

Summary of Results from Special Safety Studies

Reports for special safety studies that were submitted to the four-month safety update are reviewed as part of that section. Therefore included in that section, are protocol S2WB2005 for chest discomfort rechallenge and S2WB3006 for assessment of myocardial perfusion by PET scan.

Comparative Assessment of Oral Naratriptan on Hypertensive Response in Normals and Hypertensive Patients: Protocol C94-036 (Volume 117) was a 4-way complete crossover, parallel-group, ascending dose, randomized, placebo-controlled study in 27 (24 completed) subjects - 12 healthy (BP <140/90mmHg); 12 controlled-hypertensives (BP <150/95mmHg on anti-hypertensive drugs). Each subject was scheduled to receive 4 treatments in randomized sequence - one treatment on each of 4 separate occasions with naratriptan doses given in ascending order:

1mg and 1mg 2hrs later;

2.5 and 2.5mg 2hrs later;

5mg and 5mg 2hrs later;

placebo and placebo 2hrs later.

Baseline and serial pulse rate, and blood pressure by ABPM, were obtained for 24 hours; and ECGs and telemetric monitoring were obtained for 12 hours. Clinical labs were obtained pre-study, before each treatment, 24 hours after each treatment and post-study. No serious AEs were reported. No clinically significant changes in physical exam, ECGs or laboratory values were reported. Three subjects dropped out - 2 for personal reasons after the 1mg dose level; 1 for arrhythmia (ventricular tachycardia) following dosing with placebo which was observed during follow-up Holter monitoring.

For pharmacodynamic responses, weighted mean values and peak values were calculated over 0-4h, 4-8h, 8-12h, 0-12h and 12-24h, for each period for each subject. Baseline was subtracted from the weighted mean and peak value. Baseline blood pressures were higher in the hypertensive group (range of baseline means across treatments for hypertensives vs healthy - SBP 122-124mmHg vs 113-118mmHg; DBP range across treatments 79-80mmHg vs 75-76mmHg). The weighted mean blood pressures were calculated by dividing the calculated area under the response-time curve by time. Systolic and diastolic blood pressure results for 0-12 hours are summarized in the tables below. The 5mg+5mg dose level affected both groups while the 2.5mg+2.5mg dose level may have affected the hypertensive group only slightly; but the placebo response in the hypertensive group showed a decline from baseline for approximately the first 10 hours, possibly due to anti-hypertensive medication, compared to healthy subjects so that the hypertensive response in hypertensives may be appearing exaggerated compared to healthy subjects. Nonetheless, the hypertensive propensity of naratriptan is demonstrated in both groups at the 5mg+5mg dose level; and the response compared to placebo appears slightly greater in the hypertensive group. The blood pressure response for 12-24 hours is less pronounced but statistically significant for the 5mg+5mg dose level for healthy subjects for peak SBP and DBP response with a trend for weighted mean and statistically significant for only the 2.5mg+2.5mg dose level for hypertensives for DBP. No discussion or comparison is provided regarding the absolute weighted mean pressures or absolute peak pressures observed between the healthy and hypertensive groups.

Systolic Blood Pressure 0-12 hours - mmHg Condensed from Table 13 of Study					
Dose of Naratriptan	No. of Subjects	Difference from Baseline*	Difference from Placebo	95% Confidence Interval	p-value
Hypertensive Subjects - Weighted Mean					
(* adjusted for design imbalance)					
Placebo	12	-5			
1mg + 1mg	13	-4	2	(-3,6)	0.464
2.5mg+2.5mg	12	0	6	(2,10)	0.006
5mg+5mg	12	3	9	(5,13)	<0.001
Hypertensive Subjects - Peak					
Placebo	12	6			
1mg + 1mg	13	8	2	(-4,7)	0.501
2.5mg+2.5mg	12	14	7	(2,12)	0.006
5mg+5mg	12	16	10	(4,15)	<0.001
Healthy Subjects - Weighted Mean					
Placebo	13	0			
1mg - 1mg	14	1	1	(-3,5)	0.612
2.5mg+2.5mg	12	3	3	(-1,7)	0.135
5mg-5mg	12	8	8	(4,12)	<0.001
Healthy Subjects - Peak					
Placebo	13	11			
1mg - 1mg	14	12	1	(-4,6)	0.632
2.5mg-2.5mg	12	14	3	(-2,8)	0.273
5mg-5mg	12	19	8	(3,13)	0.004

Diastolic Blood Pressure 0-12 hours - mmHg Condensed from Table 14 of Study					
Dose of Naratriptan	No. of Subjects	Difference from Baseline*	Difference from Placebo	95% Confidence Interval	p-value
Hypertensive Subjects - Weighted Mean					
(* adjusted for design imbalance)					
Placebo	12	-3			
1mg + 1mg	13	-2	1	(-1,4)	0.305
2.5mg+2.5mg	12	1	4	(1,7)	0.003
5mg+5mg	12	4	7	(4,10)	<0.001
Hypertensive Subjects - Peak					
Placebo	12	7			
1mg + 1mg	13	8	1	(-3,5)	0.615
2.5mg+2.5mg	12	10	3	(-1,7)	0.148
5mg+5mg	12	16	9	(5,13)	<0.001
Healthy Subjects - Weighted Mean					
Placebo	13	0			
1mg + 1mg	14	2	2	(-1,4)	0.224
2.5mg+2.5mg	12	2	2	(0,5)	0.073
5mg-5mg	12	6	6	(3,8)	<0.001
Healthy Subjects - Peak					
Placebo	13	9			
1mg + 1mg	14	10	1	(-3,6)	0.489
2.5mg-2.5mg	12	12	3	(0,7)	0.084
5mg-5mg	12	16	7	(3,11)	0.002

Assessment of Subcutaneous Naratriptan on Cardiac Hemodynamics, Coronary Artery Diameter and ECG: The sponsor conducted one trial (S2WB3009 - Volume 119) to assess the cardiac effects of naratriptan in patients eligible for cardiac catheterization to investigate coronary artery disease. Patients underwent pulmonary artery catheterization for serial hemodynamics and arterial catheterization for aortic pressure measurement and coronary arteriography by digital subtraction angiography.

Study Design: Single-Center, Open-label [10 subjects exposed(44-69 yrs) / 8 considered protocol-correct]; Subcutaneous placebo injection at -10minutes followed by subcutaneous naratriptan 1.5mg at 0 minutes. Nine of the 10 subjects had normal coronary arteries and one had insignificant coronary artery disease. The sponsor concluded that compared to the 10 minute period following placebo administration, increases were observed in:

- aortic systolic (+7%), diastolic (+8%) and mean (+8%) pressure;

- pulmonary artery systolic (+15%) diastolic (+20%) and mean (+18%) pressure;
- pulmonary capillary wedge pressure (% not presented);
- systemic vascular resistance (+8%)
- heart rate (+1%)
- systemic vascular resistance (8+%)
- pulmonary vascular resistance (-6%).

The sponsor also reports that coronary artery lumen diameters were reduced after naratriptan administration compared to pre-placebo baseline by the following ranges:

- 0 minutes: -11 to +3%
- 10 minutes: -5 to +1%
- 20 minutes: -10 to -1%
- 30 minutes: -7 to -1%

Four subjects experienced adverse events classified described by the investigator as "chest discomfort."

Drug Interactions: Below are summaries of the results reported by the sponsor for several naratriptan drug interaction studies with of alcohol, subcutaneous sumatriptan, dihydroergotamine, and Ercaf[®] (ergotamine/caffeine).

Alcohol 0.6g/kg/ Naratriptan 5mg po (C93-087 - Volume 105) -

Two-way crossover: ethanol followed 30 minutes later by naratriptan vs placebo-ethanol followed 30 minutes later by naratriptan (16 subjects).

Pre-dosing with a single dose of ethanol resulted in a statistically significant decrease in naratriptan C_{max} by 14% but not statistically significant decrease in AUC_(Last). Pre-dosing with ethanol did not result in a statistically significant effect on weighted mean or peak blood pressure (0-12hrs) but did result in an increase of 5bpm in weighted mean pulse rate (0-12hrs) with the greatest increase after ethanol but before naratriptan administration. No significant laboratory abnormalities or changes in ECGs were reported. Psychometric testing was not conducted.

Sumatriptan 6mg SO/ Naratriptan 2.5mg po (S2WB1003 - Volume 105) -

Four-way crossover: naratriptan+sumatriptan vs naratriptan+placebo vs placebo+sumatriptan vs placebo+placebo(12 subjects).

Co-administration of single doses of sumatriptan with naratriptan did not substantially modify exposure to either drug: only a statistically significant increase of 22% in sumatriptan t_{1/2} was noted. There were no effects on weighted mean SBP or DBP for any treatment period except for a decrease in 2mmHg during 4-8 hours after sumatriptan administration; but there was a statistically significant increase up to 8mmHg in mean peak SBP (difference from placebo) and 11mmHg in DBP(difference from placebo) following co-administration of naratriptan and sumatriptan. No significant laboratory abnormalities or changes in ECGs were reported.

Dihydroergotamine (DHE) 1mg IM/ Naratriptan 2.5mg po (S2WA1010 - Volume 105) -

Four-way crossover (16 subjects randomized):

- Treatment A: Day -1 placebo-naratriptan;
Day 1 naratriptan + placebo-DHE
- Treatment B: Day -1 placebo-naratriptan;
Day 1 placebo-naratriptan + DHE
- Treatment C: Day -1 placebo-naratriptan;
Day 1 naratriptan + DHE
- Treatment D: Day -1 naratriptan;
Day 1 placebo-naratriptan + DHE

After concomitant administration, mean AUC and C_{max} for naratriptan were 15% and 20% lower,

respectively. No statistically significant differences were noted for weighted mean and peak SBP or DBP. No subject had laboratory values outside the threshold range at screening or post-study or clinically significant change in ECG.

Ercaf[®] - Ergotamine 2mg with Caffeine 200mg po/ Naratriptan 2.5mg po (S2WA1011 - Volume 105) -

Four-way crossover (12 subjects randomized):

- Treatment A: Day -1 placebo-naratriptan;
Day 1 naratriptan + placebo-ergot
- Treatment B: Day -1 placebo-naratriptan;
Day 1 placebo-naratriptan + ergot
- Treatment C: Day -1 placebo-naratriptan;
Day 1 naratriptan + ergot
- Treatment D: Day -1 naratriptan;
Day 1 placebo-naratriptan + ergot

After concomitant administration, no statistically significant differences were noted for AUC, C_{max} and T_{max}; and a small statistically significant difference was noted for t_{1/2} but this represented less than 1 hour in the difference in the mean values. No statistically significant differences were noted for weighted mean and peak DBP for any treatments; and a small (<5mmHg) statistically significant increase was noted for weighted mean and peak SBP between concomitant administration and naratriptan alone.

Three subjects had potassium values outside the threshold range post-study which were considered by the investigator not to be clinically relevant. No subjects had clinically significant changes in ECG.

Effects on Psychomotor Performance: The sponsor conducted one trial (C94-045) to assess the effect of naratriptan on saccadic eye movement, choice reaction time, rapid visual processing, and automated visual analogue scales for alertness/sedation/tranquility.

Study Design: Four-way Crossover (16 subjects randomized): Naratriptan 5mg + Temazepam-placebo vs Naratriptan 10mg + Temazepam-placebo vs Naratriptan-placebo + Temazepam-placebo vs Naratriptan-placebo + Temazepam 20mg

The sponsor concluded that:

- temazepam caused significant impairment of psychomotor function in all tests except for rapid visual information processing;
- naratriptan 5mg was not significantly different from placebo in any test except decreased minimum peak deceleration of saccadic eye movements;
- naratriptan 10mg impaired psychomotor function as determined by decreased peak velocity and decreased peak deceleration of saccadic eye movements, increased choice reaction times and impaired rapid visual information processing.

Withdrawal/ Addiction Potential: The sponsor conducted one trial (S2WA1004 - Volume 105) to assess the effect of naratriptan on a variety of self-reported subjective measures for abuse liability (e.g. ARCI and Cole/ARCI scales; Elation subscale of POMS; subjective price estimate) and objective measures (e.g. Psychomotor performance; Pupil diameter; Physiologic monitoring).

Study Design: Seven-way Crossover (12 subjects randomized): Naratriptan 1mg, 2.5mg, 5mg and Codeine 30mg, 60mg, 90mg and Placebo

The sponsor concluded that under the conditions of the study, evidence suggested that naratriptan 1mg-5mg had a lower liability than codeine 30mg-90mg.

Ocular Effects: The sponsor conducted one trial (S2WB1006 - Volume 122) to assess the effect of

naratriptan on slit-lamp eye examination including fluorescein tear-film break-up time, intraocular pressure by puff tonometer, and visual acuity tests.

Study Design: Two-way Crossover: Naratriptan 2.5mg single dose vs Naratriptan-placebo single dose (8 subjects randomized)

The sponsor concluded that:

---there were no statistically significant differences between naratriptan and placebo for weighted mean or minimum intraocular pressure after dosing and that naratriptan was not associated with detectable ocular effects in healthy female subjects.

Human Reproduction Experience

In the original NDA submission, the sponsor provides brief narratives of 10 patients who became pregnant during participation in naratriptan trials. Nine were exposed to naratriptan and one to sumatriptan. Four healthy infants were delivered to naratriptan-randomized patients; the results of the other six pregnancies was pending at the time of NDA submission. The 4-month safety update reports the delivery via Caesarean section one additional healthy infant girl to a Subject (ID-3616), a 31 year old, who treated the first and only attack with naratriptan about 9 months earlier. (Case - B0042205)

Overdose Experience

The clinical study report for clinical pharmacology protocol C92-055 (Vol 105) reports the effects of the largest single oral dose (25mg) of naratriptan given to any subject in the NDA - subject #006 experienced an increase in blood pressure from 120/67 to 191/113 at 5.5 hours post-dose which returned to baseline 8 hours later. The subject also experienced lightheadedness, tension in the neck, tiredness and loss of coordination. Peak plasma concentration was 83ng/ml. Subjects in this trial doses above 2.5mg produced statistically significant increases in weighted mean and peak blood pressure over 0-8 hours (systolic respectively-14mgHg and 12mgHg; diastolic respectively - 10mmHg and 9mmHg). See review section on changes in vital signs for more detailed discussion of this study.

Other overdose/ excessive dose information is available in the NDA and should be examined.. Several subjects took excessive doses (range 7.5mg - 12.5mg) in some instances on multiple occasions during the long-term open-label safety trial, S2WB3004 (See review comments for Four-Month Safety Update). Additionally, subjects who participated in the subcutaneous naratriptan trials S2WB2001 and S2WB2002 received doses up to 10mg with the relative bioavailability of subcutaneous naratriptan is greater than oral.

The NDA does not provide information on the effectiveness of hemodialysis or peritoneal dialysis in removing naratriptan or their effects on plasma concentrations of naratriptan.

Four Month Safety Update

The four month safety update consists of 5 study reports for the protocols listed discussed below. No deaths were reported between August 20, 1996 the data cut-off for the NDA and March 14, 1997. Eleven patients experienced 12 serious AEs between August 20, 1996 and March 17, 1997 with all serious AEs reported in the safety update coming from the long-term open safety trial, S2WB3004.

S2WA1012 - A study to Investigate the Pharmacokinetics of Oral Naratriptan in Adolescent Migraine Patients Outside a Migraine Attack.

Seven adolescent (12-16 years) migraine patients were each exposed to one 2.5mg naratriptan tablet on one occasion with serum and urine samples collected. The C_{max} was 8.0ng/ml and serum half-life 4.9 hours. There were no serious adverse events or withdrawals. Two subjects reported adverse events - mild drowsiness in one and mild tingling, numbness and swelling of the right arm in the other. Mean baseline systolic and diastolic blood pressure were not increased more than 4 and 7mmHg, respectively over 24 hours after exposure. There were no clinically significant changes in post-treatment laboratory screens. The sponsor reports that there were no clinically significant changes in 12-lead ECGs; listings for ECG data were not submitted.

S2WB3006 - A Double-Blind, Randomized, Placebo-Controlled, Crossover Study to Assess the Effects of SC Naratriptan on Myocardial Perfusion in Migraineurs By Positron Emission Tomography (PET).

Forty migraineurs (21-58 years; 21<45 years; 13>45 years) with no history of ischemic heart disease were recruited, of which 35 were exposed in random sequence to one dose of naratriptan 1.5mg subcutaneously or placebo subcutaneously on two separate occasions separated by at least 5 days. Myocardial blood flow (MBF) was measured at rest and during hyperaemia induced by IV dipyridamole (0.56mg/kg). Both measurements were made using ¹⁵O-labeled water and PET. Baseline MBF following sc naratriptan was not statistically significantly lower than after placebo; but during hyperaemia, MBF following naratriptan was statistically significantly lower than after placebo (-13%; p=0.008, excluding baseline covariate; -11%; p=0.026, adjusted for baseline covariate). Coronary vasodilator reserve (CVR) following sc naratriptan was statistically significantly lower than after placebo (-12%; p=0.032); but was not significant (-7%; p=0.197) when corrected for rate-pressure product (an index of myocardial oxygen consumption). Minimal coronary resistance (i.e. that measured during hyperaemia) was statistically significantly higher after naratriptan than after placebo (+19%, p=0.004 excluding baseline covariate; +18%, p=0.008 adjusted for baseline covariate).

There were no deaths or serious adverse events. One subject (5122) was withdrawn from study. The patient experienced hypertension (150-160/90-85mmHg prior to naratriptan; 180/110mmHg 5 minutes after naratriptan lasting about 30 minutes) and had an ECG taken 16 minutes after naratriptan administration which was viewed by the investigator as abnormal, lasting about 35 minutes. The sponsor indicates that an independent assessment judged the ECG not to be significantly different from baseline and assessed the abnormality as sinus bradycardia (normal variant, present at baseline) with normal left axis deviation. CK and CK-MB performed immediately after the adverse event were normal and LDH was slightly elevated at 376 IU/L (normal range of 100-340 IU/L). Repeat labs performed the following day were all normal. Three other subjects had significant changes in vital signs - following placebo (HR decrease below 50 BPM), placebo/dipyridamole (HR increase above 120 BPM) and naratriptan/dipyridamole (DBP- 50mmHg 30minutes after dipyridamole). Eight patients had significant ECG changes from baseline after treatment. In 5 patients the changes occurred only after the placebo/dipyridamole treatment or occurred after treatment on both study days with ECGs returning to normal at the end of each treatment day; another developed first degree AV block after naratriptan and first degree AV block/sinus tachycardia/QT separation after placebo/dipyridamole; another developed QRS/T

axes separation/sinus tachycardia/possible left anterior hemiblock after naratriptan/dipyridamole and QRS/T axes separation after placebo/dipyridamole; another one subject developed sinus arrhythmia (normal variant) and a single nodal ectopic beat at the end of the study after receiving naratriptan/dipyridamole. No changes in laboratory data were reported as adverse events but repeat laboratory measurements were obtained only if deemed clinically necessary by the investigator. Adverse events which were reported (Table 22) following naratriptan administration were: increase blood pressure (1); abnormal ECG (1); feeling of heaviness(1), injection site reaction (1), nasal inflammation (1); muscle stiffness tightness rigidity (1), dizziness (2), menstruation symptoms (1); skin erythema (1).

S2WB3005 - A Double-Blind, Randomized, Placebo-Controlled, Crossover Study to Assess the Effects of IV Ergotamine on Myocardial Perfusion in Migraineurs By Positron Emission Tomography.

The sponsor conducted this trial which using similar methodology to that conducted with naratriptan protocol (S2WB3006) reviewed above. Fifteen migraineurs (>45 years) with no history of ischemic heart disease were exposed in random sequence to one dose of ergotamine 0.25mg intravenously or placebo on two separate occasions. Baseline MBF following ergotamine was not statistically significantly lower than after placebo. During hyperaemia, MBF following ergotamine was statistically significantly lower than after placebo (-31%; p=0.003, excluding baseline covariate; -28%; p=0.010, adjusted for baseline covariate). Coronary vasodilator reserve (CVR) following IV ergotamine was statistically significantly lower than after placebo (-27%; p=0.007); and also (-29%; p=0.003) when corrected for rate-pressure product (an index of myocardial oxygen consumption). Coronary resistance was statistically significantly greater for ergotamine compared to placebo (+48%; p=0.004 - adjusted for baseline; +52%; p<0.001 - excluding baseline).

S2WB2005 - A Double-Blind Crossover Study to Rechallenge Patients with Oral GR85548 who Previously Experienced an Adverse Event Involving Discomfort or Pain in the Chest Following GR85548 Administration

Only two subjects were enrolled and the study was terminated due to low recruitment. Only 1 subject completed the trial; and the other failed to return for treatment after Visit 1. There were no adverse events or serious adverse events. All ECGs were considered normal and all laboratory results were considered not to be of clinical significance.

S2WB3004 - An Open Study of the Long Term Safety and Efficacy of Oral Naratriptan 2.5mg in the Acute Treatment of Migraine -- 12 Month Report.

The sponsor provides the data in the final report from this trial in support of long-term safety and efficacy of naratriptan.

Trial Design of S2WB3004: This trial was a multi-center (29), multinational (Australia, France, The Netherlands). open-label study in which patients were ask to treat all their migraine attacks over a 12 month period. Patient demographics: 18-66 years (mean - 42.5 years); 82% female; 99% Caucasian. Following a baseline visit (Visit 1) and issue of study medication (Visit 1 or 2), subjects returned to clinic every 3 months for Visits 3-6. Exclusionary criteria are similar to those for other clinical trials and provide for the exclusion of patients with ischemic heart disease or signs and symptoms of ischemic heart disease: Prinzmetal's angina; coronary vasospasm; history of atherosclerotic disease; cardiac arrhythmias requiring medication: uncontrolled hypertension (SBP>160mmHg; DBP>95mmHg); pregnant or likely to become pregnant; breast feeding; concurrent medical condition which might affect interpretation of safety or efficacy data: history of epilepsy or structural brain lesions; renal failure; history of basilar or hemiplegic migraine; receiving lithium; abusing opiates, psychoactive drugs, ergotamine, alcohol; hypersensitivity to

naratriptan or sumatriptan; prophylactic medication containing ergotamine, DHE or methysergide. Patients were to take 2.5mg of naratriptan at the onset of severe or moderate migraine and a second tablet 4-24 hours later if headache recurred. Subjects intolerant to the 2.5mg starting dose were permitted to reduce the dose to 1.0mg. Subjects were permitted to use their usual rescue (not sumatriptan, ergotamine, dihydroergotamine) medicine if inadequate relief was obtained by 4 hours. Sumatriptan, ergotamine, dihydroergotamine were not to be used for 24 hours following naratriptan administration. For each attack, patients were to document study drug administration on the medication pack and migraine symptoms and adverse events in their diary booklet. Vital signs were recorded at baseline and Visit 6 and at other visits if clinically indicated. ECGs and clinical laboratory tests were obtained at baseline but thereafter only if clinically indicated. If an adverse event of possible cardiac origin occurred, CK-total and MB fraction and LDH were to be obtained and repeated in 12-24 hours if measured within 5 days of the adverse event.

Patient Accounting and Dropouts for Study S2WB3004 in 4-Month Safety Update: No deaths are reported by the sponsor.

451- Patients Enrolled

34 - Patients Enrolled But Not Exposed (Appendix 7 - Patients recruited but withdrew without taking study treatment; matches patient accounting in study Table 1)

417- Patients Exposed (Appendix 8 - Patients in safety population by country and investigator; matches patient accounting in study Table 2)

115- Patients Exposed But Withdrawn (Appendix 10 - ID of patients withdrawn from study; safety population; matches patient accounting in study Table 3)

302 - Exposed Not Withdrawn

According to Table 4 (Attendance at clinic visits), 300 patients attended clinic for Visit 6 (last visit); according to the tally above 302 patients should have completed the trial by attending Visit 6.

According to Appendix 10 - there were 115 withdrawals for the following reasons:

69 - Loss of efficacy

18 - Others

12 - Failure to return

11 - Adverse Events (AEs)

5 - Failed to treat attack in specified time

115 - Total

For AEs the reasons for withdrawal listed in Appendix 10 (ID of patients who withdrew from study) are listed below. The sponsor provides narratives only for serious AEs and not for all withdrawals due to AEs. CRFs have not been submitted for patient 3879.

2-reason not specified (3631; 3879)

1-increased blood pressure (3662)

2-depressive moods/disorders (3665; 3757)

1-nausea, vomiting (3667)

1-primary malignant GI neoplasia (3752)

1-GI hernia (3758)

1-chest pain/discomfort (3882)

1-breast discharge (3907)

1-headaches, hyposalivation, oral swelling, warm/hot sensation (4198)

11 - Total

According to Appendix 22 (Withdrawals from study due to adverse events) 15 subjects were withdrawn due to AEs; this figure is at odds with that from Appendix 10.

For "Others" category, the reasons for withdrawal listed in Appendix 10 are as follows:

- 3-no attacks (3529; 3533; 3570)
- 1-epilepsy for longer periods of time (3549)
- 1-another drug works (3536)
- 2-pregnancy (3616; 3737)
- 4-pregnancy planned/ contraception discontinued (3731; 3782; 3850; 4116)
- 1-noncompliance (3836)
- 1-protocol violation (3840)
- 1-leaving country (3716)
- 1-not as good as "imigran" (3601)
- 3-migraine frequency increased above inclusion criteria level (4091; 4156; 4201)
- 18 Total

The following patient is described further because of the nature of the event: # 3549 is listed as an "other" withdrawal with the following causal listing "appeared to have epilepsy for a longer period of time;" 53 yo female was withdrawn following a severe clonic/tonic seizure 139 hours after treating attack 14 with naratriptan 2.5mg + 2.5mg; treated with carbamazepine; experienced tonic/clonic seizure prior to study entry.

Appendix 21 lists patients who experienced serious adverse events; 4 of these patients (3752; 3757; 3758; 3882) are listed in Appendix 21 as withdrawn due to an AE. These patients are also listed in Appendices 10 and 22 with the same respective reason listed for discontinuation. Patient 3752 also had a narrative submitted in the 4 month safety update; the others had narratives submitted in the original NDA.

Extent of Exposure for Study S2WB3004 in 4-Month Safety Update:
See the section of this review for description of the ISS population.

Serious AEs for Study S2WB3004 in 4-Month Safety Update: Study Appendix 21 provides the line listings for 25 patients who experienced 26 serious AEs for which there are 26 narratives. An additional, 27th, narrative is presented for a pregnancy. Fourteen of these serious AEs from protocol S2WB3004 were reported in the ISS of the original NDA submission. The 12 additional case narratives are summarized below. I compared the updated versions for the 14 previously submitted narratives and noted only that the age of one patient had changed from 35 to 49 (Case - B0036854; ID-4089) and that more detailed information was made available for another (Case - B0036920; ID-4167) which does not materially influence the previous assessment of the case. For the cases listed below, it is difficult to ascribe causality to naratriptan for any with the possible exception of case 8 below. Case 8 seems to describe an adverse event, heaviness of limbs, which fits the event class, characteristic sensations, generally attributed to 5HT agonists. The numbers preceding each case description below represents their sequence in Volume 1. Appendix 3 of the 4 month safety update.

1-- 50 yo female (ID-3744) fractured her ankle in an accidental fall after treating 19 attacks with naratriptan 2.5mg; event was reported as incapacitating. (Case - B0043210)

- 2-- 51 yo female (ID-3752) underwent surgery for adenocarcinoma of the colon after treating 32 attacks with naratriptan 2.5mg and was withdrawn from the study.(Case - B0043062)
- 3-- 62 yo female (ID-3874) with right hallux valgus experienced inflammation and pain at the hallux valgus after treating 34 attacks and 8 days after treating her last attack with naratriptan 2.5mg; hospitalized for surgery; after discharge the inflammation recurred but resolved following treatment with tenoxicam. (Case - B0043372)
- 4-- 41 yo female (ID-4455) with carpal tunnel syndrome was hospitalized for surgery for worsening carpal tunnel syndrome after having treated 38 attacks with naratriptan 2.5mg.(Case - B0041334)
- 5-- 34 yo female (ID-3639) experienced moderate vomiting which resolved after 10 hours after treating her 50th attack with 3 tablets of naratriptan 2.5mg within 24 hours, which amounted to an overdose. (Case - B0043665)
- 6-- 44 yo female (ID-3641) experienced mild burning feeling in her oesophagus 25 minutes after treating her 22nd attack with 3 tablets of naratriptan 2.5mg, which amounted to an overdose; resolved after 30 minutes. (Case - B0043449)
- 7-- 44 yo female (ID-3641) was hospitalized for "status migrainosus" after treating 69 attacks with naratriptan 2.5mg; resolved after 12 days; event was reported as incapacitating. (Case - B0043593)
- 8-- 50 yo female (ID-4074) experienced moderate heaviness and aching in all 4 limbs after treating her 18th attack with 3 tablets of naratriptan 2.5mg within a 24 hour period, which amounted to an overdose; event occurred after each dose; after the last dose resolved in 2 hours; was not withdrawn from study. (Case - B0042766)
- 9-- 50 yo female (ID-4093) experienced dry mouth and cracked lips after each of 3 doses of naratriptan 2.5mg taken within a 24 hour period, amounting to an overdose; this occurred on 3 separate occasions of overdose; also experienced these events when taking naratriptan according to protocol. (Case - B0043283)
- 10--50 yo female (ID-4097) detected a lump in her right breast and hospitalized for lumpectomy for the benign lump after having treated 105 attacks with naratriptan 2.5mg (Case - B0041945)
- 11-- 47 yo female (ID-4126) was diagnosed with breast carcinoma following surgery to remove a lump 15 days after her last dose of naratriptan and after treating 37 attacks; oral sumatriptan was also taken.(Case - B0041587)
- 12-- 49 yo female (ID-4130) experienced worsening painful "arc syndrome" of the left shoulder and underwent unsuccessful arthroscopy after treating 21 attacks with naratriptan 2.5mg. (Case - B0042412)

Overall AEs for Study S2WB3004 in 4-Month Safety Update: Incidence of AEs were analyzed by the sponsor by attack, patient, time, and frequency of use, as displayed in the tables below. No analysis of AEs was conducted by patient age. The higher rates observed in the 1mg dose groups might be explained by the small numbers of patients in those dose groups and the fact that the starting dose was 2.5mg from which patients were allowed to reduce the dose to 1mg if they were intolerant to the 2.5mg starting dose. This suggests that the 1 mg dose groups may have been a more sensitive in general. From the tables below it does not appear that taking a second dose of 2.5mg increased the incidence of AEs overall or by attack, patient, 6-month time period, or increased frequency of use with the exception of an increase from 31% to 44-49% for frequency of use. Event rates for most common events were also compiled by the sponsor for attack and patient and are reproduced below for the 2.5mg dose groups. Overall incidence of AEs by month is also provided in Table 27 (corrected version of Table 27 submitted July 1, 1997) which shows 36% of patients experienced any AE during the first month and 19% during the 12th month (range 17%-36%) but this data may represent only the number of patients taking single doses of 2.5mg since a column for repeat dose (2.5mg +2.5mg) rates do not appear to be submitted.

Attack (i.e. the number of treated attacks associated with an AE)

Overall Incidence By Attack (From Table 14)				
	1mg	1mg +1mg	2.5mg	2.5mg + 2.5mg
Number of Attacks Treated	66	17	10376	4842
Number of Attacks with an Associated AE	51 (77%)	10 (59%)	1689 (16%)	693 (14%)

Number of Treated Attacks with Most Common ($\geq 2\%$ in the 2.5mg groups) AEs by Group Term (From Table 17)		
	2.5mg	2.5mg + 2.5mg
Number of Attacks Treated	10376	4842
Nausea	293 (3%)	85 (2%)
Drowsiness and Sleepiness	254 (2%)	68 (1%)
Hyposalivation	208 (2%)	101 (2%)
Malaise and Fatigue	154 (1%)	75 (2%)

Patient (i.e. number of patients who reported an AE on one or more occasion during 12 months of treatment by total dose taken to treat the attack)

Overall Incidence By Treated Patient (From Table 19)				
	1mg	1mg +1mg	2.5mg	2.5mg + 2.5mg
Number of Patients Treated	10	6	409	360
Number of Patients with an Associated AE	8 (80%)	3 (50%)	225 (55%)	161 (45%)

Number of Treated Patients with Most Common ($\geq 2\%$ in the 2.5mg groups) AEs by Group Term (From Table 22)		
	2.5mg	2.5mg + 2.5mg
Number of Patients Treated	409	360
Nausea	46 (11%)	34 (9%)
Drowsiness and Sleepiness	36 (9%)	16 (4%)
Malaise and Fatigue	32 (8%)	24 (7%)
Musculoskeletal Pain	22 (5%)	10 (3%)
Dizziness	15 (4%)	9 (3%)
Hyposalivation	13 (3%)	10 (3%)
Paresthesia	13 (3%)	8 (2%)
Headaches	13 (3%)	9 (3%)
Diarrhea	7 (2%)	5 (1%)

Time (i.e. 0-6 months and 6-12 months)

Overall Incidence By Period (From Table 25)					
		1mg	1mg +1mg	2.5mg	2.5mg + 2.5mg
0-6 months	Number of Attacks Treated	20	5	5400	2543
	Number of Attacks with an Associated AE	12 (60%)	1 (20%)	951 (18%)	387 (15%)
>6-12 months	Number of Attacks Treated	45	12	4818	2192
	Number of Attacks with an Associated AE	38 (84%)	9 (75%)	701(15%)	298 (14%)

Frequency of use (i.e. 1-12 attacks; 13-24 attacks; 25-36 attacks; >36 attacks)

Overall Incidence By Frequency of Use (From Table 28)

		1mg	1mg + 1mg	2.5mg	2.5mg + 2.5mg
1-12 Attacks	Number of Patients Treated	4	2	87	45
	Number of Patients with an Associated AE	3 (75%)	0	44 (51%)	14 (31%)
13-24 Attacks	Number of Patients Treated	2	2	70	65
	Number of Patients with an Associated AE	2 (100%)	1 (50%)	34 (49%)	29 (45%)
25-36 Attacks	Number of Patients Treated	3	2	68	62
	Number of Patients with an Associated AE	2 (67%)	2 (100%)	43 (63%)	27 (44%)
>36 Attacks	Number of Patients Treated	1	0	184	186
	Number of Patients with an Associated AE	1 (100%)	0	104 (57%)	91 (49%)

Labs for Study: S2WB3004 in 4-Month Safety Update: In study Table 30, the sponsor reports that only 24 subjects had a baseline and at least one post-baseline measurement, since post-exposure measurements were not required unless viewed as clinically indicated by the investigator. Not all analytes were repeated for all subjects: for example only 7 patients had post exposure WBC differentials conducted. Only outlier analysis was conducted on available data. This implies that the sponsor presents limited laboratory safety data from long term exposure. Additional testing during longer-term exposure should be conducted, perhaps as a phase 4 commitment, in patients exposed to naratriptan tablets at least twice monthly for several months. Both outlier analyses and mean change from baseline analyses should be conducted on the data obtained. The sponsor identified 3 patients that had lab data that met pre-defined outlier criteria:

- #3516 - treated 74 attacks - at Visit 6 lymphocyte count below threshold with a normal WBC;
- #3519 - treated 63 attacks - urea level above threshold at Visit 1 which normalized at Visit 3 but was elevated above normal at Visit 6;
- #3882 - treated 3 attacks - potassium decreased to below threshold at Visit 2, was withdrawn for serious AE. chest pain.

Study Appendix 23 lists laboratory profiles of 39 patients for threshold laboratory data; but I count that only 6 patients had baseline and post-baseline measurements.

Vital Signs: The sponsor reports that 370 patients had vital signs recorded before and after. Only outlier analysis was conducted on available data. Only 6 patients, identified by the sponsor in Appendix 24, are listed as having a change in vital signs which met outlier criteria. Two were withdrawn. Outlier criteria

was defined as SBP \geq 180mmHg and 20mmHg increase or \leq 90mmHg and 20mmHg decrease; DBP \geq 105 mmHg and 15mmHg increase or \leq 50mmHg and 15mmHg decrease; pulse \geq 120bpm and 15bpm increase or \leq 50bpm and 15bpm decrease.

3662 - 150/95 to 180/110 at Visit 2 after treating attack 17 with one dose of 2.5mg - withdrawn from study after 3 months

3628 - 140/90 to 170/115 at Visit 3 after treating attack 9 with one dose of 2.5mg - withdrawn from study

3519 - 140/80 to 200/110 at study end (Visit 6)

3655 - 140/90 to 150/105 at study end (Visit 6)

3759 - 110/65 to 90/60 at study end (Visit 6)

3761 - 140/75 to 180/100 at study end (Visit 6)

ECGs for Study S2WB3004 in 4-Month Safety Update: In Table 32 the sponsor indicates that 24 patients had ECGs recorded before and after exposure to study treatment. One patient had a significant change from baseline classed as normal to abnormal.

3637 - 51 yo female experienced moderate palpitations 69 minutes after treating her 7th attack with one dose of 2.5mg; ECG was read as flat or negative T waves in anterior chest leads and increase in difference between QRS/T axes suggestive of ischemia, possibly rate related; CK, CK-MB and LDH were normal but there is no information about the time relative to the event; not withdrawn from study.

Cardiac enzymes for Study S2WB3004 in 4-Month Safety Update: In Appendix 26, the sponsor identifies 13 patients had cardiac enzymes drawn for events of possible cardiac origin with only one showing abnormality.

4156 - 44 yo female had total CK elevated (227U/L - normal 0-170) with normal CK-MB and LDH at undescribed time after experiencing palpitation and tachycardia after treating attack 31 with one dose of 2.5mg; had also taken salbutamol; the sponsor reports that the ECG performed immediately after event suggested possible ischemia or an effect of digitalis (lanoxin is listed in Appendix 12 as concomitant medication for this patient) but ECG data in Appendix 25 for this patient lists that baseline ECG was abnormal and follow-up ECG was normal.

Patients exposed to greater than 5mg in 24 hours for Study S2WB3004 in 4-Month Safety Update: Appendix 11 lists the patients and dates when 3 (7.5mg) or more tablets were taken within 24 hours on at least one occasion. Of the 77 patients are listed in Appendix 11, 17 patients took 4 tablets (10mg) on at least one occasion and 1 patient took 5 tablets (12.5mg) on one occasion. No discussion summarizing the safety experience from these patients is included.

Conclusion

The sponsor should examine further the database for NDA 20-763 for naratriptan tablets. It is recommended that the review issues and safety questions outlined in the section below, Pending Review Issues and Follow-up Safety Questions, be forwarded to the sponsor for their examination and response. Several general issues stand out as requiring further clarification and verification by the sponsor. They are:

- a) disposition of patients, particularly numbers and classification of those listed as withdrawing due to adverse events, serious adverse events and those listed as "other;"
- b) re-analyses of AEs by defining AEs as events which occurred within a set period of time after exposure to drug;
- c) re-analyses of AEs following remapping of paresthesia-related terms, throat-related terms, and syncope-related terms;
- d) examination of cases described by investigator verbatim text terms which may reflect potentially important terms for labeling;
- e) examination of AE rates in patients following subcutaneous administration and following excessive doses in protocol S2WB3004;
- f) plans for obtaining clinical laboratory data following longer-term exposures in additional subjects;
- g) reporting new cases of deaths, serious AEs, and pregnancy outcomes and updates of previously reported cases.
- h) further examination of the naratriptan database and databases for other 5HT agonists for data that corroborates or refutes the increase in pulmonary artery pressure observed in study S2WB3009.

Labeling Recommendations

More balanced information regarding the magnitude of naratriptan's pressor response, including its capacity to increase pulmonary artery pressure, should be included in the clinical pharmacology section that discusses blood pressure effects. This section should include dose response information across the 2.5-20mg range of doses.

Consideration should be given to warn patients with primary pulmonary hypertension to avoid taking naratriptan since its impact on this disease is unknown.

Once the sponsor has collected the information from clinical experience from trial S2WB3004 where some patients took doses in excess of 5mg in 24hours on multiple occasions and has analyzed further the safety data from the higher doses of subcutaneous trials, S2WB2001 and S2WB2002, any relevant information should be included in the "overdose" and "adverse event" sections.

Information concerning pharmacokinetics in hepatically impaired patients should specify that patients actually tested were in Child-Pugh A and B categories.

Consideration should be given to indicate that long-term experience is limited to intermittent dosing and not daily dosing for longer than 5 consecutive days.

Pending Review Issues and Follow-up Safety Questions

Patient Exposure

- 1) We note that 77 subjects were reported in July 25, 1997 exposed to naratriptan in more than one trial. Please explain how these patients and their multiple exposures were counted in the denominator for frequency analyses for safety parameters such as adverse events and descriptors of the ISS population.
- 2) Please check the accuracy of the following exposures as listed in the Table indicated: 407 for total number of patients treated in Table 13 of study S2WB3004 (4 month safety update) and 271 for sumatriptan in Table 8 of the ISS and confirm that the appropriate denominators were used in calculating adverse event and outlier rates for these exposures.

Withdrawals

- 3) In comparing individuals listed in Table 75 (Patient Withdrawals Due to AEs) to individuals listed for the overall index of submitted case report forms, it was noticed that 80 patients were listed in Table 75 but CRFs for 84 subjects were submitted which includes 4 additional patients who appear to have discontinued from clinical pharmacology studies (C93-070 - Subjects #07 and #22; WHP:9006 - Subjects #03 and 04) due to adverse events. Please clarify why these patients were not included in Table 75.
- 4) While comparing Table 75 (Patient Withdrawals Due to AEs) and Table 74 (Patients Experiencing Serious AEs) and Chart 18 of the ISS (Patients Experiencing Serious AEs) it was noted that Table 75 lists 13 subjects who experienced serious AEs, 12 of which are listed as withdrawing due to serious AEs and the remaining subject withdrawing due to other non-serious AEs. Table 74 lists only 11 subjects who discontinued study drug and Chart 18 identifies 10 patients who had serious AEs which resulted in study withdrawal. Please examine these tables and chart and identify the reason(s) for the apparent discrepancy in numbers of patients who had serious AEs resulting in study withdrawal and resubmit corrected tables/chart if correction is necessary.
- 5) In Table 74 (Patients Experiencing Serious AEs) of the ISS we note that several subjects did not have their correct subject identifying number listed but rather treatment number. Two of these subjects are S2WB3004-05007 (corrected number-4094) and S2WB3004-04008 (corrected number-4078). These two subjects are listed as having discontinued study drug but are not listed in Table 75 as withdrawals and have no case report forms submitted. Please verify the withdrawal status of these patients and why they were omitted from Table 75 if in fact they discontinued study drug due to an adverse event.
- 6) Narratives for patients who discontinued due to adverse events are presented in Appendix 2 of the ISS. However, we note that narratives have been submitted for only those patients who discontinued due to serious adverse events and not for all 84 patients who discontinued due to adverse events. Please submit brief narratives for the additional patients who withdrew due to adverse events.
- 7) We note that the ISS provides Charts 19, 20 and 21 which lists subject/patient withdrawals due to adverse events from oral clinical pharmacology and clinical trials whose reason for withdrawal was considered "drug-related." We note no comparable charts of all withdrawals regardless of ascribed drug-relatedness. Further, we note no summary or discussion describing all subject/patient withdrawals by age-range, gender, dose and duration of treatment, concomitant disease states, or most frequent AEs resulting in withdrawal or most frequent serious AEs resulting in withdrawal. Please provide such summaries/discussions for all withdrawals regardless of drug attribution for reason of withdrawal so that

any trend by these sub-groups could be seen.

8) Table 11 in the ISS displays patient disposition and discontinuation from oral studies across the ISS. The numbers and percentages of withdrawals are listed under three reasons for withdrawal (i.e. adverse event, lack of efficacy, or other). We note that for several trials the frequency for withdrawal that is listed as "other" is clearly larger in the naratriptan-treated group compared to the placebo group (e.g. S2WA3003 - 16% vs 5%; S2WB3002 - 17% vs 12%). Please describe in greater detail what dropouts listed under "other" represent across the clinical and clinical pharmacology database and how they account for the increased rates in the naratriptan-treated groups compared to placebo in some of the trials. For those trials where dropouts may be listed as "lost to follow-up" or "failed to return to clinic," please summarize what efforts were required of the investigators in the respective protocols to ascertain the reason for loss of patient contact and that death or serious adverse events were not responsible for patient discontinuation. Also please note that the comparator placebo rates are missing from Table 12 (disposition for subcutaneous trials in protocol S2WB2002) and should be submitted.

Database Clarifications

9) For protocol S2WB2003, we note by our count that the randomization code for the safety population (Vol. 161 - Appendix 8) appears to have 81 patients listed as part of the safety database, yet the clinical study report indicates that only 80 patients were randomized and treated. The additional patient is listed in the randomization code as having been assigned to the high dose active group, naratriptan 10mg. Please clarify this apparent discrepancy, explain how it occurred and describe the fate of this subject if exposed to study treatment. If this is not a typographical error, please verify and confirm that similar apparent patient accounting discrepancies have not occurred in the other databases for each of the other clinical trials.

10) For protocol S2WB2003, we note that patient data listings 1 through 16 appear to have patients unblinded to incorrect treatment. The data listings have patients listed as having been administered 1mg, 2.5mg or 5mg, whereas the clinical study report and randomization code indicated that patients were randomized to 5mg, 10mg or placebo. Please examine these data listings for accuracy, verify that unblinding procedures used are reliable, submit corrected listings and explain how any errors occurred during data analysis and study report preparation. Please verify and affirm that any discovered errors will not have impacted on interpretation of efficacy or safety results of this trial and the integrated analyses for the NDA.

11) For protocol S2WB2003, we note the patient data listings for ambulatory blood pressure monitoring (Vol. 164 - Listing 17) are difficult to understand. A significant number of recordings display blood pressures that appear to be listed as having been taken within a few minutes of one another and yet are displayed as taken on separate days (e.g. almost all line listings on page 3 of Vol. 164 show blood pressure measurements a few minutes apart, yet these measurements are intermittently listed as having been obtained on Day 1 or Day 2). Further, both of these "Day" listings, Day 1 and 2, correspond to the same "TEST" column as having been obtained during the same day, "migraine free" day. Additionally, the code for these data listings on page 1 is also confusing in that it shows that the "Day" column represents "Test number 11&12=sessions 4&6"; but it is not clear what this means. Please verify that these listings are correct, clarify what they mean, and confirm that any discovered errors will not have impacted on analysis and interpretation of blood pressure data for this trial or any other clinical trial.

12) In the description of patient disposition in the clinical study report for protocol S2WB3002, we note that 13 patients are reported to have been exposed to additional study treatment in addition to the treatment

to which they were randomized in this parallel trial. Please clarify if the additional treatment received by each of these patients was the same treatment to which they were randomized (i.e. additional exposure to randomized treatment), describe how this occurred during the trial, and explain how these additional patient-exposures were counted in the denominator of the safety database.

13) We note that for protocol S2WA3003, Data Listing #2, which lists reasons for exclusion of patients from the safety population and the intent-to-treat populations, lists "no efficacy data" as the apparent reason for excluding the first 12 patients from the safety population. If these subjects were in fact exposed to study treatments, their safety data should be included in the safety database regardless of their lack of efficacy data. Please verify and confirm the status of these patients in the safety database and examine the analogous data listings for all other clinical protocols to confirm a similar circumstance has not occurred.

14) Regarding patient accounting for protocol S2WB3004, we note the following. According to Table 4 (Attendance at clinic visits), only 300 patients attended clinic for Visit 6 (last visit). According to Appendix 8 (Patients in the safety population) 417 patients were exposed and according to Appendix 10 (I.D. of patient withdrawals), 115 patients were withdrawn for all reasons, which means 302 patients should have completed the trial and been seen at Visit 6. According to Appendix 10 (ID of patients withdrawn) 11 withdrawals were due to adverse events but according to Appendix 22 (Withdrawals due to adverse events) 15 subjects were withdrawn due to adverse events. Listings on page 6 (Volume 1) of the body of the safety update lists that only 13 subjects withdrew due to adverse events. Please re-examine the patient accounting for this trial, clarify these apparent discrepancies between appendices and Table 4, and confirm that patient accounting is accurate.

15) For final report for protocol S2WB3004 in the four month safety update, we do not find case report forms for subject 3879 (withdrawal due unspecified adverse event). Please direct us to its location if it has been submitted or submit them.

Adverse Events

16) We note that your analyses of adverse events counted those events which occurred after exposure to study drug and at any at any time after exposure. Since exposure to study drug was intermittent in multi-attack studies, some events which occurred after study drug administration but remote in time from administration may not be true adverse events. Please conduct additional analyses of adverse event rates defining an adverse event as one which occurred within 48 hours of last study drug administration.

17) We note that Tables 69 and 70 in the ISS were generated from adverse events from four placebo-controlled oral clinical trials (S2WB2004; S2WA3001; S2WB3002; S2WA3003) and are the tables proposed for extracting event rates for labeling. Please clarify why AEs from S2WA1007- Part 2 were not included in these tables since it is a placebo-controlled trial. Please submit versions of Table 69 and 70 with data from S2WA1007- Part 2 included and compare the event rates between the 2 versions.

18) We note that Tables 98 and 101 in the ISS present the number (%) of patients experiencing a particular adverse event by group term with subgroup analyses (i.e. age, gender) but find that no discussion of these analyses is presented. Please condense these tables to compare, by subgroups, those AEs which occur $\geq 1\%$ in any active treatment group and greater than placebo and examine these tables for adverse events which may be occurring at significantly greater rates in any one subgroup.

19) Examination of the mappings of verbatim terms in the AE coding dictionary in the ISS revealed a

number of verbatims which may be related to one another but have been mapped to different hierarchical terms. These verbatims and their mapped terms as they are listed in the coding dictionary are grouped together, below under a possible common attribute. Please re-examine the adverse event reports for these listings for appropriateness of mapping and reexamine the adverse event rates with the terms combined.

A. Paresthesia-related terms -

4 listings - "creeping sensation in the thighs" to "disturbance of tactile sensation" to "dysesthesia" to "characteristic sensations"

5 listings - "cerebral swarming" to "formication" to "dysesthesia" to "characteristic sensations"

24 listings - "lips tingling" to "oral and circumoral paresthesias" to "paresthesia" to "characteristic sensations"

78 listings - "chest paresthesias" to "paresthesia" to "paresthesia" to "characteristic sensations"

9 listings - "left arm pins and needles" to "pins and needles" to "paresthesia" to "characteristic sensations"

4 listings - "prickling in nose" to "prickling sensation" to "prickling sensation" to "characteristic sensations"

1 listing - "prickling sensation of the anterior side of the thorax" to "prickling sensation of chest" to "prickling sensation" to "characteristic sensations"

1 listing - "sensation of tickling of the mouth" to "tickling of mouth" to "tickling sensation" to "characteristic sensations"

5 listings - "feeling of tickling on face" to "tickling sensation" to "tickling sensation" to "characteristic sensations"

217 listings - "cephalic tingle" to "tingling" to "tingling" to "characteristic sensations"

3 listings - "chest tingling" to "tingling of chest" to "tingling" to "characteristic sensations"

B. Throat-related terms -

31 listings - "feeling of narrowness in the neck" to "tightness in neck" to "feeling of tightness" to "characteristic sensations"

34 listings - "clenched throat" to "tightness of throat" to "feeling of tightness" to "characteristic sensations"

2 listings - "feeling of strangulation" to "strangulation" to "drowning and suffocation" to "drug interaction overdose and trauma"

1 listing - "laryngeal tightening" to "laryngospasm" to "larynx spasm" to "ear nose and throat"

5 listings - "compression of throat and breast" to "constriction of throat" to "throat constriction" to "ear nose and throat"

2 listings - "feeling of throat constriction" to "feeling of throat closing" to "throat constriction" to "ear nose and throat"

1 listing - "structure of pharynx" to "pharyngostenosis" to "throat constriction" to "ear nose and throat"

2 listings - "feel a lump in ones throat" to "sensation of foreign body in pharynx" to "throat constriction" to "ear nose and throat"

1 listing - "clenched throat" to "throat spasm" to "throat constriction" to "ear nose and throat"

5 listings - "globus hystericus in the throat" to "globus hystericus" to "psychogenic disorders" to "psychiatry."

C. Syncope-related terms -

5 listings - "mild hypotonus = dizziness" to "dizziness due to hypotension" to "hypotension" to "cardiovascular"

- 1 listing - "collapse" to "collapse" to "syncope" to "cardiovascular"
- 1 listing - "fainted on getting up" to "fainted on getting up" to "syncope" to "cardiovascular"
- 3 listings - "lipothymia" to "syncope" to "syncope" to "cardiovascular"
- 12 listings - "slight faint" to "faintness" to "faintness" to "non-site specific"
- 1 listing - "orthostatic problem" to "orthostatic condition(s)" to "non-specific conditions" to "mobility disorders"

20) Certain investigator text terms reflect potentially important AEs for labeling. Below is a list of potentially important investigator text terms reproduced as presented in Appendix 1 in the ISS and as mapped to preferred term and to group term and should have clinical summaries provided.

- "Leuconeutropenia" to "neutropenia" to "decreased white blood cells"
- "Hemoglobinuria" to "hemoglobinuria" to "hemolytic anemias and hemolysis"
- "Superficial petechiae" to "petechiae" to "petechiae"
- "Decreasing platelets" to "thrombocytopenia" to "quantitative platelet defects"
- "Amaurosis" to "amaurosis" to "blindness and low vision"
- "Vision black" to "loss of sight" to "blindness and low vision"
- "Acute torticollis = spasm in cervical muscles" to "spasm of neck" to "muscle cramps and spasms"
- "Convulsions" to "convulsions" to "convulsions"
- "Tonic-clonic seizure to "grand mal epileptic convulsion" to "convulsions"
- "Clenched jaws" to "clenching of jaw" to "dystonic movements"
- "Tetany attack" to "tetany" to "tetany"
- "Allergies" to "allergy to drug" to "allergies and allergic reactions"

For protocol S2WB3004, the following additional AE terms were identified in the dictionary submitted in the 4 month safety update, as potentially important for labeling.

- "Torticollis" mapped to "spasm of neck" to "muscle cramps and spasms"
- "Rash over entire body" mapped to "generalized rash" to "skin rash"
- "Sun allergy" mapped to "sensitivity of skin to sunlight" to "skin photosensitivity"

21) We note that in general, exclusion criteria for the clinical trials in migraineurs provided for the exclusion of patients with hypertension, coronary artery disease, angina, Raynauds disease, peripheral vascular disease, cerebrovascular disease. In your databases from blinded and controlled clinical trials, please identify patients who were noted to be violators of these exclusion criteria and examine their adverse event and vital sign databases for any increased severity and rates of adverse events and outlier values, compared to rates in the rest of the exposed population.

22) We note that in general, exclusion criteria for the clinical trials in migraineurs provided for the exclusion of patients who were exposed to ergotamine, dihydroergotamine, methysergide with 24 hours of naratriptan administration. In your databases from blinded and controlled clinical trials, please identify patients who were noted to be violators of these exclusion criteria and examine their vital sign and adverse event databases for any increased severity and rates of adverse events and outlier values, compared to rates in the rest of the exposed population.

23) We note that in some centers/countries that exposure to 5HT re-uptake inhibitors was an exclusion criteria. We also note that you have identified 8 subjects (listed in Appendix 11 of the ISS) from protocol S2WA3003 who experienced serotonin syndrome-like events while taking SSRIs. We are uncertain if the entire clinical database was examined for SSRI concomitancy. According to Table 106 of the ISS all oral clinical trials were examined except S2WA1007 (Part 1), while neither of the clinical subcutaneous trials

(S2WB2001; S2WB2002) appear to have been examined for SSRI concomitancy. Please examine these additional databases for concomitancy with 5HT re-uptake inhibitors and identify any other subjects who may have experienced serotonin syndrome-like events

24) We note that Tables 61, 64, and 67 in the ISS present incidence of adverse events following administration of subcutaneous placebo, naratriptan (0.5mg-10mg) and sumatriptan (6mg). Since relative bioavailability of subcutaneous administration is greater than oral administration, examination of these tables may provide valuable information which might be viewed as relative overdose compared to the exposure expected from oral doses proposed for marketing and may also identify more clearly those adverse events which naratriptan has a propensity to cause. Please prepare and submit a condensed table for each of Tables, 61, 64 and 67 that shows the incidence of adverse events which are greater than or equal to 1% for any dose of naratriptan and simultaneously greater than that for placebo. Please examine the condensed tables and identify those of adverse events which appear more frequently at naratriptan doses which provide systemic exposures equal to and in excess of exposure which is expected to provide anti-migrainous efficacy. Additionally please identify those adverse events which appear to exhibit a dose response to naratriptan. Relevant information derived from these examinations should be included in the appropriate sections of the proposed labeling.

25) We note for protocol S2WB3004, that Appendix 11 lists the patients and dates when more than 2 tablets were taken within 24 hours. On at least one occasion, 77 patients took 3 tablets, 17 patients took 4 tablets, and 1 patient took 5 tablets in 24 hours. Please examine the AEs and AE rates at the times of these exposures for these subjects as a sub-group since these patients represent multiple exposures to excessive doses and may provide valuable information for the overdose section of the label.

26) Please submit a list of all patients along with their line listings from all clinical trials which may have had laboratory values, ECG changes or vital sign changes which were considered to be adverse events by the investigator.

Clinical Laboratory Data

27) We have assumed that outlier definitions used for the outlier analyses for laboratory values were the same across clinical trials. Please examine your outlier definitions across clinical trials and report any differences in definitions you may have used in evaluating outlier status.

28) Table 80 appears to be incorrect. Table 80 lists that laboratory data from S2WA1007- part 2 have been incorporated into Table 80 but the protocol for S2WA1007 indicates that for "part 1 only, laboratory tests were performed at screening and at 24 hours after administration of study drug for the non-migraine period." indicating that post-exposure laboratory data would not be available for outlier analysis from part 2. Additionally, the number of patients listed for the certain dose levels do not appear to equal the total number of patients exposed at the respective dose levels for the trials listed as contributing data to Table 80. Please verify and confirm that the data in Table 80 accurately reflects the correct number of patients and incorporation of appropriate data from appropriate protocols.

29) ISS Table 85 (laboratory results) and ISS Table 95 (vital signs) for protocol S2WB2002 do not display data from 3 other treatment groups (i.e. single doses of 2.5mg, 5mg or placebo, the only pure placebo comparator for this trial) as does a comparable table for this trial Table 67 (adverse events). Please examine all Tables which incorporate data from this trial, confirm the accuracy of patient accounting and submit versions of the tables including Tables 85 and 95 which compare results across all treatment groups

for protocol S2WB2002, including those who took only single doses of active treatments or placebo.

30) For protocol S2WB3004, protocol for long-term exposure, we note that only 24 subjects had a baseline and one post-exposure clinical laboratory measurement, since repeated measurements were not required unless deemed clinically necessary by the investigator. Further not all 24 subjects had all analytes repeated, for example only 7 patients had post exposure WBC differentials conducted. This implies that limited laboratory safety data has been collected during long term exposure. Please consider agreeing to a phase 4 commitment to conduct such testing. Please plan to conduct not only an outlier analysis but also analyses of mean change from baseline for active treatment compared to placebo. Please also plan to conduct these analyses on subgroups of patients stratified by frequency of monthly exposure to treatment.

Vital Signs Data

31) For protocol C94-036, which examines blood pressure effects of naratriptan in healthy and hypertensive subjects, we note analyses of change from baseline compared to placebo between the two groups but no discussion comparing the absolute means of peak and mean blood pressures achieved between the groups. For the time period 0-4 hours and 0-12 hours post dosing, please provide a comparison between the healthy and hypertensive groups for the absolute weighted mean systolic and diastolic blood pressure and peak blood pressure.

ECGs

32) Charts 24-27 present ECG changes considered to be significant with 7 patients listed as having ST/T wave changes. Please identify these patients and submit a brief narrative describing the clinical events surrounding these ECG changes.

Miscellaneous Requests

33) We note that in study S2WB3009 that an abrupt increase in pulmonary artery pressure was observed following administration of naratriptan 1.5mg subcutaneously. Across the NDA please identify and summarize any other data that corroborates or refutes this finding. In addition, please examine your databases for other 5HT agonists and summarize any data that demonstrates a similar response.

33) In responding to this letter please include any reports of death and serious adverse events since the March 1997 data cut-off dates for the four month safety update and an update of pregnancy outcomes for women who were exposed to naratriptan during there pregnancy.

34) In responding to this letter please include an updated summary of world-wide actions which have been executed by foreign regulatory agencies.

APPEARS THIS WAY
ON ORIGINAL

Submissions List for NDA 20-763 - Naratriptan Tablets

December 04, 1996 - Original NDA 20-763 for Naratriptan Tablets.

January 20, 1997 - General Correspondence - clarification regarding which adverse event coding dictionaries were used in NDA 20-763.

January 23, 1997 - Response to FDA Request - Disketts requested by Dr Levin for:

- a) PDF files for protocol S2WB3004,
- b) SAS Transport files for additional data included in the ISS,
- c) reformatted data for protocol S2WB3002.

February 19, 1997 - General Correspondence to DSI - submission of clinical investigations data to support clinical inspections.

February 26, 1997 - Response to FDA Request - submission of analysis of available laboratory data from patients who had long term exposure to naratriptan tablets -

- a) clinical pharmacology trial C94-071
- b) clinical trials S2WA3003 and S2WB3004

February 27, 1997 - General Correspondence to DSI - submission of clinical investigations data to support clinical inspections.

March 10, 1997 - General Correspondence to DSI - submission of clinical investigations data to support clinical inspections.

March 17, 1997 - General Correspondence - notification that 4-month safety update would be submitted in mid-May 1997.

April 10, 1997 - Response to FDA Fax Request - description of ECG data available at the time of NDA submission and also provided on diskette.

April 15, 1997 - Response to FDA Request - compilation of Time and Events tables for each protocol along with protocol summary.

May 1, 1997 - Response to FDA Request - description of adverse event coding dictionaries, SYMPKEY and MIDAS. identification of dictionary use in each clinical and clinical pharmacology trial, and diskette with dictionary for conversion of SYMPKEY terms to MIDAS.

May 15, 1997 - Four Month Safety Update

May 27, 1997 - Response to FDA Request - information on additional analysis (Randomized Dose analysis) performed in the Integrated Summary of Safety described on page 47 of the ISS and in Tables 30-32.

June 26, 1997 - Response to FDA Request - corrected Table 69 (1% Treatment Emergent Adverse Events)

and Tables 70-73 (frequent, infrequent, and rare adverse events) of the ISS to reflect "total dose analysis" (i.e. revised Tables include all adverse events from the first attack which occurred after the first or second dose) and revised wording for the package insert.

July 1, 1997 - General Correspondence - corrected Table 27 (Incidence of AEs by month) for study S2WB3004.

July 3, 1997 - Response to FDA Request - response to Dr Levin's request for clarification regarding patient enrollment in more than one trial.

July 25, 1997 - Response to FDA Request - response to Dr Sevka's request for clarification regarding
a) number of patients in US oral clinical trials who enrolled in more than one clinical trial
b) number of patients in European oral clinical trials who enrolled in more than one clinical trial
c) clarification of the definition of "subject" and "protocol-subject" in the electronic databases.

August 1, 1997 - Response to FDA Request - Modified Table 31 (Number of Patients Experiencing A Particular AE by Group Term in Placebo-Controlled Studies With Oral Naratriptan) from ISS to include only placebo, 1mg and 2.5mg treatments.

August 5, 1997 - Response to Inquiry - submission of Appendix 5 (randomization code) for protocol S2WB3006 which was missing from the original submission of the 4 month safety update.

August 29, 1997 - Response to FDA Request - response to Dr Sevka's request for clarification regarding the specificity of the Adverse Event Coding Dictionary in the ISS (Appendix 1 - Vol 194) for only the naratriptan NDA and clarification regarding the number of patients represented by each line-listed verbatim term.

APPEARS THIS WAY
ON ORIGINAL

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Naratriptan Safety Review - List of Attachments

- 1) Sponsor's Proposed Labeling for Naratriptan
- 2) Schematic Representation of Naratriptan Metabolism
- 3) Descriptive Table of Clinical Pharmacology and Clinical Trials (Table 1 from ISS - Vol 192)
 - Clinical Pharmacology - pages 1-18 of Vol 192
 - Controlled and Uncontrolled Clinical Trials - oral and subcutaneous - pages 19-25 of Vol 192
- 4) ISS Tables 2 and 3 - Demographics Summary - Oral and SubQ Naratriptan
- 5) ISS Tables 6,7,8,9,10 - Extent of Exposure to Study Treatments [Overall by Formulation]
Oral. Oral by Dose, SubQ, SubQ by Dose
- 6) Protocol S2WB3004 Table 5 - Number of Attacks Treated with Study Treatment by Clinic Visit; and
Protocol S2WB3004 Table 13 from 4-Month Safety Update - Patient Exposure to Oral Naratriptan; and
Protocol S2WB3004 Table 14 from 4-Month Safety Update - Number of Attacks Associated with AEs; and
- 7) ISS Tables 11 and 12 - Disposition and Discontinuation From Studies - Oral and Sub Q
- 8) ISS Table 74 and 4-Month Safety Update Table 2 (Volume 1) - Serious Adverse Events
- 9) ISS Appendix 11 - Line Listing of Patients with Serotonin Syndrome-Like Adverse Events
- 10) ISS Table 69 - Treatment Emergent Adverse Events in Placebo-controlled Trials - at least 1% of patients and more common than placebo) (Revised version as of 6/26/97)
ISS Table 70 - Treatment Emergent Adverse Events in Placebo-controlled Trials - equal to or more common than placebo) (Revised version as of 6/26/97)
ISS Tables 71, 72, 73 - Frequent, Infrequent, and Rare Adverse Events in all oral clinical trials (Revised version as of 6/26/97)
- 11) ISS Table 96 - Occurrence of Adverse Events (Subgroup Analysis)

**TABLE 1
NARATRIPTAN TABLETS
TABLE OF CLINICAL PHARMACOLOGY STUDIES¹**

Protocol/ Report ^a	Study Title	Study Objective	Design	Patients Per Treatment** (randomized/treated at least once)	Age Range	%Sex (F/M)	Study Status (Starting Date)	1)Country 2)Formulation Code***	Full Report (F) Summary Report (S) [Data Listing] Vol./pg.
1. Bioavailability Studies									
C94-034/ GCP/94/034	A Study to Determine the Absolute Bioavailability of Oral Naratriptan	To estimate the absolute oral bioavailability of naratriptan administered as a tablet.	Open-label, two way cross-over randomized	5mg as tablet: 24/24 1.5mg IV infusion: 24/23 Total completed: 23	20-47	F: 50% M: 50%	Completed (Jul 12 1994)#	United Kingdom C, D	69/1 (F)
C93-006/ GCP/93/006	A Pilot Study to Estimate the Oral Bioavailability of Naratriptan Administered as a Tablet and as an Oral Solution	1) To provide an estimate of the oral bioavailability of naratriptan administered as a tablet and as an oral solution. 2) To compare the pharmacokinetics of naratriptan administered as a tablet and as an oral solution and to further assess the safety and tolerability of oral naratriptan.	Open-label, three-way cross- over, randomized	1.5mg as IV infusion: 6/6 10mg as tablet: 6/6 10mg as oral solution: 6/6 Total completed: 6	30-41	M:100%	Completed (May 10, 1993)	United Kingdom A, B, D	69/262 (F)

¹ Report also included in Clinical Data Section

² Report also included in Human Pharmacokinetics and Bioavailability Section

^a Investigators are listed, by protocol, in Appendix 1 to this table

** Randomized patients may not have received any treatment; Total completed are those who completed all treatments and follow-up examinations which were required by protocol.

*** Formulations Codes are contained in Appendix 2 to this table: A. Oral Solution, B. White Tablet, C. Green Tablet, D. Injection presented as ampules (mannitol), E. Injection presented as ampules (NaCl),

E** Radiolabelled injection presented as ampules (NaCl), F. Radiolabelled Oral Solution, G. Injection presented as pre-filled syringes (mannitol), H. Nasal solution

Date of first treatment

TABLE 1
NARATRIPTAN TABLETS
TABLE OF CLINICAL PHARMACOLOGY STUDIES (cont'd)

Protocol/ Report*	Study Title	Study Objective	Design	Patients Per Treatment** (randomized/treated at least once)	Age Range	%Sex (F/M)	Study Status (Starting Date)	1)Country 2)Formulation Code***	Full Report (F) Summary Report (S) [Data Listing] Vol./pg.
2. Pharmacokinetic Studies									
C92-055/ GCP/92/055	The Safety and Tolerability of Naratriptan Administered as an Oral Solution	To determine: 1) The safety and tolerability of naratriptan administered as an oral solution. 2) The pharmacokinetics of oral naratriptan (administered as a solution) to estimate the oral bioavailability and the relationship between the pharmacokinetic profile and the hemodynamic response.	Double-blind, ascending dose, randomized, placebo- controlled. Each subject received three doses of naratriptan (two subjects received two doses) with a randomized placebo.	0.5mg: 2/2 1.0mg: 2/2 2.5mg: 4/4 5.0mg: 10/10 10.0mg: 16/16 15.0mg: 13/13 20.0mg: 4/4 25.0mg: 1/1 Placebo: 18/18 Total completed: 16	20-38	M:100%	Completed (Jan 5, 1993)	United Kingdom A	72/1 (F) ¹
C93-060/ GCP/93/060	A Study to Investigate the Safety, Tolerability, Pharmacodynamic and Pharmacokinetic Response to Two Doses of Oral Naratriptan Separated by 4 Hours	To investigate the safety, tolerability, pharmacodynamic and pharmacokinetic response to two doses of naratriptan tablets separated by 4 hours.	Double-blind, placebo- controlled, four- way cross-over, ascending dose	5mg +5mg: 9/9 7.5mg+7.5mg: 9/8 10mg+10mg: 9/8 Placebo+Placebo: 9/8 Total completed: 8	27-41	M: 100%	Completed (Oct 6, 1993)	United Kingdom B	76/1 (F) ¹

¹ Report also included in Clinical Data Section

² Report also included in Human Pharmacokinetics and Bioavailability Section

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E** Radiolabelled Injection presented as ampules (NaCl), F. Radiolabelled Oral Solution, G. Injection presented as prefilled syringes (mannitol), H. Nasal solution

Date of first treatment

Nov 14, 1990

TABLE 1
NARATRIPTAN TABLETS
TABLE OF CLINICAL PHARMACOLOGY STUDIES (cont'd)

Protocol/ Report*	Study Title	Study Objective	Design	Patients Per Treatment** (randomized/treated at least once)	Age Range	%Sex (F/M)	Study Status (Starting Date)	1)Country 2)Formulation Code***	Full Report (F) Summary Report (S) [Data Listing] Vol./pg.
2. Pharmacokinetic Studies (cont'd)									
S2WA1002/ RM1996/ 0056/00	A Study to Evaluate the Safety and Pharmacokinetics of Two Doses of 1.0mg, 2.5mg and 5.0mg Naratriptan Tablets Separated by 2 Hours in Healthy Volunteers	To evaluate : 1) The safety of two doses of 1.0mg, 2.5mg, and 5.0mg naratriptan tablets administered two hours apart compared to placebo in healthy male subjects 2) The pharmacokinetics of two doses of 1.0mg, 2.5mg, and 5.0mg naratriptan tablets administered two hours apart in healthy male subjects.	Randomized, double-blind, placebo- controlled, four- period, cross- over	1.0mg + 1.0mg: 12/12 2.5mg +2.5mg: 12/12 5.0mg + 5.0mg: 12/12 Placebo + Placebo: 12/12 Total completed: 12	18-46	M: 100%	Completed (May 19, 1994)#	United Kingdom B	74/1 (F) ¹
C93-070/ GCP/93/070	A Study to Investigate the Dose Proportionality of Oral Tablet Naratriptan	To investigate the dose proportionality of naratriptan tablet pharmacokinetics in healthy female subjects.	Open-label, randomized, cross-over	2.5mg: 26/24 5.0mg: 26/25 7.5mg: 26/25 10mg: 26/23 Total completed: 23	18-45	F: 100%	Completed (Jan 17, 1994)#	United Kingdom B	70/1 (F)

¹ Report also included in Clinical Data Section

² Report also included in Human Pharmacokinetics and Bioavailability Section

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E** Radiolabelled injection presented as ampules (NaCl), F. Radiolabelled Oral Solution, G. Injection presented as pre-filled syringes (mannitol), H. Nasal solution

Date of first treatment

TABLE 1
NARATRIPTAN TABLETS
TABLE OF CLINICAL PHARMACOLOGY STUDIES (cont'd)

Protocol/ Report*	Study Title	Study Objective	Design	Patients Per Treatment** (randomized/treated at least once)	Age Range	%Sex (F/M)	Study Status (Starting Date)	1)Country 2)Formulation Code***	Full Report (F) Summary Report (S) [Data Listing] Vol./pg.
2. Pharmacokinetic Studies (cont'd)									
C94-071/ GCP/95/037	A Study to Investigate the Safety, Tolerability and Pharmacokinetics of Repeat Dosing with Oral Naratriptan for 5 Days	To investigate 1) the safety, tolerability and pharmacokinetics of repeat dosing with naratriptan tablets for 5 days 2) the neuroendocrine response to naratriptan.	Ascending dose, double-blind, placebo-controlled, cross-over	5mg: 12/12 10mg: 12/11 Placebo: 12/12 Total completed: 11	23-53	F: 100%	Completed (Feb 13, 1995)#	United Kingdom B	77/1 (F) ¹
S2WA1003/ RM1996/001 12/00	A Study to Determine the Effect of Food on the Pharmacokinetics of Oral Naratriptan Tablets in Healthy Female Volunteers	To determine the effect of food (standard breakfast) on the pharmacokinetics of naratriptan tablets.	Open, randomized, two-period, cross-over	2.5mg after overnight fast: 20/20 2.5mg 5 minutes after a standardized breakfast: 20/20 Total completed: 20	18-58	F 100%	Completed (Jul 25, 1995)#	USA C	93/1 (F)

¹ Report also included in Clinical Data Section

² Report also included in Human Pharmacokinetics and Bioavailability Section

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Date of first treatment

TABLE 1
NARATRIPTAN TABLETS
TABLE OF CLINICAL PHARMACOLOGY STUDIES (cont'd)

Protocol/ Report*	Study Title	Study Objective	Design	Patients Per Treatment** (randomized/treated at least once)	Age Range	%Sex (F/M)	Study Status (Starting Date)	1)Country 2)Formulation Code***	Full Report (F) Summary Report (S) [Data Listing] Vol./pg.
2. Pharmacokinetic Studies (cont'd)									
548-01/ JJC/95/001	Naratriptan Phase I Study (Single Oral Dose in Healthy Male Volunteers)	To evaluate: 1) The safety, tolerability and pharmacokinetics of a single dose of naratriptan tablets (1, 2.5, 5, 7.5 and 10mg) in healthy male volunteers 2) The effects of a meal on the pharmacokinetics of 5mg naratriptan.	Ascending dose, placebo- controlled	1) Fasted subjects 1.0mg: 6/6 2.5mg: 6/6 5.0mg: 6/6 7.5mg: 6/6 10.0mg: 6/6 Placebo: 4/4 2) After meal 5.0mg:6/6 Total completed: 16	20-24	M: 100%	Completed (Jun 1994)	Japan B	73/307 (F) ¹
548-02 JJC/95/006	Naratriptan Phase I Study (Oral Repeated Dose)	To evaluate the safety, tolerability and pharmacokinetics of repeat doses of naratriptan tablets in healthy male volunteers.	Placebo- controlled, 5 day repeat dose double-blind, randomised	5mg: 6/6 Placebo: 2/2 Total completed: 8	20-26	M: 100%	Completed (Aug 1994)	Japan B	78/361 (F) ¹

¹ Report also included in Clinical Data Section

² Report also included in Human Pharmacokinetics and Bioavailability Section

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Date of first treatment

TABLE 1
NARATRIPTAN TABLETS
TABLE OF CLINICAL PHARMACOLOGY STUDIES (cont'd)

Protocol/ Report*	Study Title	Study Objective	Design	Patients Per Treatment** (randomized/treated at least once)	Age Range	%Sex (F/M)	Study Status (Starting Date)	1)Country 2)Formulation Code***	Full Report (F) Summary Report (S) [Data Listing] Vol./pg.
3. ADME Studies									
C94-007/ GCP/94/007	A Radioisotope Study to Investigate the Metabolic Disposition of Oral Naratriptan in Man	To investigate the absorption, metabolism and excretion of ¹⁴ C-naratriptan and to determine a total mass balance for the excretion of drug related material following a 10mg oral dose of naratriptan.	Open-label, single-dose	10mg as oral solution: 2/2 Total completed: 2	48-49	M: 100%	Completed (Apr 27, 1994)#	United Kingdom F	79/140 (F) 105/32 (S)
3.1 Disease Interaction Studies									
C93-081/ GCP/95/053	A Study to Investigate the Pharmacokinetics of Oral Naratriptan in Subjects with Impaired Renal Function	To describe the pharmacokinetics of oral naratriptan in subjects with renal impairment and compare this with naratriptan tablets pharmacokinetics in healthy subjects with normal renal function.	Open-label, single-dose parallel group	Healthy/mild renal impairment 5mg: 16/16 Moderate renal impairment 2.5mg: 7/7 Total completed: 23	21-58	F: 35% M: 65%	Completed (Nov 2, 1994)#	United Kingdom B, C	86/8 (F) ¹
S2WB1004/ C95-036 GCP/96/018	A Study to Investigate the Pharmacokinetics of Oral Naratriptan in Subjects with Impaired Hepatic Function	To investigate the pharmacokinetics of naratriptan tablets in subjects with impaired hepatic function.	Open label, single-dose, parallel group.	2.5mg: 16/16 Total completed: 16	43-63	F: 50% M: 50%	Completed (Oct 23, 1995)#	United Kingdom C	87/1 (F) ¹

¹ Report also included in Clinical Data Section

² Report also included in Human Pharmacokinetics and Bioavailability Section

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Date of first treatment

Nov 14, 1996

TABLE 1
NARATRIPTAN TABLETS
TABLE OF CLINICAL PHARMACOLOGY STUDIES (cont'd)

Protocol/ Report*	Study Title	Study Objective	Design	Patients Per Treatment** (randomized/treated at least once)	Age Range	%Sex (F/M)	Study Status (Starting Date)	1)Country 2)Formulation Code***	Full Report (F) Summary Report (S) [Data Listing] Vol./pg.
3.2 Drug Interaction Studies									
C93-087/ GCP/96/010	A Study to Investigate Whether Alcohol Has an Effect on the Safety, Tolerability, Pharmacokinetics or Pharmacodynamics of Naratriptan	To investigate whether alcohol has an effect on the safety, tolerability, pharmacokinetics or pharmacodynamics of naratriptan.	Double-blind randomized, placebo-controlled, two-way cross-over	5mg+0.6g/kg Alcohol: 16/16 5mg + Placebo 16/16 Total completed: 16	20-38	F: 100%	Completed (Apr 12, 1994)#	United Kingdom B	92/1 (F) 105/25 (S)
S2WB1003 (C95-035)/ GCP/96/012	A Study to Investigate the Effect of Subcutaneous Sumatriptan on the Safety, Pharmacodynamics and Pharmacokinetics of Oral Naratriptan	To investigate the effects of concomitant administration of naratriptan tablets and subcutaneous sumatriptan on: 1) systolic and diastolic blood pressure. 2) the pharmacokinetic profiles of each drug.	Double-blind, double-dummy randomized, four-way cross-over placebo-controlled	2.5mg oral: 12/12 Placebo oral: 12/12 Sumatriptan SC 6mg: 12/12 2.5mg oral + Sumatriptan 6.0mg SC: 12/12 Total completed: 12	21-36	F: 100%	Completed (Feb 7, 1996)#	United Kingdom C	88/1 (F) 105/1 (S)

* Report also included in Clinical Data Section

** Report also included in Human Pharmacokinetics and Bioavailability Section

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Date of first treatment

Nov 14, 1996

TABLE 1
NARATRIPTAN TABLETS
TABLE OF CLINICAL PHARMACOLOGY STUDIES (cont'd)

Protocol/ Report*	Study Title	Study Objective	Design	Patients Per Treatment** (randomized/treated at least once)	Age Range	%Sex (F/M)	Study Status (Starting Date)	1)Country 2)Formulation Code***	Full Report (F) Summary Report (S) [Data Listing] Vol./pg.
3.2 Drug Interaction Studies (cont'd)									
S2WA1010 (534/040)/ UCP/96/001	A Study to Investigate the Interaction of Naratriptan and Dihydroergotamine in Healthy Volunteers	To determine if there is an interaction between naratriptan and dihydroergotamine (DHE) on blood pressure, and the pharmacokinetic profiles when they are administered concomitantly and 24 hours apart.	Double-blind, randomized, placebo controlled, four-way cross-over	Day -1, Day 1 24h apart Placebo, Placebo +2.5mg: 16/14 Placebo, Placebo + 1mg DHE: 16/15 Placebo, 1mgDHE + 2.5mg: 16/14 2.5mg, Placebo + 1mg DHE: 16/13 Total completed: 12	21-52	F: 100%	Completed (Sep 16, 1995)#	Canada C	89/132 (F) 105/9 (S) [90/1]
S2WA1011 (534/050)/ NN1996/00001/ 00	A Study to Investigate the Interaction of Naratriptan and Ergotamine in Healthy Volunteers	To determine if there is an interaction between naratriptan and ergotamine 2mg on blood pressure, and the pharmacokinetic profiles when they are administered concomitantly and 24 hours apart.	Double-blind, randomized, placebo-controlled, four-way cross-over	Day-1 Day 1 24h apart Placebo, Placebo + 2.5mg: 12/10 Placebo, Placebo + Ergotamine 2mg: 12/12 Placebo, 2.5mg + Ergotamine 2mg: 12/10 2.5mg, Placebo + Ergotamine 2mg: 12/11 Total completed: 10	19-52	F: 100%	Completed (Oct 27, 1995)#	Canada C	91/1 (F) 105/17 (S) [91/233]

* Report also included in Clinical Data Section

** Report also included in Human Pharmacokinetics and Bioavailability Section

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Date of first treatment

Nov 14, 1996

TABLE 1
NARATRIPTAN TABLETS
TABLE OF CLINICAL PHARMACOLOGY STUDIES (cont'd)

Protocol/ Report*	Study Title	Study Objective	Design	Patients Per Treatment** (randomized/treated at least once)	Age Range	%Sex (F/M)	Study Status (Starting Date)	1)Country 2)Formulation Code***	Full Report (F) Summary Report (S) (Data Listing) Vol./pg.
3.3 Demographic Studies									
S2WA1012/ GM1996/ 00008/00	A Study to Investigate the Pharmacokinetics of Oral Naratriptan in Adolescent Migraine Patients Outside a Migraine Attack	To determine the pharmacokinetics of naratriptan tablets in adolescent migraine patients outside a migraine attack	Open single-dose	2.5mg : 7/7 Total completed: 7	12-17	F: 57% M: 43%	Ongoing (May 11, 1996)#	USA C	80/265 (S) ¹
S2WB1002/ GCP/96/008	A Study to Compare the Safety, Tolerability, Pharmacodynamics and Pharmacokinetics of Oral Naratriptan in Young and Elderly Subjects	To compare the safety, tolerability, pharmacodynamics and pharmacokinetics of naratriptan tablets in young and elderly subjects.	Ascending-dose, double-blind, randomized, placebo controlled.	1mg + 1mg: 25/25 2.5mg + 2.5mg: 25/24 Placebo + Placebo: 25/24 Total completed: 24	Young: 24-44 Elderly : 65-77	F: 48% M: 52%	Completed (Aug 17, 1995)#	United Kingdom C	81/1 (F) ¹

¹ Report also included in Clinical Data Section

² Report also included in Human Pharmacokinetics and Bioavailability Section

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Date of first treatment

Nov 14, 1996

TABLE 1
NARATRIPTAN TABLETS
TABLE OF CLINICAL PHARMACOLOGY STUDIES (cont'd)

Protocol/ Report*	Study Title	Study Objective	Design	Patients Per Treatment** (randomized/treated at least once)	Age Range	%Sex (F/M)	Study Status (Starting Date)	1)Country 2)Formulation Code***	Full Report (F) Summary Report (S) {Data Listing} Vol./pg.
4. Pharmacodynamic and Dose Tolerance Studies									
4.1 Cardiovascular Effects									
C94-036/ GCP/96/009	An Ascending Dose, Parallel Group Study to Compare the Effects of Oral Naratriptan on Blood Pressure in Healthy Subjects and in Hypertensive Patients Taking Anti-hypertensive Therapy	To determine the pressor response to naratriptan in controlled hypertensive patients taking anti-hypertensive therapy and compare this with the response in healthy subjects.	Double-blind, randomized, placebo-controlled, parallel group, ascending dose	1mg + 1mg: 27/27 2.5mg + 2.5mg: 27/24 5mg + 5mg: 27/24 Placebo + Placebo: 27/25 Total completed: 24	40-60	M: 37% F: 63%	Completed (Jul 20, 1994)#	Netherlands B	95/1 (F) ¹
4.2 Central Function									
C94-045/ GCP/96/011	A Study to Investigate the Potential Central Function Effect of Naratriptan	To investigate any impairment of cognitive and psychomotor function after naratriptan administration.	Placebo-controlled, double-blind, double-dummy, randomised, four-way, crossover	5mg: 16 10mg: 16 Temazepam 20mg: 16 Placebo: 16 Total completed: 16	25-44	F: 100%	Completed (Sep 27, 1994)#	United Kingdom C	121/269 (F) 86/1 (S)
4.3 Ocular Effects									
S2WB1006 (C95-071)/ GCP/96/013	A Study to Evaluate the Ocular Effects of Naratriptan in Healthy Subjects	To evaluate the ocular effects of naratriptan tablets in healthy female subjects.	Double-blind placebo-controlled randomized, two-way cross-over	2.5mg: 8/8 placebo: 8/8 Total completed: 8	20-54	F: 100%	Completed (Feb 1, 1996)#	United Kingdom C	122/299 (F) 96/437 (S)

¹ Report also included in Clinical Data Section

² Report also included in Human Pharmacokinetics and Bioavailability Section

* Investigators are listed, by protocol, in Appendix 1 to this table

** Randomized patients may not have received any treatment; Total completed are those who completed all treatments and follow-up examinations which were required by protocol.

*** Formulations Codes are contained in Appendix 2 to this table: A. Oral Solution, B. White Tablet, C. Green Tablet, D. Injection presented as ampules (mannitol), E. Injection presented as ampules (NaCl),

E** Radiolabelled injection presented as ampules (NaCl), F. Radiolabelled Oral Solution, G. Injection presented as prefilled syringes (mannitol), H. Nasal solution

Date of first treatment

TABLE 1
NARATRIPTAN TABLETS
TABLE OF CLINICAL PHARMACOLOGY STUDIES (cont'd)

Protocol/ Report*	Study Title	Study Objective	Design	Patients Per Treatment** (randomized/treated at least once)	Age Range	%Sex (F/M)	Study Status (Starting Date)	1)Country 2)Formulation Code***	Full Report (F) Summary Report (S) [Data Listing] Vol./pg.
5. Drug Abuse Potential									
S2WA1004 (S34/010)/ NN1996/ 00004/00	A Comparative Study of the Pharmacologic Effects of Naratriptan, Codeine and Placebo in Experienced Psychoactive Substance Users	1) To compare the relative pharmacologic effects of naratriptan tablets and codeine in subjects who are experience psychoactive substance users. 2) To assess the safety and tolerability of Naratriptan in subjects who are experienced psychoactive substance users.	Randomized, double-blind, double-dummy, placebo- controlled, cross-over	1.0mg: 12/12 2.5mg: 12/12 5.0mg: 12/12 30mg Codeine: 12/12 60mg Codeine: 12/12 90mg Codeine: 12/12 Placebo: 12/12 Total completed: 12	21-35	F: 17% M: 83%	Completed (Oct 27, 1995)#	Canada C	123/1 (F) 96/432 (S)

* Report also included in Clinical Data Section

** Report also included in Human Pharmacokinetics and Bioavailability Section

*** Investigators are listed, by protocol, in Appendix 1 to this table

**** Randomized patients may not have received any treatment; Total completed are those who completed all treatments and follow-up examinations which were required by protocol.

***** Formulations Codes are contained in Appendix 2 to this table: A. Oral Solution, B. White Tablet, C. Green Tablet, D. Injection presented as ampules (mannitol), E. Injection presented as ampules (NaCl), F. Radiolabelled Injection presented as ampules (NaCl), G. Injection presented as ampules (mannitol), H. Nasal solution

Date of first treatment

TABLE 1
SUBCUTANEOUS NARATRIPTAN
TABLE OF CLINICAL PHARMACOLOGY STUDIES

Protocol/ Report*	Study Title	Study Objective	Design	Patients Per Treatment** (randomized/treated at least once)	Age Range	%Sex (F/M)	Study Status (Starting Date)	1)Country 2)Formulation Code***	Full Report (F) Summary Report (S) [Data Listing] Vol./pg.
I. Pharmacodynamic and Dose Tolerance Studies									
W91-013/ WMH/91/023	The Safety and Tolerability of Subcutaneous Naratriptan in Healthy Subjects	To determine the safety, tolerability and pharmacokinetics of subcutaneous naratriptan.	Double-blind, cross-over, placebo-controlled, ascending-dose, randomized Each subject received three subcutaneous injections of naratriptan with a randomized placebo.	0.025mg: 2/2 0.05mg: 4/4 0.10mg: 6/6 0.25mg: 6/6 0.5mg: 6/6 1.0mg: 10/10 2.5mg: 8/8 5.0mg: 6/6 Placebo: 16/16 Total completed: 16	21-44	M: 100%	Completed (Jun 4, 1991)	United Kingdom D	113/1 (F) 79/1 (S)
W91-023/ WMH/91/026	The Safety and Tolerability of 10mg Naratriptan Administered as a 1ml Subcutaneous Injection in Healthy Subjects	1) To determine the safety, tolerability and pharmacokinetics of 10mg naratriptan administered as a 1ml subcutaneous injection. 2) To investigate the relationship between the pharmacokinetic profile and the hemodynamic response.	Double-blind, cross-over, placebo-controlled, ascending-dose, randomized Each subject received two subcutaneous injections of naratriptan with a randomized placebo.	5.0mg: 6/6 10.0mg: 6/6 Placebo: 6/6 Total completed: 6	26-45	M: 100%	Completed (Feb 27, 1992)	United Kingdom D	114/1 (F) 79/7 (S)

* Report also included in Clinical Data Section

** Report also included in Human Pharmacokinetics and Bioavailability Section

*** Investigators are listed, by protocol, in Appendix 1 to this table

**** Randomized patients may not have received any treatment; Total completed are those who completed all treatments and follow-up examinations which were required by protocol.

***** Formulations Codes are contained in Appendix 2 to this table: A. Oral Solution, B. White Tablet, C. Green Tablet, D. Injection presented as ampules (mannitol), E. Injection presented as ampules (NaCl), F. Radiolabelled Injection presented as ampules (NaCl), G. Injection presented as prefilled syringes (mannitol), H. Nasal solution

Date of first treatment

TABLE 1
SUBCUTANEOUS NARATRIPTAN
TABLE OF CLINICAL PHARMACOLOGY STUDIES (cont'd)

Protocol/ Report*	Study Title	Study Objective	Design	Patients Per Treatment** (randomized/treated at least once)	Age Range	%Sex (F/M)	Study Status (Starting Date)	1)Country 2)Formulation Code***	Full Report (F) Summary Report (S) [Data Listing] Vol./pg.
2. Other Pharmacodynamic Studies									
2.1 Cardiovascular Effects and Blood Flow Effects									
S2WB3006/ GCV/96/010	A Double-Blind, Randomized, Placebo-Controlled, Crossover Study to Assess the Effects of SC Naratriptan on Myocardial Perfusion in Migraineurs by Positron Emission Tomography	To compare the coronary reserve after SC naratriptan 1.5mg as compared to placebo in Migraineurs. To assess ECG changes of MI or arrhythmia after SC naratriptan 1.5mg vs. placebo. To estimate the pharmacokinetics in the patients selected and relate to myocardial blood flow, coronary reserve and any ECG change that occur following administration of SC naratriptan 1.5mg.	Double-blind, randomized, placebo-controlled, crossover	1.5mg: Placebo:	18 - 65	F: 80% M: 20%	Ongoing	United Kingdom Belgium D	96/428 (S) ¹
S2WB3009/ GCV/96/011	A Study to Assess the Effect of 1.5mg SC Naratriptan on Cardiac Hemodynamics in Patient Volunteers with Existing or Suspected Coronary Artery Disease	To determine the effects of naratriptan (1.5mg SC) on cardiac hemodynamics, coronary artery dimensions and the electrocardiogram.	Open-label	Placebo + 1.5mg: 10/10 Total completed: 8	44 - 69	F: 80% M: 20%	Completed (Sep 26 1995)	United Kingdom D	119/1 (F) 96/417 (S)

¹ Report also included in Clinical Data Section

² Report also included in Human Pharmacokinetics and Bioavailability Section

³ Investigators are listed, by protocol, in Appendix 1 to this table

⁴ Randomized patients may not have received any treatment; Total completed are those who completed all treatments and follow-up examinations which were required by protocol.

⁵ Formulations Codes are contained in Appendix 2 to this table: A. Oral Solution, B. White Tablet, C. Green Tablet, D. Injection presented as ampules (mannitol), E. Injection presented as ampules (NaCl),

E** Radiolabelled injection presented as ampules (NaCl), F. Radiolabelled Oral Solution, G. Injection presented as prefilled syringes (mannitol), H. Nasal solution

Date of first treatment

Nov 14, 1996

TABLE 1
SUBCUTANEOUS NARATRIPTAN
TABLE OF CLINICAL PHARMACOLOGY STUDIES (cont'd)

Protocol/ Report*	Study Title	Study Objective	Design	Patients Per Treatment** (randomized/treated at least once)	Age Range	%Sex (F/M)	Study Status (Starting Date)	1)Country 2)Formulation Code***	Full Report (F) Summary Report (S) [Data Listing] Vol./pg.
2.1 Cardiovascular Effects and Blood Flow Effects (Cont'd)									
S2WB3010/ GCV/96/008	A Double-Blind, Randomized, Placebo- Controlled Study to Assess the Effects of Subcutaneous Naratriptan (1mg, 5mg and 10mg) on Forearm Perfusion in Migraineurs by Strain Gauge Plethysmography	To assess: 1) Forearm perfusion after either SC naratriptan (1.0, 5.0, 10.0mg) or placebo by reserve volume (ratio of hyperemic blood flow to baseline blood flow) 2) Forearm perfusion after either SC naratriptan (1.0, 5.0, 10.0mg) or placebo by basal forearm blood flow.	Double-blind, randomized, placebo- controlled four- way crossover	1.0mg: 20/19 5.0mg: 20/19 10.0 mg: 20/19 Placebo: 20/19 Total completed: 19	19-43	F: 53% M: 47%	Completed (May 19, 1995)	United Kingdom G	120/1 (F) 96/423 (S)

* Report also included in Clinical Data Section

** Report also included in Human Pharmacokinetics and Bioavailability Section

*** Investigators are listed, by protocol, in Appendix 1 to this table

**** Randomized patients may not have received any treatment; Total completed are those who completed all treatments and follow-up examinations which were required by protocol.

***** Formulations Codes are contained in Appendix 2 to this table: A. Oral Solution, B. White Tablet, C. Green Tablet, D. Injection presented as ampules (mannitol), E. Injection presented as ampules (NaCl),

E** Radiolabelled injection presented as ampules (NaCl), F. Radiolabelled Oral Solution, G. Injection presented as pre-filled syringes (mannitol), H. Nasal solution

Date of first treatment

TABLE 1
INTRAVENOUS NARATRIPTAN
TABLE OF CLINICAL PHARMACOLOGY STUDIES

Protocol/ Report*	Study Title	Study Objective	Design	Patients Per Treatment** (randomized/treated at least once)	Age Range	%Sex (F/M)	Study Status (Starting Date)	1)Country 2)Formulation Code***	Full Report (F) Summary Report (S) [Data Listing] Vol./pg.
I. ADME Studies									
W91-019/ WMH/91/035	A Radioisotope Study to Investigate the Metabolic Disposition of Intravenous Naratriptan in Man	To determine: 1) The total mass- balance for the excretion of ¹⁴ C- naratriptan in man. 2) The metabolic profile of naratriptan and the identification, if possible, of any metabolites formed.	Open-label single-dose	1.5mg Naratriptan as a 15 min. IV infusion: 2/2 Total completed: 2	41, 51	M: 100%	Completed (Apr 13, 1992)	United Kingdom E**	79/19 (F) 105/37 (S)
W91-004/ WMH/91/003	A Study to Measure Naratriptan in Gastric Contents Following Intravenous Administration of Naratriptan in Healthy Subjects	To determine the concentration of naratriptan in gastric juice in man following intravenous administration of naratriptan.	Open-label, single-dose	20µg/kg as a 15min IV infusion: 4/4 Total completed: 4	27-42	M: 100%	Completed (Apr 16, 1991)	United Kingdom E	80/92 (F) 105/42 (S)

* Report also included in Clinical Data Section

** Report also included in Human Pharmacokinetics and Bioavailability Section

*** Investigators are listed, by protocol, in Appendix 1 to this table

**** Randomized patients may not have received any treatment; Total completed are those who completed all treatments and follow-up examinations which were required by protocol.

***** Formulations Codes are contained in Appendix 2 to this table: A. Oral Solution, B. White Tablet, C. Green Tablet, D. Injection presented as ampules (mannitol), E. Injection presented as ampules (NaCl),

F** Radiolabelled injection presented as ampules (NaCl), F. Radiolabelled Oral Solution, G. Injection presented as pre-filled syringes (mannitol), H. Nasal solution

Date of first treatment

Nov 14, 1996

TABLE 1
 INTRAVENOUS NARATRIPTAN
 TABLE OF CLINICAL PHARMACOLOGY STUDIES (cont'd)

Protocol/ Report*	Study Title	Study Objective	Design	Patients Per Treatment** (randomized/treated at least once)	Age Range	%Sex (F/M)	Study Status (Starting Date)	1)Country 2)Formulation Code***	Full Report (F) Summary Report (S) [Data Listing] Vol./pg.
1.1 Pharmacodynamic and Dose Tolerance Studies									
WHP:90:06 WMH/91/004	The Safety and Tolerability of Intravenous Naratriptan in Healthy Subjects	To determine the safety, tolerability and pharmacokinetics of intravenously administered naratriptan in healthy subjects.	Double-blind, ascending-dose, placebo- controlled, randomized. Each subject received three doses of Naratriptan with a randomised placebo.	0.25µg/kg: 2/2 0.5µg/kg: 2/2 1.0µg/kg: 6/6 2.5µg/kg: 4/4 5.0µg/kg: 10/10 6.25µg/kg: 2/2 10.0µg/kg: 8/8 12.5µg/kg: 1/1 20.0µg/kg: 5/5 Placebo: 16/14 Total completed: 11	25-45	M: 100%	Completed (Nov 29, 1990)	United Kingdom E	115/1 (F) 79/13 (S)

* Report also included in Clinical Data Section

** Report also included in Human Pharmacokinetics and Bioavailability Section

*** Investigators are listed, by protocol, in Appendix 1 to this table

**** Randomized patients may not have received any treatment; Total completed are those who completed all treatments and follow-up examinations which were required by protocol.

***** Formulations Codes are contained in Appendix 2 to this table: A. Oral Solution, B. White Tablet, C. Green Tablet, D. Injection presented as ampules (mannitol), E. Injection presented as ampules (NaCl), F. Radiolabelled injection presented as ampules (NaCl), G. Radiolabelled Oral Solution, H. Injection presented as prefilled syringes (mannitol), I. Nasal solution

Date of first treatment

TABLE 1
INTRANASAL NARATRIPTAN
TABLE OF CLINICAL PHARMACOLOGY STUDIES (cont'd)

Protocol/ Report*	Study Title	Study Objective	Design	Patients Per Treatment** (randomized/treated at least once)	Age Range	%Sex (F/M)	Study Status (Starting Date)	1)Country 2)Formulation Code***	Full Report (F) Summary Report (S) [Data Listing] Vol./pg.
I. Intranasal Studies									
S2WB1001 (C95-017) GCP/95/052	A Study to Assess the Safety, Tolerability and Pharmacokinetics of Intranasal Naratriptan in Healthy Female Subjects	To assess the safety, tolerability, and pharmacokinetics of intranasal naratriptan in healthy female subjects.	Double-blind, randomised ascending dose, placebo controlled, cross-over study	Placebo: 8/8 0.25mg IN: 8/8 0.50mg IN: 8/8 1.00mg IN: 8/8 Total completed: 8	24-35	F: 100%	Completed (Jul 25, 1995)#	United Kingdom H	94/1 (F) ¹

¹ Report also included in Clinical Data Section

² Report also included in Human Pharmacokinetics and Bioavailability Section

* Investigators are listed, by protocol, in Appendix 1 to this table

** Randomized patients may not have received any treatment; Total completed are those who completed all treatments and follow-up examinations which were required by protocol.

*** Formulations Codes are contained in Appendix 2 to this table: A. Oral Solution, B. White Tablet, C. Green Tablet, D. Injection presented as ampules (mannitol), E. Injection presented as ampules (NaCl),

E** Radiolabelled Injection presented as ampules (NaCl), F. Radiolabelled Oral Solution, G. Injection presented as pre-filled syringes (mannitol), H. Nasal solution

Date of first treatment

TABLE 1
NARATRIPTAN TABLETS
TABLE OF CONTROLLED CLINICAL STUDIES IN MIGRAINE PATIENTS

Protocol/ Report*	Study Title	Study Objective	Design	Patients Per Treatment** (randomized/treated at least once)	Age Range	%Sex (F/M)	Study Status (Starting Date)	1)Country 2)Formulation Code***	Full Report (F) Summary Report (S) [Data Listing] Vol./pg.
1. Placebo-Controlled US Studies									
S2WA3001 RM1996/0020/00	A Randomized, Double-Blind, Placebo-Controlled, Dose Ranging Study to Evaluate the Efficacy and Safety of Four Doses of Oral Naratriptan in the Acute Treatment of a Single Migraine Attack	To evaluate the efficacy and safety of 0.1mg, 0.25mg, 1.0mg, and 2.5mg oral naratriptan compared to placebo in the treatment of a single migraine attack.	Double-blind, randomized, placebo-controlled, parallel design	0.1mg: 142/128 0.25mg: 143/119 1.0mg: 132/117 2.5mg: 140/127 Placebo: 137/122 Total completed: 611	19-65	F = 87% M = 13%	Completed (Jul 10, 1995)	USA C	124/18 (F) [126/3]
S2WA3003 RM1996/00008/00	A Randomized, Double-Blind, Placebo-Controlled, Crossover Study to Evaluate the Safety and Efficacy of Oral Naratriptan in the Acute Treatment of Four Migraine Attacks	To evaluate the efficacy and safety of 0.25mg, 1.0mg, and 2.5mg oral naratriptan compared to placebo in the treatment of four migraine attacks.	Double-blind, randomized, placebo-controlled, crossover	0.25mg: 1.0mg: 2.5mg: Placebo: 740/682 Total completed: 513	19-65	F = 90% M = 10%	Completed (Jul 10, 1995)	USA C	131/1 (F) [133/1]
S2WA3012 RM1996/00188/00	A Randomized, Double-Blind, Placebo-Controlled, Parallel Study to Evaluate the Efficacy, Safety and Tolerability of Oral Naratriptan in an Adolescent Migraine Population	To evaluate the efficacy and safety of 0.25mg, 1.0mg, and 2.5mg oral naratriptan compared to placebo in the treatment of a single migraine attack, in adolescent subjects.	Double-blind, randomized, placebo-controlled, parallel design	0.25mg: 91/78 1.0mg: 90/78 2.5mg: 80/70 Placebo: 89/74 Total completed: 299	12-17	M = 46% F = 54%	Completed (Sep 1, 1995)	USA C	143/1 (F) [145/1]

* Report also included in Clinical Data Section

* Report also included in Human Pharmacokinetics and Bioavailability Section

* Investigators are listed, by protocol, in Appendix 1 to this table

** Randomized patients may not have received any treatment; Total completed are those who completed all treatments and follow-up examinations which were required by protocol.

*** Formulations Codes are contained in Appendix 2 to this table: A. Oral Solution, B. White Tablet, C. Green Tablet, D. Injection presented as ampules (mannitol), E. Injection presented as ampules (NaCl),

E** Radiolabelled injection presented as ampules (NaCl), F. Radiolabelled Oral Solution, G. Injection presented as prefilled syringes (mannitol), H. Nasal solution

Date of first treatment

Nov 14, 1996