-Blind, Placebo-Controlled Study to Evaluate Headache Pain Relief with Sumatriptan Nasal Spray (5mg, 10mg, and 20mg) Across Three Migraine Attacks
S2B-T47	A Double-Blind, Placebo-Controlled, Parallel Group Study to Evaluate Four Dose Levels of Sumatriptan Intranasal (2.5, 5, 10, 20mg) in the Acute Treatment of Migraine
S2B-T50	A Double-Blind, Placebo-Controlled, Parallel Group Study to Evaluate Two Dose Levels (10mg and 20mg) of Sumatriptan Nasal Spray in the Acute Treatment of a Migraine Attack with an Optional Repeat Dose for Headache Recurrence
S2B-T05	The Acute Treatment of Migraine with Intranasal GR43175N - A Placebo-Controlled Double-Blind Study

S2B-T35 A Double-Blind, Placebo-Controlled Study to Evaluate Intranasal GR43175N (1mg, 5mg, 10mg, 20mg, and 40mg) in the Acute Treatment of Migraine (one nostril application)

S2B-T39 A Double-Blind, Placebo-Controlled Study to Evaluate Intranasal GR43175N (1, 5, 10, 20, and 40mg) in the Acute Treatment of Migraine (two-nostril application)

The clinical investigations are defined as "new" as they have not been relied on by the FDA to demonstrate substantial evidence of effectiveness of a previously approved drug product for any indication or of safety for a new patient population and do not duplicate the results of any such investigations.

These investigations were "conducted or sponsored by Glaxo Wellcome" in that Glaxo was the sponsor of the investigational new drug application (IND) under which the investigations essential to approval of the application were conducted.

PEDIATRIC PAGE

(Complete for all original applications and all efficacy supplements)

NDA/PLA # 20-626 Supplement # _____ Circle one: SE1 SE2 SE3 SE4 SE5 SE6

HFD-120 Trade (generic) name/dosage form: Imitrex (Sumatriptan) Nasal Spray Action: AP (AE) NA _

Applicant GlaxoWellcome Therapeutic Class _____

Indication(s) previously approved _____ Pediatric labeling of approved indication(s) is adequate ___ inadequate ___

Indication in this application acute tx of migraine attack with or without aura (For supplements, answer the following questions in relation to the proposed indication.)

X 1. **PEDIATRIC LABELING IS ADEQUATE.** Appropriate information has been submitted in this or previous applications and has been adequately summarized in the labeling to permit satisfactory labeling for all pediatric subgroups. Further information is not required.

___ 2. **PEDIATRIC STUDIES ARE NEEDED.** There is potential for use in children, and further information is required to permit adequate labeling for this use.

___ a. A new dosing formulation is needed, and applicant has agreed to provide the appropriate formulation.

___ b. The applicant has committed to doing such studies as will be required.

___ (1) Studies are ongoing,

___ (2) Protocols were submitted and approved.

___ (3) Protocols were submitted and are under review.

___ (4) If no protocol has been submitted, explain the status of discussions on the back of this form.

___ c. If the sponsor is not willing to do pediatric studies, attach copies of FDA's written request that such studies be done and of the sponsor's written response to that request.

___ 3. **PEDIATRIC STUDIES ARE NOT NEEDED.** The drug/biologic product has little potential for use in children. Explain, on the back of this form, why pediatric studies are not needed.

___ 4. **EXPLAIN.** If none of the above apply, explain, as necessary, on the back of this form.

EXPLAIN, AS NECESSARY, ANY OF THE FOREGOING ITEMS ON THE BACK OF THIS FORM.

Mariel J Mills 3/20/97 (Dr. Levin see memo dated 3/25/97)

Signature of Preparer and Title (PM, CSO, MO, other) Date

cc: Orig NDA/PLA # 20-626
HFD-120/Div File
NDA/PLA Action Package
HFD-510/GTroendle (plus, for CDER APs and AEs, copy of action letter and labeling)

NOTE: A new Pediatric Page must be completed at the time of each action even though one was prepared at the time of the last action.

3/96

Imitrex®(sumatriptan) Nasal Spray
NDA 20-626

DEBARMENT CERTIFICATION

In accordance with the certification provision of the Generic Drug Enforcement Act of 1992 as outlined in correspondence dated July 29, 1992, from Daniel L. Michels, Office of Compliance, Glaxo hereby certifies that to the best of its knowledge and belief, it did not and will not use in any capacity the services of any person debarred under section 306(a) or (b) of the Generic Drug Enforcement Act of 1992 in connection with this application.

Richard Kiernan
Worldwide Director, GLP and GCP Compliance

Date

M E M O R A N D U M

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

DATE: March 25, 1997

FROM: Glenna G. Fitzgerald, Ph.D.
Pharmacology Team Leader
Division of Neuropharmacological Drug Products, HFD-120

TO: NDA 20-626
Sumatriptan, Imitrex™
Sponsor: Glaxo Wellcome Inc.
Nasal spray, 5, 10, 20 mg
Indicated for acute migraine

SUBJECT: Recommendation for approvable action and overview of toxicology issues

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Background:

It was recommended that this NDA not be approved when it was originally submitted because of concerns about the inadequacy of the animal studies to address the carcinogenic potential of the intranasal dosage form. The issues are summarized in my June 28, 1996 memo, and were relayed to the sponsor in our August 28, 1996 letter (both attached to this memo). In lifetime carcinogenicity studies in mice and rats by the oral route Imitrex, which is not genotoxic, was not carcinogenic. However, the sub-chronic studies conducted to examine local effects on nasal and respiratory tissues had raised more questions than they answered. Those studies ranged in duration from 2 to 13 weeks only, used very low multiples of human exposures, and were conducted with a variety of formulations (only one 2 week dog study used the clinical formulation). Even though there was no chronic exposure, several pathologies of nasal and respiratory tissues were reported, including hyperplasia, squamous metaplasia, keratinization, necrosis. Reversibility was shown to occur to a major degree in one 35 day rat study, but there was no assurance that this would happen after chronic exposure.

New information to address non-approvable issues:

The sponsor has responded to our concerns by obtaining a consultation from an independent Dr. Andrea Powell has summarized the sponsor's response and report in great detail in her review of February 24, 1997. original report is appendix 1 of her review. states that his objective was not to re-read the four studies he was given (35 day rat, 14 day dog with clinical formulation, two 3 month dog studies), but to assess the quality of the original study pathologists interpretations and to draw his own conclusions on treatment-related changes. He was not blinded to treatment group, and he did not in all cases examine control animals. The sponsor has concluded, based on report which examined the previously submitted preclinical studies, that "The information provided supports the conclusion that the pathology observations in the Imitrex Nasal Spray preclinical studies are reflective of adaptive changes rather than proliferative or pre-neoplastic changes and that the most appropriate animal species for this route of administration is the dog rather than the rat."

Because no new toxicology studies had been conducted, the Division decided to obtain a consultative review of the slides from the studies which had already been conducted. Dr. LuAnn McKinney, a board certified veterinary pathologist at AFIP, agreed to provide that service. Because of time constraints on the part of the Agency, she actually examined only selected slides from the 2 week and two 13 week dog studies so she was not blinded to treatment. For the rat study she reviewed the study protocols and the pathology reports, original and consultants'. After completing her review she held in-depth discussions with Dr. Powell and me, and the details from those discussions are carefully presented in Dr. Powell's review summary and evaluation, from page 9 on. Dr. McKinney's formal report is attached to this memo. With respect to the rat studies, she states that the changes were limited to hyperplasia, simple metaplasia and/or tissue damage and death, and were related to direct toxicity and irritancy. They were considered adaptive rather than mutational. Her opinion after examining slides from the dog studies was that the expert consultant's review was thorough and complete and the conclusions drawn by the sponsor did not differ from hers. That is, adaptive rather than mutational tissue responses were occurring from drug exposure. For both rat and dog studies she concluded that there was no evidence for neoplastic transformation. She pointed out, however, that conclusions about long term exposure could not be made.

Remaining unresolved issues:

These reviews of the studies provide us with a fairly comforting interpretation of the nature of the pathologies which occurred in all of the intranasal/inhalation studies. Both the sponsor's and the FDA's consulting pathologists concluded that exposure to intranasal Imitrex for up to 3 months does not produce pre-neoplastic lesions in nasal/respiratory tissues. However, several issues that were raised in our non-

approvable letter could not be addressed without additional studies, and these include the local effects of more chronic exposure, the effects of drug administered in the clinical formulation (only the 2 week dog study used that formulation), the effects of exposures that represent greater multiples of human exposure. Also, normally for drugs to be used for chronic intermittent indications, carcinogenicity studies by the appropriate route are required for approval. A draft guideline, which is followed by the Division of Pulmonary Drug Products[1], states that, "While not optimal, carcinogenicity studies by the oral route may be sufficient to support inhalation or intranasal clinical routes when no toxicity suggesting proliferative or pre-neoplastic changes, such as metaplasia or hyperplasia, is observed in chronic inhalation or intranasal toxicity studies and when adequate local airway exposure by the oral route is demonstrated."

Dr. Andrea Powell, the reviewing pharmacologist, has recommended that "the preclinical information provided in the original NDA submission and the supplements does not support approval". Her primary reason is that there are no studies which examine the chronic toxicity of the clinical formulation, which would determine whether or not carcinogenicity studies by the intranasal route would be required.

I agree with Dr. Powell that the potential for the occurrence of neoplasia in nasal and respiratory tissues should be examined in a properly designed chronic study, and I shall recommend that the conduct of this study during phase 4 be made a condition of approval. I disagree that the absence of this study at this time is of sufficient concern to withhold approval. My reasons for this decision are based on a combination of three factors: 1) there is no evidence for neoplastic change after 3 months of intranasal dosing, 2) Imitrex is not genotoxic and it is not carcinogenic when given orally, and 3) migraine therapy, while technically considered to be chronic intermittent drug use, in actual fact probably falls short of chronic use.

Dr. Powell also has several secondary issues in Appendix 5 of her review which she wishes to have addressed. Issue 1) parts a. and b. and issue 2) parts a. and b. are presented to address the adequacy of sampling in the studies reviewed and the interpretation of apparent treatment related histopathologic findings. These issues are taken from her original review of 4/15/96 and are updated to reflect her current concern. I believe that issues related to interpretation of results have been adequately addressed by Dr. McKinney, and that issues about study design will be handled by assuring that the requested phase 4 chronic intranasal study is properly conducted. Issue 3) discusses corneal opacities seen in intranasal studies in dogs. Since similar changes were seen after oral and subcutaneous Imitrex, and these findings are already in

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1. Considerations for Toxicology Studies of Respiratory Drug Products. DeGeorge, Joseph J, et.al., Division of Pulmonary Drug Products, CDER,FDA. Draft report, Feb. 24, 1997

labeling, I see no need to investigate the issue further. Issue 4) discusses the possible instability of the formulation used in a monkey study. Since this study apparently did not contain any findings not seen in other studies, was not reviewed by either pathologist, and was not used to support approval, the issue does not need to be addressed at this time. Issue 5) discusses the need for ocular irritation studies. I believe that since the submitted study was conducted by UK GLP regulations that it will suffice. Issue 6) discusses the lack of summary pathology tables for a one month dog study which Dr. Powell did not review and requests that the sponsor submit summary tables now. I examined the individual necropsy reports of that study, at the time we were selecting studies for which to request slides, to determine if there were findings which differed from other studies. Having determined that there was nothing extraordinary in that study I see no need to submit summary tables now. Issue 7) states that 3 intranasal one week dog studies were not reviewed. Since the longer studies were reviewed, there is no necessity for reviews of these studies.

Recommendations:

Because expert veterinary pathologists agree that the nasal and respiratory findings in rats and dogs dosed intranasally for one to three months represent adaptive rather than mutational changes, with no evidence for neoplastic transformation, I recommend that this NDA be considered approvable for pharmacology/toxicology. As a condition of approval the sponsor must submit a phase 4

Labeling should include a description of the animal nasal and respiratory findings under Warnings, Local Irritation, as follows:

In inhalation studies in rats dosed daily for up to one month at exposures equal to or greater than one half of the maximum daily human exposure (based on dose per surface area of nasal cavity), tissue responses consisting of epithelial hyperplasia, simple metaplasia and necrosis were observed. These changes were partially reversible after a two week drug-free period and appeared to be related to direct toxicity and irritancy. Tissue responses also occurred when dogs were dosed daily with various formulations by intranasal instillation for 13 weeks at exposures of two to four times the maximum daily human exposure. These responses consisted of epithelial hyperplasia

and focal squamous metaplasia, bronchial granulomas, bronchitis, and fibrosing alveolitis. In both species the changes observed were adaptive rather than mutational, and showed no evidence for preneoplastic or neoplastic transformation.

Local effects on nasal and respiratory tissues after chronic intranasal dosing in animals have not been studied. Therefore, although preneoplastic or neoplastic changes did not occur with short-term exposure, conclusions about the effects of chronic exposure may not be drawn.

Glenna G Fitzgerald
Glenna G. Fitzgerald
Pharmacology Team Leader

c.c. NDA 20-626
Div. File
HFD-120, Leber, Katz, Levin, Powell, Fitzgerald, Mille

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Attachment I

CSPV

MEMORANDUM

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

DATE: June 28, 1996

FROM: Glenna G. Fitzgerald, PhD GGF
Pharmacology Team Leader
Division of Neuropharmacological Drug Products, HFD-120

TO: NDA 20-626
Sumatriptan hemisulfate; Imitrex®
Nasal Spray; 50, 100 or 200 mg(base)/ml

SUBJECT: Pharmacology and Toxicology Overview

The intranasal and inhalation toxicology studies which have been submitted in support of this NDA for intranasal Imitrex for the acute treatment of migraine headache are summarized in the accompanying review by Dr. Andrea Powell. The full battery of toxicology studies normally required to assess the systemic toxicity of any new drug has been submitted to and reviewed for NDA 20-080 and NDA 20-132, for Imitrex subcutaneous injection and Imitrex tablets. These studies include oral and subcutaneous chronic toxicology and reproduction studies, a genetic toxicology screen, and oral carcinogenicity studies in mouse and rat.

Dr. Powell has recommended that additional information be submitted prior to approval of this dosage form, and has identified two areas of concern. The first relates to inadequate information about the metabolic profile of intranasally administered Imitrex, both in humans and in animals. Only minimal urinary information is available for intranasal Imitrex in rats, dogs and humans. In humans, these data indicate that the relative percentages of parent compound
are comparable in urine after either oral or intranasal drug. After subcutaneous drug, the percentage of parent compound is considerably higher than after the other two routes. The accompanying table summarizes these data. It would be desirable to have plasma level data for the parent and major metabolite as well, but the urinary data provide us with some assurance that the metabolic profile after intranasal drug is similar to that seen after oral drug, with the exception that a small amount of glucuronide of the ester is formed after oral drug. Intranasal studies in Sprague Dawley rats (Allen and Hansbury albino, which are Wistar/Sprague Dawley derived were used in the inhalation toxicology study) and in dogs suggest that 7 (rats) and 9 (dogs) components are recovered in urine. Both parent and
are found in both species at relatively high levels, with one additional major peak in dogs. We also have some information about the metabolic profile in Sprague Dawley and AHA rats after oral and subcutaneous drug from which we may be able to obtain information

about the effect of route on profile. It has been reported that, after either route, in Sprague Dawley rats at least 9 components plus parent were present in urine, with the major component being parent and the major (also in humans) and This is very similar to the profile seen after intranasal administration. All three of these major components were recovered in comparable amounts in urine of both strains of rats studied. Analysis of the plasma in dogs receiving oral or subcutaneous drug also revealed comparable profiles. The major components were parent and a highly polar, unidentified metabolite. The two known found in rats (one found in humans) were also present, though in lesser amounts. Again, the profiles do not appear to differ significantly with respect to from that seen after intranasal dosing. Although the data are incomplete, it seems unlikely that the exposure achieved in humans receiving intranasal drug represents a significantly different profile of drug and than that achieved after oral or subcutaneous drug. While a better characterization of metabolic profile following the intranasal route of administration, particularly in humans, would provide us with more assurance that the animal studies provided good models for assessing toxicity, it is my conclusion that this lack does not constitute a reason to withhold approval of this dosage form.

The second deficiency identified by Dr. Powell concerns the inadequacy of the submitted animal studies to address the carcinogenic potential of intranasal Imitrex. Imitrex use is considered to be chronic/intermittent, and CDER policy has been to require the complete battery of toxicology studies, including carcinogenicity, for this category of drug. Imitrex is not genotoxic and there are carcinogenicity studies in mice and rats using the oral route. However, as Dr. Powell points out in her review, the policy in the Division of Pulmonary Drug Products is to accept oral studies in support of intranasal clinical routes when "the chronic (6 months) intranasal toxicity studies have not demonstrated histopathology which is suggestive of proliferative or pre-neoplastic changes and the sponsor has carried out the necessary pharmacokinetic studies to demonstrate local (i.e., nasal and respiratory tissue) exposure to the drug by the oral route".

The accompanying three tables summarize the intranasal toxicology studies in rats, dogs and monkeys which were submitted to this NDA. Several aspects of the design of these studies are less than ideal. These include the following:

1) The longest studies are 35 days in rats, 13 weeks in dogs, 14 days in monkeys.
2) The only study which employed the clinical formulation was a 14 day dog study. In the other studies a variety of preserved, buffered, unbuffered, sweetened formulations were used.
3) Very low multiples of human exposure (on a mg/cm^2 basis) were used with the exception of high dose in the monkey study.

There is no six month intranasal study. However, one might argue that Imitrex use is not continuous and therefore does not need chronic toxicology studies. The average use in the clinical trials was every 24 days, and in the long term study it was every 10 days. With that pattern of use perhaps a one month rat and a three month dog intranasal study would be considered adequate if they were "clean". However, an examination of the data indicates

that several potentially worrisome lesions are occurring after sub-acute exposure. It is difficult to interpret the various findings in the dog studies. There is, however, one finding of focal squamous metaplasia of the bronchial epithelium in the 14 day dog study in which the clinical formulation was used. In the 35 day rat study and in the 8 day preliminary study, in which drug was administered by inhalation, several laryngeal findings are reported in different epithelial areas, including hyperplasia, keratinization, hyperplasia with squamous metaplasia, and necrosis of the ventral cartilage. Necrosis of the ventral cartilage appears to result from exposure to the vehicle. Hyperplasia and keratinization appear to be occurring with vehicle as well, but there is an increase in incidence with drug exposure. Hyperplasia with squamous metaplasia is occurring only in drug treated groups, and does reverse after two weeks off drug. The data from the preliminary rat study indicate that squamous metaplasia is occurring after only 3 and 8 days of treatment.

The interpretation of these data is difficult, particularly without a more detailed report of the pathology. For example, it would be important to distinguish between adaptive squamous metaplasia and squamous metaplasia with prominent keratinization, the latter being a more ominous finding with respect to a progression to a neoplastic lesion. The type of epithelium in the larynx which is being affected needs to be determined, since the larynx represents a transitional area for epithelium from squamous to respiratory, where hyperplasia is more apt to occur. Apparently keratinization in the respiratory epithelium may mean metaplastic changes, while keratinization of the squamous epithelium refers to the accumulation of the intercellular product (see addendum to pharmacology review). A review of all sides from relevant intranasal studies by a panel of experts should be considered as one approach to obtaining more definitive information about the relevance of these lesions. One might argue that none of this is relevant since the findings in the rat larynx were essentially reversed in two weeks. The problem is that we do not know if the pathology would have become more serious and/or more widespread with chronic exposure, or if there would still be reversibility. Additionally, the exposures achieved in rats in which pathology is occurring are only equal to or twice the estimated exposure in humans receiving the maximum total daily dose; the exposure margin in dogs is two to four times human exposure. A no-effect level has not been determined. Some comfort may be taken from the fact that Imitrex is not genotoxic and that the lesions observed are probably the result of local irritation and cytotoxicity. This issue could be better evaluated if we knew whether or not the nasal and respiratory tissues were adequately exposed to Imitrex in the oral carcinogenicity studies, and whether or not these tissues were subjected to careful histopathological examination.

RECOMMENDATIONS:

This NDA should not be approved until additional information is obtained about the potential for lesions observed in rat and dog nasal passages, laryngeal tissue and lungs to progress to neoplasia. If a review of the slides (rat 8 day and 35 day studies, dog 14 day and 3 month studies) by expert consultants does not provide definitive reassurance that the metaplasia observed is not of the type that could possibly progress to neoplasia, an additional, carefully designed study of at least six months duration should be conducted in the most appropriate species. This study should be designed to include a reversibility phase. Depending upon the results of these studies, a lifetime carcinogenicity study by the intranasal route may be

required.

The following should be transmitted to the sponsor in a not approvable letter:

Preclinical data submitted have raised concerns about the carcinogenic potential of this treatment that must be addressed prior to any decision about the approvability of this application. The results of subchronic testing with Imitrex indicate that squamous metaplasia occurred in the nasal and laryngeal epithelium of rats after 3,8 or 35 days of inhalation treatment and in the bronchial epithelium of one dog after 14 days of intranasal treatment with the clinical formulation. Although no metaplasia were reported in dogs treated intranasally with other formulations for 13 weeks, other pathologies of respiratory tissues, which are difficult to interpret given the information which was submitted, were reported.

We are concerned about these findings for several reasons:

1) The interpretation of the significance of the finding of metaplasia is impossible without a more detailed report of the pathology. For example, it would be important to distinguish between adaptive squamous metaplasia and squamous metaplasia with prominent keratinization in order to assess the potential for progression to neoplasia. It also is important to determine the type of epithelium in the larynx which is being affected, squamous or respiratory, since the latter may be more indicative of metaplastic changes.

2) Although the pathologies reported in the 35 day rat inhalation study appear to be reversible after a 2 week period, there is no assurance that this would be the case after chronic (at least 6 months) treatment. There also is no assurance that the pathology would not have become more serious or widespread with longer exposure. Imitrex use is considered to be chronic/intermittent, and as such it is considered to be prudent to evaluate the potential risks associated with chronic use.

3) The estimated exposures in mg/cm^2 which were achieved in rats in which pathology is occurring are only equal to or twice the estimated exposure in humans receiving the maximum total daily dose. The margin of exposure in dogs is two to four times human exposure. The fact that there is virtually no safety margin for the observed pathology heightens our concern.

While we do not dispute that a more conveniently administered dosage form of Imitrex would be desirable, it must first be established that administration by the nasal route is not associated with the occurrence of pre-neoplastic lesions. We therefore request that the issues enumerated above be resolved. It may be necessary for you to conduct a six month intranasal study with a reversibility phase in the most appropriate species in order to determine whether or not the squamous metaplasia which was observed in subacute studies progresses in severity over time. If it can be determined that there is no toxicity suggestive of proliferative or pre-neoplastic changes observed as a consequence of intranasal Imitrex administration, the oral carcinogenicity studies may support the intranasal dosage form.

Our staff would be happy to work with you in order to design studies which would answer the concerns we have raised.

NDA 20-626
HFD-120:
Leber
Katz
Levin
Fitzgerald
Powell
Grilley
Itrex.wpd

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METABOLISM OF SUMATRIPTAN (GR43175) IN HUMANS BY DIFFERENT ROUTES					
route	dose (mg(base))	time frame studied	urinary recovery	fecal recovery	plasma metabolic profile
oral	200	168 hrs	57% of dose recovered in urine - 3% as - 35% as - 8% as ester glucuronide of	38% of dose recovered in feces - ≥9% as - ≥11% as	not reported and/or not determined
subcutaneous	6	?	% of dose recovered in the urine not reported - 22% as - 38% as	% of dose recovered in feces not reported and/or not determined	not reported and/or not determined
subcutaneous	12	?	% of dose recovered in urine not reported - 25% as - 38% a	% of dose recovered in feces not reported and/or not determined	not reported and/or not determined
intranasal	20	?	% dose recovered in urine not reported - 3% as - 42% a	% of dose recovered in feces not reported and/or not determined	not reported and/or not determined

It is not clear from the reports if the above mentioned radioactive components were the only components recovered, or the only ones identified, or the only ones measured.

BASED ON 3 DAYS OF EXPOSURE:

Table 2a: Histopathology Results from Preliminary Study in Rats		
		3 days of treatment
hours/day of exposure to test formulation (or vehicle)		2
lung	foamy macrophage aggregate	1/1
lung	alveolar hemorrhage	1/1
larynx	widespread submucosal acute inflammation	1/1
larynx	epithelial hyperplasia of ventral region	1/1
larynx	ulceration in ventral region	1/1
nasal cavity	squamous metaplasia lining of the ventral meatus	1/1

Maximum total daily dose exposure estimate (dose/nasal cavity surface area) for this animal is 2.6 mg/cm^2
Maximum total daily dose exposure estimate (dose/nasal cavity surface area) for humans is 0.5 mg/cm^2

Exposure estimate based on literature values for surface area of the nasal cavity: Gizurarson, S., Animal models for intranasal drug delivery studies: a review article, Acta Pharm. Nord. 2(2):105-122, 1990.

BASED ON 8 DAYS OF EXPOSURE

Table 2b: Histopathology Results from Preliminary Study in Rats				
		8 days of treatment		
		vehicle	low dose	high dose
hours/day of exposure to test formulation (or vehicle)		2	1	2
Maximum total daily dose exposure estimate (dose/nasal cavity surface area) (mg/cm^2)		0	0.9 - 1.2	1.8 - 2.6
lung	foamy macrophage aggregate	0/10	1/10	1/9
larynx	submucosal inflammatory cell infiltrate	1/10	0/10	3/8
larynx	epithelial hyperplasia on arytenoid process	0/10	9/10	6/8
larynx	epithelial hyperplasia (ventral region)	0/10	1/10	7/8
larynx	squamous metaplasia	0/10	2/10	6/8
larynx	mononuclear cell focus in ventral pouch	0/10	0/10	1/8
larynx	small glandular cyst(s) ventral pouch	0/10	2/10	0/8

Maximum total daily dose exposure estimate (dose/nasal cavity surface area) for humans is 0.5 mg/cm^2

Exposure estimate based on literature values for surface area of the nasal cavity: Gizurarson, S., Animal models for intranasal drug delivery studies: a review article, Acta Pharm. Nord. 2(2):105-122, 1990.

BASED ON 35 DAYS OF EXPOSURE

Table 3: Histopathology Results from Main Study in Rats

	35 days of treatment					35 days of treatment + 2 week recovery period		
	air control	vehicle control	low dose	mid dose	high dose	air control	vehicle control	high dose
hours exposure to test formulation (or vehicle or air)	1	1	0.25	0.5	1	1	1	1
total daily dose exposure estimate (dose/nasal cavity surface area) (mg/cm^2)	0	0	0.17 - 0.31	0.35 - 0.64	0.69 - 1.2	0	0	0.69 - 1.2
larynx necrosis of the ventral cartilage	0/20	17/20	9/20	18/20	20/20	0/10	8/10	10/10
larynx ventral epithelium								
- hyperplasia	0/20	7/20	10/20	15/20	17/20	0/10	2/10	0/10
- keratinization	0/20	2/20	0/20	2/20	8/20	0/10	0/10	0/10
larynx ventrolateral epithelium								
- hyperplasia	0/20	0/20	2/20	5/20	0/20	1/10	1/10	3/10
- hyperplasia with squamous metaplasia	0/20	0/20	2/20	2/20	14/20	0/10	0/10	0/10
larynx lateral epithelium								
- hyperplasia	0/20	0/20	0/20	7/20	12/20	0/10	0/10	0/10
- keratinization	0/20	0/20	0/20	0/20	7/20	0/10	0/10	0/10
larynx epithelium of the arytenoid projection								
- hyperplasia	9/20	7/20	18/20	16/20	18/20	5/10	5/10	5/10
- keratinization	1/20	0/20	2/20	10/20	13/20	0/10	0/10	0/10
tracheal bifurcation epithelium								
- apparent loss of cilia	1/20	0/20	1/20	0/20	3/20	1/10	1/10	1/10

Maximum total daily dose exposure estimate (dose/nasal cavity surface area) for humans is 0.5 mg/cm^2

Exposure estimate based on literature values for surface area of the nasal cavity: Gizurarson, S., Animal models for intranasal drug delivery studies: a review article, Acta Pharm. Nord. 2(2):105-122, 1990.

Table 1: Histopathology Summary from Intranasal Studies

species	study #	formulation	concentration mg(base)/ml	dosing regimen	maximum daily total dose mg(base)	maximum total daily exposure estimate (dose/nasal surface area) (mg/cm²)	effects
dog 14 day	D13901	buffered (clinical)	200	0.3 ml, b.i.d. (1 nostril dosed)	120	1.1	1/8 focal squamous metaplasia of bronchial epithelium (grade 1)
dog 13 week	D12787	unbuffered	0	0.6 ml, b.i.d. (2 nostrils dosed)	0	-	1/8 fibrosing alveolitis (slight focal)
			200		240	1.1	1/8 fibrosing alveolitis (minimal) 2/8 bronchitis (slight - minimal)
			400		480	2.2	3/8 fibrosing alveolitis (slight - minimal) 2/8 bronchitis (slight - moderately severe) 2/8 granuloma 1/8 lymphoid hyperplasia-larynx (minimal) 1/8 lymphoid hyperplasia of respiratory region of nasal passages (minimal)
dog 13 week	D13342	sweetened	0	0.6 ml, b.i.d. (2 nostrils dosed)	0	-	1/8 fibrosing alveolitis (minimal) 1/8 granuloma (lung) 1/8 reactive bronchial lymph node (minimal)
			200		240	1.1	2/8 fibrosing alveolitis (minimal) 3/8 granuloma (lung) (*)
			400		480	2.2	4/8 fibrosing alveolitis (minimal) 1/8 pleural fibrosis/adhesion (moderate - multifocal) 4/8 granuloma (lung) (*) 1/8 bronchiolitis associated with low grade epithelial hyperplasia 3/8 reactive bronchial lymph node (minimal) 1/8 focal erosion of nasal cavity (minimal) 1/8 epithelial hyperplasia (maxilloturbinates) (minimal)
dog 1 month	D12279	preserved	0 (water)	0.6 ml, b.i.d. (2 nostrils dosed)	0	0	Histopathology was not formally reviewed. The sponsor did not submit the standard summary tables. Findings are reported in the 30 individual animal reports from necropsy.
			0 (vehicle)		0	0	
			10		12	0.05	
			63.3		76	0.3	
			400		480	2.2	
monkey 14 day	P11224	unbuffered	200	0.2 ml, q.i.d. (2 nostrils dosed)	160	2.6	-
			400		320	5.2	1/4 focal pulmonary fibrosis and pleural adhesion
human	proposed	buffered (clinical)	200 (maxi mum)	0.1 ml, b.i.d. (maximum) (1 nostril dosed)	40	0.5	-

(*) dose related increase in degree affected

Exposure estimate based on literature values for surface area of the nasal cavity: Gizurarson, S., Animal models for intranasal drug delivery studies: a review article, Acta Pharm. Nord. 2(2):105-122, 1990.

Note that the estimate for the nasal cavity surface area in monkeys is based on a 7 kg monkey of unknown strain. The toxicity study in monkeys employs the much smaller (< 3.0 kg) cynomolgus monkeys.

Attachment F

REGISTRY OF TOXICOLOGIC PATHOLOGY FOR ANIMALS

The Registry of Toxicologic Pathology for Animals
Armed Forces Institute of Pathology
Washington, D.C. 20306-6000

Third-Party review of Toxicologic pathology data submitted by GlaxoWellcome to the FDA (Neuropharmacology), from Inhalation studies

LuAnn McKinney, DVM, DACVP
LTC, US Army
Director, Registry of Toxicologic Pathology for Animals, American Registries of Pathology, The Armed Forces Institute of Pathology.

This review of the data was undertaken to answer a series of questions generated by the FDA reviewing Toxicologists. A blind review of selected treatment and control groups was not conducted. An initial review of the toxicologist's summaries of the animal studies was followed by a review of the animal data sheets and summary data from the original submissions. Lastly, a selective review of slides from the dog studies and a broad review of the rat data was conducted.

The rat inhalation studies were conducted by the company to determine irritancy. Lesions were documented by photograph as well as tabulated. The anatomic locations were clearly documented. The changes were limited to hyperplasia, simple metaplasia and/or tissue damage and death. All changes appeared to be related to direct toxicity and irritancy. Adaptive, rather than mutational, tissue responses were observed. Because the studies were short-term, conclusions about long-term exposure could not be made with certainty; however, there was no evidence of a neoplastic transformation during these short-term exposures.

An initial series of questions was posed by the toxicologist and an extended telephonic consultation followed. After analyzing the data and reading the independent interpretation report on the dog intra-nasal instillation studies, both the individual animal data and selected glass slides of the dog studies were reviewed and selected literature citations were also perused. The independent interpretation was determined to be an expert opinion rendered after academic review of the original data. It is the opinion of this reviewer that the expert review was thorough and complete; although there were subtle differences in terminology and subjective assessment of severity, the ultimate conclusions about product toxicity remained the same. Adaptive, rather than mutational tissue responses were caused by exposure to the compounds. Finally, although there is no evidence of neoplastic change, conclusions about long term exposure could not be made with certainty.

A second telephonic consultation followed, and the above opinions were stated. This reviewer then edited the final documents to best express the opinions of a pathologist, and the review was concluded.

LuAnn McKinney, DVM, DACVP

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