CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

20-132/S-015

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

CLINICAL PHARMACOLOGY/BIOPHARMACEUTICS REVIEW

DRUG: Imitrex ® (Sumatriptan)
NDA: 20-132 /SCF 015
FORMULATION: Fast Disintegrating Tablet
APPLICANT: GlaxoSmithKline

PRIMARY REVIEWER: Andre Jackson
TYPE: NDA
STRENGTH: 25 mg, 50mg and 100 mg

Submission Dates: February 28, 2003
March 20, 2003
March 31, 2003

INDICATIONS: Migraine
Generic Name: Sumatriptan

Executive Summary

Imitrex ® (Sumatriptan) tablet was approved for the treatment of migraine. The firm has recently developed a FDT (fast disintegrating tablet). The current submission contains 4 studies to show that the new FDT is bioequivalent to the currently marketed tablet. The submitted studies were:

SUM10948	Pilot relative bioavailability of two FDT versus the currently marketed sumatriptan 50 mg.
SUM10950	Bioequivalence of FDT compared with the currently marketed sumatriptan tablets.
SUM10954	Food versus fasting bioequivalence of FDT compared with the currently marketed tablet.
SUM10961	Bioequivalence of FDT dissolved in water compared to the currently marketed sumatriptan tablet

The important findings were:

1. Bioequivalence of the FDT formulation, relative to the standard sumatriptan tablet, was demonstrated for C_{max}, $AUC_{(0-\infty)}$ and $AUC_{(0-t)}$ at both 50 mg and 100 mg doses under fasting conditions.
2. Food caused the FDT to have a 23% lower Cmax compared to the marketed tablet after food, 90% CI(65-87).
3. Food also caused the Cmax and AUC for the FDT to be 15% and 12% higher respectively, than in the fasting state for the FDT.
4. Bioequivalence of the FDT formulation dissolved in water, relative to the standard sumatriptan tablet, was demonstrated for C_{max}, $AUC_{(0-\infty)}$ and $AUC_{(0-t)}$ at the 100 mg dose under fasting conditions.
5. The range of Tmax and mean AUC(0-2) hr values for the different treatments were:

Treatment	Tmax range	AUC(0-2)
50 mg Standard Tablet	0.5-4 hr	37.8 ng/mlxhr
50 mg Fast dissolving tablet	0.33-3hr	38.2 ng/mlxhr
100 mg Standard Tablet	0.5-4 hr	61.2 ng/mlxhr
100 mg Fast dissolving tablet	0.33-3hr	64.8 ng/mlxhr

6. Tmax values ranged from 0.5-4 hr for the standard 100 mg tablet and the 100 mg FDT after food.

The dissolution conditions and specifications for the FDT are:
The dissolution testing will be conducted in — of —1 HCL at —
using USP apparatus 2 (paddle) at —rpm. Q= — of Sumatriptan FDT is dissolved in 15 min.

Recommendation: NDA 21476 is acceptable to OCPB.

Introduction and Background

Sumatriptan (**IMITREX /IMIGRAN**) is a 5-HT1B/1D agonist approved for the acute treatment of migraine with and without aura. Sumatriptan is available as an injection, a tablet formulation, as a nasal spray, and (outside the US) as a suppository. Following oral dosing of sumatriptan solution to healthy subjects, drug absorption is rapid, with maximum plasma concentrations achieved in approximately 1 hour. Standard tablet formulations reach median maximal plasma concentrations a short time after, sometimes up to 2 hours post-dose. Bioavailability via the oral route is low, estimated at 15% relative to the subcutaneous injection, primarily due to pre-systemic metabolism and partly due to incomplete absorption.

Marketed sumatriptan tablets rely upon tablet surface erosion in the stomach to initiate the release of sumatriptan, and this process is assisted by gastric motility. Fast disintegrating sumatriptan tablets, have been developed as a reformulated product to allow for possible increased disintegration while maintaining bioequivalence to the currently approved product. The soluble lactose filler in the existing tablet has been replaced by insoluble dibasic calcium phosphate filler and the level of existing disintegrants — together with the addition of a — level of sodium bicarbonate. This combination is designed to ensure that the tablet swells and breaks apart, rather than disintegrating by tablet surface erosion, even under conditions of low shear analogous to gastric stasis found during migraine.

Submission Content:

This submission contains 4 bioavailability/bioequivalence studies:

Study #	Objective
SUM10948	To determine via a pilot study the relative bioavailability of two newly formulated fast disintegrating sumatriptan 50 mg tablets versus the currently marketed sumatriptan 50 mg tablets in healthy volunteers-THIS STUDY WHICH WAS USED TO SELECT THE BEST SODIUM BICARBONATE FORMULATION WILL NOT BE REVIEWED
SUM10950	To demonstrate the bioequivalence of fast disintegrating sumatriptan tablets (50 and 100 mg tablets) compared with the currently marketed sumatriptan tablets (50 and 100 mg **IMITREX /IMIGRAN** tablets), in healthy male and female volunteers in the fasted state.

SUM10954	To demonstrate the bioequivalence of fast disintegrating sumatriptan 100 mg tablet compared with the currently marketed sumatriptan 100 mg tablet administered immediately after food and the fast disintegrating tablet administered in the fasted state to healthy male and female subjects
SUM10961	To demonstrate the bioequivalence of fast disintegrating sumatriptan 100 mg tablet dissolved in water compared to the currently marketed sumatriptan 100 mg tablet administered in the fasted state to healthy male and female subjects

Labeling:

FIRM'S PROPOSED LABELING

Pharmacokinetics: The mean maximum concentration following oral dosing with 25 mg is 18 ng/mL (range, 7 to 47 ng/mL) and 51 ng/mL (range, 28 to 100 ng/mL) following oral dosing with 100 mg of sumatriptan. This compares with a C_{max} of 5 and 16 ng/mL following dosing with a 5- and 20-mg intranasal dose, respectively. The mean C_{max} following a 6-mg subcutaneous injection is 71 ng/mL (range, 49 to 110 ng/mL). The bioavailability is approximately 15%, primarily due to presystemic metabolism and partly due to incomplete absorption. The C_{max} is similar during a migraine attack and during a migraine-free period, but the T_{max} is slightly later during the attack, approximately 2.5 hours compared to 2.0 hours. When given as a single dose, sumatriptan displays dose proportionality in its extent of absorption (area under the curve [AUC]) over the dose range of 25 to 200 mg, but the C_{max} after 100 mg is approximately 25% less than expected (based on the 25-mg dose).

[redacted] .A food effect study involving administration of IMITREX Tablets 100 mg to healthy volunteers under fasting conditions and with a high-fat meal indicated that the C_{max} and AUC were increased by 15% and 12%, respectively, when administered in the fed state.

FDA PROPOSED LABELING

Pharmacokinetics: The mean maximum concentration following oral dosing with 25 mg is 18 ng/mL (range, 7 to 47 ng/mL) and 51 ng/mL (range, 28 to 100 ng/mL) following oral dosing with 100 mg of sumatriptan. This compares with a C_{max} of 5 and 16 ng/mL following dosing with a 5- and 20-mg intranasal dose, respectively. The mean C_{max} following a 6-mg subcutaneous injection is 71 ng/mL (range, 49 to 110 ng/mL). The bioavailability is approximately 15%, primarily due to presystemic metabolism and partly due to incomplete absorption. The C_{max} is similar during a migraine attack and during a migraine-free period, but the T_{max} is slightly later during the attack, approximately 2.5 hours compared to 2.0 hours. When given as a single dose, sumatriptan displays dose proportionality in its extent of absorption (area under the curve [AUC]) over the dose range of 25 to 200 mg, but the C_{max} after 100 mg is approximately 25% less than expected (based on the 25-mg dose).

[redacted] A food effect study involving the administration of an IMITREX fast dissolving tablet 100 mg to healthy volunteers under fasting conditions and with a high fat meal indicated that the Cmax and AUC were increased by 15% and 12% respectively, when administered in the fed state. The Cmax of the fast dissolving tablet was lowered by 23% compared to the standard tablet following a high fat meal. AUC for the fast dissolving and standard tablet were the same following a high fat meal.

Comment to the Firm: Please adopt the following dissolution method and specifications for all three strengths 25 mg, 50 mg and 100 mg sumatriptan FDT's.

The dissolution conditions and specifications for the FDT are:
The dissolution testing will be conducted in — ml of — HCL at —
using USP apparatus 2 (paddle) at — rpm. Q= — % of Sumatriptan FDT is dissolved in
15 min.

Please forward this comment to the firm.

Study Number: 10950

Objectives:
To demonstrate bioequivalence between a fast disintegrating sumatriptan 50 and 100 mg tablet compared with the currently marketed sumatriptan 50 and 100 mg tablet, in healthy male and female subjects in the fasted state.

To evaluate the early pharmacokinetic profile of a fast disintegrating sumatriptan 50 and 100 mg tablet versus the currently marketed sumatriptan tablet as assessed by AUC(0-2) and tmax.

Overall Study Design

This was a single-centre, single-dose, open, randomised, four-treatment, crossover study. Thirty-two subjects (a minimum of 18 females) were recruited in order to achieve 26 evaluable subjects. Subjects participated in a screening phase, a treatment phase (consisting of four separate dosing periods, each held in the clinical study unit) and a study completion evaluation. There was a minimum 3-day washout period between administration of the treatments to allow for complete washout of residual drug from the previous treatment.

Description of Investigational Products

Test Formulations Used in Study SUM10950

Formulation	Strength	Appearance	Batch #
Standard	50 mg sumatriptan	pink, capsule-shaped, biconvex film-coated tablet	BO56176
Standard	100 mg sumatriptan	white, capsule-shaped, biconvex film-coated tablet	BO62222
Fast disintegrating	50 mg sumatriptan	Triangular-shaped white tablet	E02B78
Fast disintegrating	100 mg sumatriptan	Triangular-shaped white tablet	E02B33

No. of Sequences	4 ADBC, DCAB, CBDA or BACD	**Crossover**	Y
No. of Periods	4		N
No. of Treatments	4	**Washout Period**	3 days
Blood Sampling Times	Serial blood samples (approximately 5 mL) for determination of sumatriptan plasma concentrations were collected pre-dose and nominally at 5, 10, 15, 20, 30, 40, 50, 60, 90, 120, 150 min and 3, 4, 6, 8, 10, 12, 14 and 16 h after dosing in each session.		

Treatment A: Standard sumatriptan 50 mg tablet; Treatment B: Standard sumatriptan 100 mg tablet; Treatment C: fast disintegrating sumatriptan 50 mg tablet; Treatment D: fast disintegrating sumatriptan 100 mg tablet.

Fasting Study-Demographics

Table 1 Demographic Characteristics for Study SUM 10950

N = 32	Age (y)	Weight (kg)
Mean	33.8	70.2
SD	7.6	12.0
Range	21-51	48-89

Female 66%, male 34%

Table 2. Formulation data

Composition of Sumatriptan FDT 25 mg, 50 mg and 100 mg

Component	Quantity (mg/tablet) 25 mg Tablet	50 mg Tablet	100 mg Tablet	Function	Reference to Standard
Tablet Core					
Sumatriptan Succinate					GlaxoSmithKline
Dibasic Calcium Phosphate, Anhydrous					USP
MicrocrystallineCellulose					NF
Sodium Bicarbonate					USP
					NF
					NF
					USP
Target Compression Weight					-
Film Coat					
					USP
Target Film Coated Tablet Weight					-

Notes:

1. Equivalent to 25 mg, 50 mg and 100 mg of sumatriptan respectively.
3. Due to differing the 50 mg and 100 mg tablets are visually equivalent in size despite having different
4. Full details of the are provided in DMF (see Section 2.3.P.4. Control of Excipients).
5. The actual weight of film coat applied may vary from the target within the range w/w (of tablet core weight) Depending on coating efficiency and in order to achieve an aesthetic coat appearance.

Study Results

Clinical

Study Dates: May 27, 2002- June 20, 2002
Analysis Dates: June 27, 2002-September 16, 2002
Storage Period: 120 days

Analytical Method Validation

Parameter	Sumatriptan
Method	
Freeze-thaw	
Benchtop Extract Stability at RT	
Long term at room temperature	
Long term at room temperature	
Recovery ng/ml ng/ml	

Analytical Study 10950

Parameter	
Method	
Sensitivity/LOQ	
Linearity (Standard curve samples)	
Quality Control (QC) Samples	
Precision of Standards (%CV)	
Precision of QC Samples (%CV)	
Accuracy of Standards (%CV)	
Accuracy of QC Samples (%CV)	

Pharmacokinetic/Statistical Analysis

From the individual plasma concentration versus time curves for sumatriptan, and using the actual collection times recorded on each sampling occasion, the following parameters were calculated using the non-compartmental analysis program WinNonlin Professional Version 3.1.

Cmax maximum observed plasma concentration; tmax time of first occurrence of Cmax; AUC(0-∞) area under the plasma concentration versus time curve between zero hours and infinity, calculated using the linear trapezoidal rule for each incremental trapezoid to Cmax, and the log trapezoidal rule for each trapezoid after Cmax.; AUC(0-2) and AUC(0-0.5) area under the plasma concentration versus time curve between 0 hours and a given time (i.e., 2 hours or 0.5 hours), calculated using a combined linear-logarithmic trapezoidal method; tmax was calculated using a linear trapezoidal method; t½ - terminal elimination half-life, calculated as ln(2)/ z.

The following pharmacokinetic parameters were also derived: tlag - the time to the first quantifiable plasma concentration; Cmax/AUC(0-t) - an index related to the rate of absorption;

%Cmax - the concentration at 15, 20 and 30 minutes post-dose expressed as a percentage of the respective Cmax. The primary endpoints were sumatriptan AUC(0-∞) and Cmax. AUC(0-∞) was not determined in all instances, and hence AUC(0-t) was also derived and analysed as a primary endpoint. The secondary endpoints were AUC(0-2) and tmax.
In order to demonstrate the bioequivalence of a fast disintegrating sumatriptan tablet relative to the currently approved standard sumatriptan tablet, point estimates and 90% confidence intervals were derived for the ratio of "fast disintegrating:standard tablet" for AUC(0-∞), AUC(0-t) and Cmax of both 50 mg and 100 mg tablets (C:A and D:B).

RESULTS

Figure 1 Mean Sumatriptan Plasma Concentration-Time Profiles

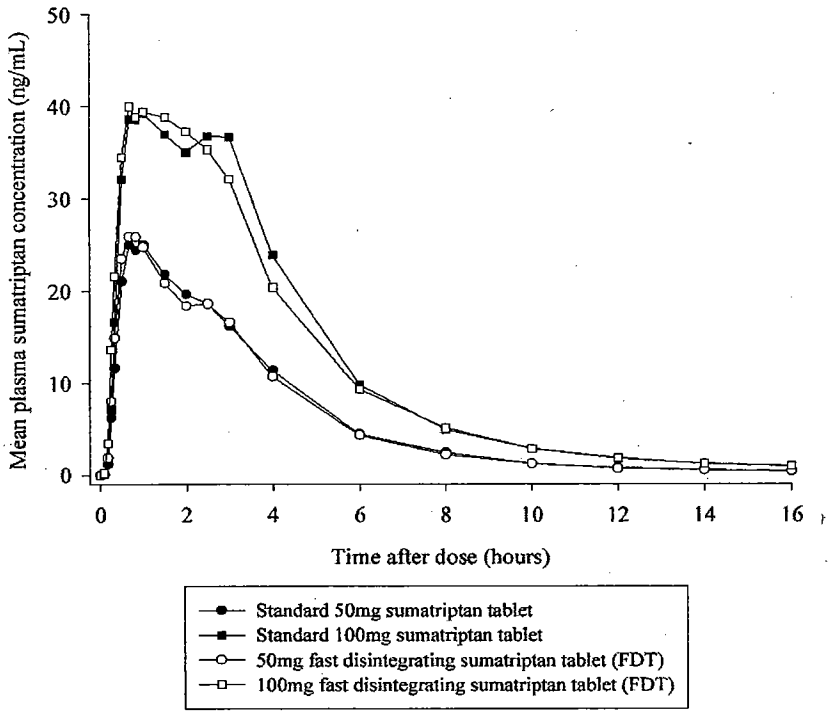

Table 3. Arithmetic mean (SD) pharmacokinetic parameters for sumatriptan by treatment regimen for Study SUM10950

Parameter [units]	50 mg Standard Tablet [A]	100 mg Standard Tablet [B]	50 mg FDT [C]	100 mg FDT [D]
N	30	31	31	30
Primary				
$AUC_{(0-\infty)}$ [ng.h/mL] [1]	105 (55.6)	167 (50.2)	103 (49.0)	199 (105)
$AUC_{(0-t)}$ [ng.h/mL]	98.5 (48.5)	190 (106)	97.1 (43.1)	185 (91.3)
C_{max} [ng/mL]	29.1 (12.3)	53.2 (29.0)	30.0 (12.5)	52.2 (21.3)
Secondary				
t_{max} [h] [2]	1.00 (0.50 – 4.00)	1.00 (0.50 – 4.00)	0.83 (0.33 – 3.00)	1.00 (0.33 – 3.00)
$AUC_{(0-2)}$ [ng.h/mL]	37.8 (16.2)	61.2 (24.1)	38.2 (15.8)	64.8 (22.6)

1. Actual number of subjects with sufficient data for analysis A (N = 23), B (N= 21), C (N = 24), D (N = 23);
2. Median (range)
3. FDT = Fast disintegrating tablet

*AUC(0-t) for B is larger than AUC(0-inf) for treatment B because N=27 for AUC(0-t) but N= equals 18 for AUC(0-∞).

Table 4. Point Estimates and 90% Confidence Intervals for treatment comparisons for Study SUM10950

Parameter	Comparison	Ratio	90% CI	CVw%
Primary				
$AUC_{(0-t)}$	C:A	0.99	(0.93,1.05)	14.5
	D:B	0.98	(0.92,1.04)	
$AUC_{(0-\infty)}$	C:A	0.97	(0.91,1.04)	13.0
	D:B	1.05	(0.98,1.12)	
C_{max}	C:A	1.03	(0.93,1.15)	24.7
	D:B	1.01	(0.91,1.12)	
Secondary				
$AUC_{(0-2)}$	C:A	1.01	(0.92,1.12)	24.1
	D:B	1.08	(0.97,1.19)	
t_{max} [1]	C-A	-0.17	(-0.84,-0.09)	
	D-B	-0.25	(-1.00,0.00)	

Source data: Section 12,Table 12.3, Tables 12.25-12.29

[1] t_{max} analysed non-parametrically, median differences along with corresponding 90% confidence intervals are presented

A: Standard 50 mg sumatriptan tablet

B: Standard 100 mg sumatriptan tablet

C: Fast disintegrating 50 mg tablet

D: Fast disintegrating 100 mg tablet

Comments:

1. Bioequivalence of the FDT formulation, relative to the standard sumatriptan tablet, was demonstrated in terms of C_{max}, $AUC_{(0-\infty)}$ and $AUC_{(0-t)}$ in the fasted state at both 50 mg and 100 mg doses as the 90% confidence intervals were completely contained within the equivalence range of 0.80-1.25.

2. The t_{max} for the fast disintegrating tablets was slightly earlier (on average, 10-15 minutes) compared with the standard tablet.

Study Number: 10954

Objectives:

a.To demonstrate bioequivalence between a fast disintegrating 100 mg tablet compared with the currently marketed sumatriptan 100 mg tablet administered immediately after a high fat breakfast, in healthy male and female subjects.

b.To demonstrate bioequivalence between a fast disintegrating 100 mg tablet administered immediately after a high fat breakfast compared with the same tablet administered to healthy male and female subjects in the fasted state.

Overall Study Design

This was a single centre, single dose, open-label, randomised, three-treatment, crossover study. Thirty-two healthy subjects (a minimum of 16 females) were to be recruited in order to achieve 28 evaluable subjects. Subjects participated in a screening phase, a treatment phase (consisting of three separate dosing periods, each held in the clinical study unit) and a study completion evaluation

Table 5 Test Formulations Used for Study SUM10954

Formulation	Strength	Appearance	Batch #
Standard	100 mg	Triangular shaped tablet	E01B273
Fast disintegrating	100 mg	Triangular shaped tablet	E02B33

No. of Sequences	6 (ABC, ACB, BCA, BAC, CAB or CBA)	**Crossover**	Y
No. of Periods	3		N
No. of Treatments	3	**Washout Period**	3 days
Blood Sampling Times	Serial blood samples (approximately 5 mL) for determination of sumatriptan plasma concentrations were collected pre-dose and nominally at 5, 10, 15, 20, 30, 40, 50, 60, 90, 120, 150 min and 3, 4, 6, 8, 10, 12, 14 and 16 h after dosing in each session.		

Treatment A: standard sumatriptan 100 mg tablet, after high fat breakfast (standard fed). Treatment B: fast disintegrating sumatriptan 100 mg tablet (FDT), after high fat breakfast (FDT fed).Treatment C: fast disintegrating sumatriptan100 mg tablet (FDT), in fasted state (FDT fasted).

Food Study-Demographics

Five male (17%) and 25 (83%) female subjects took part in the study, 27 subjects (90%) were White, two subjects (7%) were Oriental and one subject was Black (3%).

Table 6. Demographic Characteristics for Study SUM10954

n = 30	Age (y)	Weight (kg)
Mean	33	66.0
SD	8.9	6.6
Range	19-52	54.7-80.3

Study Results

Clinical

The sampling period was between August 15, 2002- September 4, 2002
Samples were analyzed between September 20, 2002-November 4, 2002
Storage period- ~90 days

Analytical Method

Analytical Study 10954

Parameter	
Method	[redacted]
Sensitivity/LOQ	[redacted] ng/ml
Linearity (Standard curve samples)	[redacted] ng/ml
Quality Control (QC) Samples	[redacted] and [redacted] ng/ml
Precision of Standards (%CV)	[redacted] ng/ml [redacted] ng/ml
Precision of QC Samples (%CV)	[redacted] ng/ml [redacted] ng/ml
Accuracy of Standards (%CV)	[redacted] ng/ml [redacted] ng/ml
Accuracy of QC Samples (%CV)	[redacted] ng/ml [redacted] ng/ml

Pharmacokinetic/Statistical Analysis

From the individual plasma concentration versus time curves for sumatriptan, and using the actual collection times recorded on each sampling occasion, the following parameters were calculated using the non-compartmental analysis program WinNonlin Professional Version 3.1. Cmax maximum observed plasma concentration; tmax time of first occurrence of Cmax; AUC(0-∞) area under the plasma concentration versus time curve between zero hours and infinity, calculated using the linear trapezoidal rule for each incremental trapezoid to Cmax, and the log trapezoidal rule for each trapezoid after Cmax.; AUC(0-2) and AUC(0-0.5) area under the plasma concentration versus time curve between 0 hours and a given time (i.e., 2 hours or 0.5

hours), calculated using a combined linear-logarithmic trapezoidal method; t_{max} was calculated using a linear trapezoidal method; $t_{½}$ - terminal elimination half-life, calculated as ln(2)/ z.

Point estimates and 90% confidence intervals for the difference between formulations in the fed state (B:A) and for the fast disintegrating tablet in the fed/fasted state (B:C were constructed using the residual variance from the ANOVA for AUC(0-∞), AUC(0-t), Cmax and $AUC_{(0-2)}$. These were exponentially back-transformed to obtain point estimates and confidence intervals (CIs) for the ratios. Bioequivalence was demonstrated if the 90% CIs for the ratios of AUC(0-∞), AUC(0-t) and Cmax, were completely contained within the range 0.80 to 1.25.

RESULTS

Table 7. Mean sumatriptan values ± SD for the three treatments. All doses were 100 mg.

	Standard Tablet Food		FDT Food		FDT Fasting	
Time (h)	Mean	Std Dev	Mean	Std Dev	Mean	Std Dev
0.00	NQ	NQ	NQ	NQ	NQ	NQ
0.08	NQ	NQ	0.148	0.266	0.270	0.558
0.17	0.928	2.110	2.599	4.206	2.084	2.136
0.25	3.465	4.116	9.786	14.896	7.656	6.828
0.33	10.173	13.146	16.572	21.329	15.976	10.098
0.50	24.288	20.692	25.615	25.774	28.882	15.018
0.67	35.229	22.744	30.409	24.273	38.774	17.239
0.83	45.419	27.109	37.901	27.090	41.757	17.077
1.00	54.227	28.216	40.094	25.028	38.362	14.106
1.50	67.063	25.418	45.098	20.139	37.079	9.714
2.00	62.072	21.269	45.800	16.521	36.383	9.877
2.50	49.899	16.021	43.171	13.324	38.868	8.792
3.00	42.516	16.235	41.204	14.190	39.335	12.730
4.00	29.732	13.759	33.048	14.467	29.071	7.867
6.00	13.697	8.853	17.074	9.810	13.148	5.945
8.00	7.142	5.309	8.645	5.637	6.498	2.855
10.00	4.045	3.264	4.785	3.159	3.529	1.619
12.00	2.227	1.945	2.662	1.898	1.984	1.219
14.00	1.470	1.112	1.470	0.998	1.315	0.785
16.00	0.942	0.635	1.026	0.760	1.026	0.684

Table 8. Mean (SD) Pharmacokinetic Parameters by Treatment Regimen for Study SUM10954

Parameter [units]	100 mg Standard Tablet [A]-after food	100 mg FDT Tablet [B]-after food	100 mg FDT Tablet [C]-fasted
N	28	29	27
$AUC_{(0-\infty)}$ [ng.h/mL]a	265 (69)	254 (64)	218 (55)
$AUC_{(0-t)}$ [ng.h/mL]	258 (71)	246 (65)	213 (52)
C_{max} [ng/mL]	77.1 (21.7)	59.6 (18.0)	50.8 (14.4)
$AUC_{(0-2)}$ [ng.h/mL]	85.4 (34.6)	66.1 (35.6)	61.8 (19.0)
t_{max}* [h]	1.50 (0.58 4.00)	2.00 (0.50 4.00)	2.00 (0.50 3.98)

A (n = 26), B (n = 28), C (n = 26)
* Median (range)
FDT = fast disintegrating tablet

Table 9. Point estimates and 90% confidence intervals for Study SUM10954

Parameter	Comparison	Ratio	90% CI**	CVwithin(%)
PrimaryAUC $_{(0\text{-}t)}$	B:A	0.94	(0.87,1.01)	15
	B:C	1.12	(1.04,1.22)	
$AUC_{(0\text{-}\infty)}$	B:A	0.93	(0.87,1.00)	12
	B:C	1.12	(1.05,1.21)	
C_{max}	B:A	0.75	(0.65,0.87)	27
	B:C	1.15	(0.99,1.33)	
SecondaryAUC $_{(0\text{-}2)}$	B:A	0.72	(0.57,0.91)	55
	B:C	0.95	(0.75,1.21)	
t_{max}*	B A	0.12*	(-0.10,0.34)	
	B C	0.11	(-0.26,0.41)	

*t_{max} analysed non-parametrically, median difference along with corresponding 90% confidence intervals
**Adjustments were made for the multiple comparisons
Regimen codes
A: standard sumatriptan 100 mg tablet (after food)
B: fast disintegrating sumatriptan 100 mg tablet (after food)
C: fast disintegrating sumatriptan 100 mg tablet (fasted)
CI = confidence intervals

Comments

1.Two subjects, Subject 1 (A) and Subject 29 (C) had quantifiable predose concentrations. These were set to zero for the purposes of pharmacokinetic analyses, as they were not deemed to be reflective of sumatriptan pharmacokinetics. The firm analyzed the data with and without the quantifiable pre-dose concentrations. The results were:

Comparison of sumatriptan $AUC_{(0-t)}$, $AUC_{(0-\infty)}$ and $AUC_{(0-2)}$ between original and re-analysis of SUM10954 data (geometric mean (range))

	Original Analysis		Re-Analysis	
Parameter [units]	100 mg Standard Tablet [A]- After food	100 mg FDT Tablet [C]- Fasted	100 mg Standard Tablet [A]- After food	100 mg FDT Tablet [C]- Fasted
$AUC_{(0-\infty)}$ [ng.h/mL]	256 (166-430)	212 (118-351)	256 (166-430)	212 (**120**-351)
$AUC_{(0-t)}$ [ng.h/mL]	248 (128-420)	207 (118-347)	248 (128-420)	**208** (**119**-347)
$AUC_{(0-2)}$ [ng.h/mL]	76.8 (20.2-148)	59.4 (39.6-118)	76.9 (20.2-148)	**59.5** (39.6-118)

Note: bolded and underlined values signify changes from the original SUM10954 analysis

2.Food caused the FDT to have a 23% lower Cmax compared to the standard tablet after food, 90% CI(65-87).
3.Food also caused the Cmax for the FDT to be 15% higher than in the fasting state.

Study Number: 10961

Objectives:
To demonstrate bioequivalence between a solution of the fast disintegrating 100 mg tablet compared with the currently marketed sumatriptan 100 mg tablet administered to healthy male and female subjects in the fasted state.

Overall Study Design

This was a single-centre, single-dose, open-label, randomised, two-treatment, crossover study. Twenty-eight subjects (a minimum of 14 females) were to receive study medication in order to achieve 24 evaluable subjects. Subjects participated in a screening phase, a treatment phase (consisting of two separate dosing periods, each done in a clinical study unit) and a study follow-up evaluation. The drug was administered under fasting conditions.

No. of Sequences	2	**Crossover**	Y
No. of Periods	2	**Replicate Design**	N
No. of Treatments	2	**Washout Period**	3 days
Blood Sampling Times	Serial blood samples (approximately 5 mL) for determination of sumatriptan plasma concentrations were collected pre-dose and nominally at 5, 10, 15, 20, 30, 40, 50, 60, 90, 120, 150 min and 3, 4, 6, 8, 10, 12, 14 and 16 h after dosing in each session.		

Treatment A: standard sumatriptan 100 mg tablet
Treatment B: FDT sumatriptan 100 mg in solution

Table 10. Test Formulations Used for Study SUM10961

Formulation	Strength	Appearance	Batch #
Standard tablet	100 mg sumatriptan	White, capsule shaped, biconvex film coated tablet	B075856
Fast disintegrating tablet	100 mg sumatriptan	Triangular shaped white tablet	EO2B33

Study-Demographics

Fourteen male and 14 female subjects took part in the study.

Table 11. Demographic Characteristics for Study SUM10961

n = 28	Age (year)	Weight (kg)
Mean	30	73.1
SD	6.8	11.8
Range	20-46	53-95

96% White, 4% Other

Study Results

Clinical

The sampling period was between October 16, 2002- October 28, 2002

Samples were analyzed between October 31, 2002-November 26, 2002
Storage period- ~30 days

Analytical Method

Parameter	
Method	
Sensitivity/LOQ	
Linearity (Standard curve samples)	
Quality Control (QC) Samples	
Precision of Standards (%CV)	
Precision of QC Samples (%CV)	
Accuracy of Standards (%CV)	
Accuracy of QC Samples (%CV)	

Pharmacokinetic/Statistical Analysis

From the individual plasma concentration versus time curves for sumatriptan, and using the actual collection times recorded on each sampling occasion, the following parameters were calculated using the non-compartmental analysis program WinNonlin Professional Version 3.1. Cmax maximum observed plasma concentration; tmax time of first occurrence of Cmax; AUC(0-∞) area under the plasma concentration versus time curve between zero hours and infinity, calculated using the linear trapezoidal rule for each incremental trapezoid to Cmax, and the log trapezoidal rule for each trapezoid after Cmax.; AUC(0-2) and AUC(0-0.5) area under the plasma concentration versus time curve between 0 hours and a given time (i.e., 2 hours or 0.5 hours), calculated using a combined linear-logarithmic trapezoidal method; t_{max} was calculated using a linear trapezoidal method; $t_{½}$ - terminal elimination half-life, calculated as ln(2)/ λz.

Point estimates and 90% confidence intervals for the difference between formulations in the fasted state (B:A) for the fast disintegrating tablet and the currently marketed tablet were constructed using the residual variance from the ANOVA for AUC(0-∞), AUC(0-t), Cmax and $AUC_{(0-2)}$. These were exponentially back-transformed to obtain point estimates and confidence intervals (CIs) for the ratios. Bioequivalence was demonstrated if the 90% CIs for the ratios of AUC(0-∞), AUC(0-t) and Cmax, were completely contained within the range 0.80 to 1.25.

RESULTS

Table 12. Mean sumatriptan ± SD for subjects that received the marketed formulation A and the FDT formulation B.

Formulation	**A**		**B**	
Time	Mean	SD	Mean	SD
0.00	NQ	.	NQ	.
0.08	0.146	0.384	0.789	1.220

0.17	0.893	1.367	4.029	2.973
0.25	3.269	2.985	10.925	4.850
0.33	10.237	6.874	20.788	6.099
0.50	27.155	13.411	34.926	9.286
0.67	38.794	18.258	42.261	11.974
0.83	45.541	23.915	44.643	12.173
1.00	47.907	28.895	44.839	14.192
1.50	43.904	23.250	44.623	12.420
2.00	45.603	17.204	42.927	13.187
2.50	43.949	15.778	41.190	12.947
3.00	40.388	13.530	38.039	11.680
4.00	30.224	10.263	31.145	10.978
6.00	13.794	6.943	13.308	8.243
8.00	6.953	3.799	6.824	3.756
10.00	3.940	2.194	3.753	1.598
12.00	2.500	1.693	2.105	1.032
14.00	1.761	1.357	1.418	0.540
16.00	1.338	0.986	1.179	0.633

NQ = Not quantifiable lower than the limit of quantification (——ng/mL)..

Table 13. Arithmetic mean (SD) pharmacokinetic parameters for sumatriptan by treatment regiment for Study SUM10961

Parameter [units]	100 mg Standard Tablet [A]	100 mg FDT in solution [B]
N	26	27
$AUC_{(0-\infty)}$ [ng.h/mL]	242 (79) [2]	235 (60) [3]
$AUC_{(0-t)}$ [ng.h/mL]	233 (73)	230 (58)
C_{max} [ng/mL]	60.2 (24.1)	53.7 (12.3)
$AUC_{(0-2)}$ [ng.h/mL]	69.0 (31.5)	72.0 (17.3)
t_{max} [1][h]	2.00 (0.83 - 4.00)	1.00 (0.67 - 6.00)

Table 14. Point estimates and 90% confidence intervals for treatment comparisons for Study SUM10961

Parameter	Comparison	Point Estimate	90% C.I.	CVw%
Primary				
$AUC_{(0-\infty)}$	B:A	0.95	(0.91,1.00)	9
$AUC_{(0-t)}$	B:A	0.98	(0.93,1.04)	11
C_{max}	B:A	0.89	(0.81,0.99)	21
SecondaryAUC $_{(0-2)}$	B:A	1.07	(0.97,1.19)	21

t_{max}[1]	B	A	-0.25	(-0.75,0.17)

1. t_{max} analysed non-parametrically, median difference along with corresponding 90% confidence intervals are presented
Treatment codes: A:Standard 100 mg sumatriptan tablet,B:100 mg FDT in solution CI = confidence intervals

Comments:

1. The FDT dissolved in water prior to administration was bioequivalent to the currently marketed tablet when both were administered under fasting conditions.

DISSOLUTION DATA

The approved method of dissolution for Imitrex is: USP Apparatus2, paddles at —pm, water.
The firm has proposed a new method which is: USP Apparatus2, paddles at —pm. —— HCL.

Detailed Dissolution Results (Individual Determinations)

Tested by USP Apparatus 2, Paddle Speed of —rpm in Water (Current Method)

Sumatriptan FDT 25 mg, Batch E02B30 (Pivotal stability batch)

Sample time (minutes)	Sumatriptan Released (% Label Claim)									
	1	2	3	4	5	6	Mean	SD	%RSD	Range
5										
10										
15										

Sumatriptan FDT 50 mg, Batch E02B78 (Pivotal stability and bioequivalence study batch)

Sample time (minutes)	Sumatriptan Released (% Label Claim)															
	1	2	3	4	5	6	7	8	9	10	11	12	Mean	SD	%RSD	Range
5																
10																
15																

Sumatriptan FDT 100 mg, Batch E02B33 (Pivotal stability and bioequivalence study batch)

Sample time (minutes)	Sumatriptan Released (% Label Claim)															
	1	2	3	4	5	6	7	8	9	10	11	12	Mean	SD	%RSD	Range
5																
10																
15																

Detailed Dissolution Results (Individual Determinations)

Tested by USP Apparatus 2, Paddle Speed of — rpm in [redacted] (Proposed Method)

Sumatriptan FDT 25 mg, Batch E02B30 (Pivotal stability batch)

Sample time (minutes)	Sumatriptan Released (% Label Claim)															
	1	2	3	4	5	6	7	8	9	10	11	12	Mean	SD	%RSD	Range
5	[redacted]															
10																
15																

Sumatriptan FDT 50 mg, Batch E02B78 (Pivotal stability and bioequivalence study batch)

Sample time (minutes)	Sumatriptan Released (% Label Claim)									
	1	2	3	4	5	6	Mean	SD	%RSD	Range
5	[redacted]									
10										
15										

Sumatriptan FDT 100 mg, Batch E02B33 (Pivotal stability and bioequivalence study batch)

Sample time (minutes)	Sumatriptan Released (% Label Claim)															
	1	2	3	4	5	6	7	8	9	10	11	12	Mean	SD	%RSD	Range
5	[redacted]															
10																
15																

Dissolution Method and Specification:

For all three strengths the dissolution testing should be conducted in 900 ml of [redacted] at [redacted] using USP XXVI apparatus 2 (paddle) at — rpm. The test product should meet the following specifications:

Q= [redacted] of Sumatriptan is dissolved in 15 min

25 mg STRENGTH

A bioequivalence study was not done on the 25 mg strength however it is compositionally proportional to the 50 mg tablet which did undergo a bioequivalence. Also the kinetics have been shown to be linear between 100 mg and 25 mg doses of Sumatriptan. In addition the 25 mg FDT dissolution is comparable to that of the 50 mg and 100 mg FDT. Therefore the in vivo bioequivalence requirement for this dosage strength can be waived.

Andre Jackson

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

Cc-NDA 20132, HFD-860(Jackson, Baweja,Sahajwalla, Mehta), Central Documents Room(Biopharm-CDR)

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