

Subgroup analyses for the primary outcome measure			
Parameter	Placebo (N=91)	1.0 mg (N=85)	2.5 mg (N=87)
Race-non White (N)	1	1	2
Sex-male (N)	10	11	11
headache relief at 4 hours	20%	55%	73%
Sex-female	81	74	76
headache relief at 4 hours	40%	65%	62%
Age ≤ 30 (N)	23	19	14
headache relief at 4 hours	52%	47%	79%
Age > 50 (N)	62	52	56
headache relief at 4 hours	32%	67%	64%
Age 31 to 50 (N)	6	14	17
headache relief at 4 hours	33%	71%	47%

Secondary outcome measures: The sponsor described over 50 analyses on secondary outcome measures. This included analyses at each time point in the study and for each variable. I have reviewed these outcome measures and have summarized some of them in the following table.

Summary of secondary outcome measures			
	Placebo (N=91)	1.0 mg (N=85)	2.5 mg (N=87)
Headache free rate at 4 hours	22%	44%	46%
% of patients with meaningful relief within 4 hours	37%	61%	66%
Mean time to meaningful relief (minutes) without censoring	82	92	97
% of patients using a rescue medication	66%	46%	34%
Time (minutes) to use of rescue medication	264	397	383
Number of patients with recurrence/ Number of patients with headache relief at 4 hours (%)	14/34 (39%)	15/55 (27%)	9/55 (16%)*

*P value < 0.05 when compared to placebo


Randy Levin, M.D.
Neurology Team Leader

Safety Review of Clinical Data

Application Information:

NDA 20-763

Sponsor: Glaxo Wellcome Inc.

Reviewed: Amendments to Original NDA

November 21, 1997 - Response to Agency Comments From Teleconference of 10/22/97

December 1, 1997 - Additional Response to Comments From 10/22/97

December 15, 1997 - Clarifications of Responses Previously Submitted

December 17, 1997 - Corrected Tables Previously Submitted

Generic Name (Code Name): Naratriptan Hydrochloride (GR85548)

Drug Characteristics:

Pharmacologic Category: 5-hydroxytryptamine, (5-HT₁) receptor agonist

Proposed Indication: Acute treatment of migraine attacks

Safety Review Conducted By: Michael J. Sevka, M.D.

Background: During the safety review of the original NDA, a number of issues were identified which needed further clarification or data analyses. These issues were communicated to the sponsor via teleconference on October 22, 1997 between Drs Levin and Sevka of the FDA and Ms Babo, and Drs Asgharnejad, Austin, Murray and O'Quinn of the sponsor. The FDA's comments were summarized by the sponsor and faxed to the Agency the following day for confirmation by the FDA. The current submission consists of 23 attachments:

- Attachment 1 - proposed labeling revised according to comments provided by the Agency during the October 21, 1997 teleconference;
- Attachment 2 - draft labels and cartons for the 1mg tablet;
- Attachment 3 - diskette containing pdf and WORD files of the proposed package insert; and a summary of non-US regulatory actions;
- Attachment 4 - core prescribing information for reference;
- Attachments 5-23 - sponsor's responses to the Agency's comments of October 22, 1997.

Subsequent to the November 21, 1997 submission, the sponsor submitted additional clarifications and information, on 1st, 15th and 17th of December 1997, which had been omitted or needed further clarification from the November 21, 1997 submission.

A) December 1, 1997 - Additional information for Comment 10 regarding AEs in patients who were concurrently exposed to naratriptan and sumatriptan or DHE. Response to Comments From 10/22/97.

B) December 15, 1997 - Final printed labeling and additional information for Comments 4, 8,10,15 and method of calculation of mean number of attacks.

C) December 17, 1997 - Corrected listings for Comment 1 regarding patient withdrawals and a narrative for patient 1546 in study S2WA3003 who had elevated LFTs

Revised Labeling

The review of the new proposed labeling was conducted by making proposed revisions on the copy accompanying the approval letter.

Non-US Regulatory Actions

Naratriptan has undergone the Mutual Recognition Procedure with Sweden acting as the Reference Member State with approval granted March 10, 1997. The application was withdrawn from the Mutual Recognition Procedure in _____ for unspecified reasons, where a national application is under consideration. Applications are pending in _____.

Response To Comment 1

The sponsor was asked to provide a listing of patient discontinuations for three studies which had a large number of patients listed as "other" as the reason for discontinuation, particularly for naratriptan-exposed patients. The listings provided on November 21, 1997 were incorrect, with a considerable number of patients listed as having participated in incorrect studies. These listings were resubmitted in corrected form on December 17, 1997. The corrected listings are summarized below. Examination of this summary appears to show no report of a patient which may have experienced a particularly concerning adverse event with the exception of patient -3549 (S2WB3004) who is reported to have "increased epilepsy duration." previously reviewed, and patient-1546 (S2WA3003) who is reported as having increased LFTs. In the sponsor's December 17, 1997 submission, the sponsor reports the actual LFT levels and that this patient had mildly elevated LFTs at screening which remained at the same levels after treating an attack with 2.5mg.

Numbers of Patients Reported as Withdrawing For the Following Reasons			
	S2WA3003	S2WB3002	S2WB3004
Adverse Events	13	21	11
Failure To Return	20	21	12
Lack of Efficacy	14	61	69
Failed to Treat Attack in Specified Time	0	136	5
Others	122	41	18
Total discontinuations	169	280 -	115

For study S2WA3003, the breakdown for "other" might be classed as follows:

- 91 - sponsor ended study
- 10 - too few headaches within the protocol window
- 6 - withdrawal of consent (3 for unspecified reasons)
- 3 - patient moving to another community
- 3 - pregnancy
- 2 - protocol violations

Of the remaining 7, the following 4 were randomized to naratriptan - difficulty completing diary, unstable potassium, uncooperative attitude, reluctance to use medication.

For study S2WB3002, the breakdown for "other" might be classed as follows:

- 10 - protocol violations
- 9 - too few attacks
- 6 - withdrawal of consent for unspecified reasons
- 4 - pregnancy/ contraceptive reasons
- 4 - medication dispensing error
- 2 - lost medication

Of the remaining 6, the following 4 were randomized to naratriptan - increased LFTs (pt.-1546), non-compliance, suspected sulfa allergy, vomiting during attack.

For study S2WB3004, the breakdown for "other" might be classed as follows:

- 6 - pregnancy/ contraceptive reasons
- 3 - increased headache frequency
- 3 - too few attacks

Of the remaining 6 all were taking naratriptan in this open-label trial - simple analgesic works. appeared to have increased epilepsy duration (pt.-3549), imigran better, leaving country, non-compliance, protocol violation.

There does not appear to be an excess of concerning AEs classified as "other."

Response To Comment 2

The sponsor was asked to:

- a) reconcile differences in patient counts and identities between Tables 74 (Serious AEs), 75 (AEs leading to withdrawal) and Chart 18 (Serious AEs);
- b) clarify the discontinuation status of patients 3879, 4094, and 4078 (S2WB3004);
- c) provide narratives for those patients exposed to naratriptan within 48 hours of withdrawal;
- d) analyze patient withdrawing due to AEs by gender, age, and AE frequency.

Table 75 was updated to correctly identify 5 miss-identified subjects and include additional omitted subjects from clinical pharmacology studies. Additionally subject 5122 (S2WB3006) who experienced an increase in blood pressure to 180/110 after 1.5mg Sub Q., also originally omitted, was added bringing the total withdrawn due to AEs to 92 instead of 91 as originally counted. New Table 75 still does not match the number of patients listed as having withdrawn due to serious AEs. I matched patients and noted that 3 are incorrectly listed on Table 75 and Chart 18 as withdrawn due to serious AEs but have "other action" status listed on Table 74 - (S2WB2002- 1833 was rechallenged without events & 1025 was hospitalized for cholecystitis 4 months after last dose) and (S2WA3012- 3352 hospitalized 13 days after last dose for dehydration and later diagnosed with lupus).

Patients 4094 (fracture of both arms) and 4078 (severe retrosternal chest pain) did not withdraw from study due to serious AEs and Table 74 was changed to reflect "no action taken." Patient 3879 was determined to be a withdrawal due to a serious AE (hospitalized for depression) and was added to the appropriate Tables.

Narratives were provided for 67 patients (33 from oral clinical trials) who experienced an AE within 48 hours after exposure to naratriptan and were subsequently withdrawn. No substantive new information was noted except for the following:

- a) 2 patients experienced abdominal pain along with other AEs (S2WB3002: 2667 - lasting 6.5 hrs; 2871 - lasting 25 minutes);
- b) approximately 5 patients were withdrawn in association with increased blood pressure;
- c) approximately 4 patients were withdrawn in association with chest pressure/tightness without post-event ECG changes;
- d) the majority of withdrawals were due to the constellation of AEs, "characteristic sensations";
- e) from Table 72, 5 cases were reclassified as syncope while on naratriptan.

No analysis was submitted by age, gender, or AE frequency of patients withdrawing due to AEs.

Response To Comment 3

For labeling the sponsor was to revise Table 69 (1% Treatment Emergent Adverse Events) for from placebo controlled clinical trials including S2WA1007. The number of patients listed per treatment group in Table 69 appears to be correctly calculated for the revised table and the sponsor has included the requested new adverse event groupings for pain/pressure sensations (throat/neck symptoms; other pain; chest symptoms; other pressure/tightness) and for characteristic sensations (temperature sensation; paresthesia). The following AEs dropped out of Table 69: headaches; throat & tonsil signs/symptoms; musculoskeletal pain; muscle stiffness/ tightness & rigidity; sweating. Tables 71-73 for frequent, infrequent and rare adverse events have also been reconstructed including data from S2WA1007 and the long-term trial S2WB3004 and including the new adverse event groupings. For Tables 71-73 the sponsor has used a denominator of 3557 patients which appears to include the double-exposure of 77 patients who were known to be exposed to naratriptan in more than one clinical trial.

Response To Comment 4

The sponsor was asked to provide an evaluation of AEs by gender and age. The sponsor has resubmitted the analysis submitted in the original NDA for overall AEs by age and gender and argues in the December 15, 1997 submission that further sub-setting by individual AEs is not warranted since the patient population is relatively homogeneous (84% females and 77.5% between the ages of 18-50 years) and AE rates were small (none greater than 3% except nausea and vomiting) so that further sub-setting would not provide a meaningful information.

Response To Comment 5

The sponsor was asked to provide to additional AE tables using the same data as for Table 69. One table for events occurring "within" 24 hours of treatment exposure and another for events occurring "after" 24 hours of treatment exposure. The table for "within" 24 hours is very similar to Table 69 except that tinnitus drops out and menstruation symptoms and viral respiratory infections move to the table of AEs for "after" 24 hours.

Response To Comment 6

The sponsor was asked to regroup certain AE groupings for Tables 69-73. This was done for Comments 3 and 5. Additionally the sponsor indicates in this submission that the AE coding dictionary submitted in the original NDA was not specific to naratriptan as was previously conveyed to the Agency. A replacement dictionary which is specific to adverse events reported during the naratriptan clinical program has been included in this submission.

Response To Comment 7

The sponsor was asked to prepare narratives for patients who experienced AEs of specific clinical concern. The sponsor indicates that neutropenia and tetany were not present in the database. According to the narratives, the majority of these AEs were mild to moderate in severity, not serious and led to only one withdrawal (S2WA3003-0801 - skin rash over lower left arm lasting 6 hours). The withdrawal status of 2 other patients is unknown, with one of these subjects (S2WB2004-0813) experiencing transient thrombocytopenia, from normal to 52,000 uL at 4 hours, after naratriptan exposure, returning to normal 7 days later. Two other patients (S2WB2002: 1152; 1154) each experienced 2 episodes of mild - moderate hemolytic anemia that did not lead to withdrawal and that reportedly had no relevant lab test abnormalities except that one subject had elevated leukocyte counts. Both patients are listed in Appendix 16 - list of AEs as having had mild or moderate hemoglobinuria.

Response To Comment 8

The sponsor was asked to submit line listings for patients with laboratory values, vital signs, and ECGs which were considered adverse events by the investigator. No clear new signal is detected from examining these listings. ECG listings were submitted December 15, 1997.

Response To Comment 9

The sponsor was asked examine the AEs observed during high doses of Sub Q administration and observed in the 77 patients from S2WB3004 who exceeded the total daily 5mg dose. The sponsor reports no new types of AEs observed in the subgroup from S2WB3004. In comparing Table 28 (oral controlled clinical trials) to Table 61 (Sub Q controlled clinical trials) from the ISS it becomes apparent that the rank order for AE groups oral naratriptan is "gastrointestinal," "neurology," "characteristic sensations," and "non-site specific" but for Sub Q is "characteristic sensations," "non-site specific," "neurology," and "gastrointestinal." There is a dose response in both tables with higher frequencies of AEs as the dose increases.

Response To Comment 10

Responses to this comment were submitted on December 1 and 15, 1997. The sponsor was to review the database including subcutaneous studies to see if any patients were exposed to concomitant SSRIs or Sumatriptan or DHE or Ergot. For sumatriptan, 231 concomitancies for oral naratriptan were noted without any apparent increase in AEs; but for subcutaneous naratriptan 49 concomitancies were noted with chest symptoms in 8 patients (16%) in the concomitant group and 37 (5%) in the "any dose" naratriptan group and 3-9% across individual naratriptan dose groups. For DHE and ergot too few concomitancies were noted (DHE 5-oral and 5-Sub Q naratriptan; ergot 59 oral and 22 Sub Q naratriptan) to detect any trend. For Sumatriptan and DHE, information was submitted in the December 1, 1997 submission and for Ergot in the December 15, 1997 submission. For SSRIs the sponsor has resubmitted Table 106 from the ISS submission, the same review as submitted in the original NDA, which does not include the subcutaneous naratriptan database.

Response To Comment 11

The sponsor's clarification of certain treatment headings in certain Tables of the ISS are adequate.

Response To Comment 12

Regarding long-term laboratory data, the sponsor indicates that additional long-term laboratory safety data is being collected in 2 ongoing trials.

Response To Comment 13

The sponsor was asked to comment on the findings of increased pulmonary artery pressure observed in S2WB3009. The sponsor comments that the majority of patients that had increases in pulmonary artery pressure that were transient and within the range of normality (15-30/3-12). However, one subject (S2W0001423) who had elevated baseline pressures (66/30) experienced still further increases to 72-74/25-33. The sponsor reports no correlation between chest pain/discomfort and increase in pulmonary artery pressure.

Response To Comment 14

The sponsor was asked to provide narratives regarding the clinical outcome of patients exposed to naratriptan who experienced ST wave changes. Nine narratives were provided. One subject (S2WB2004 - B0904), previously described in the NDA had an abnormal baseline ECG, experienced a serious event thought to be likely to be due to coronary artery spasm. Another subject (S2WB3004-3637) had a normal baseline ECG and experienced palpitations after treating her 7th attack and was noted to have changes suggestive of ischemia after treating her 10th attack with 2.5mg, but went on to treat 14 additional attacks. Another subject (S2WB2004-1071) who had baseline changes due to possible ischemia but subsequent ECGs considered normal, again had changes at the final visit, 4 days after treatment, considered abnormal due to ischemia. Another patient (S2WB2004-1076) had normal baseline ECG which developed significant abnormality 3 days after treatment with 2.5mg. Four other subjects (C94-071: 001 & 002; S2WB2004: 0905 & 1324) had normal baseline ECGs but experienced non-specific T-wave changes post treatment. Patient 0905 was treated with 1mg. Finally, an additional patient (S2WB2004-0695) had a post-treatment abnormality not considered changed from baseline. This response to Comment 14 underscores the need for contraindicating naratriptan use in patients with ischemic or vasospastic cardiac disease.

Response To Comments 15, 16, 17

Responses are adequate for these comments and provide clarifications and corrections for data listings and tables from studies S2WB2003, S2WA3003 and S2WB3004.

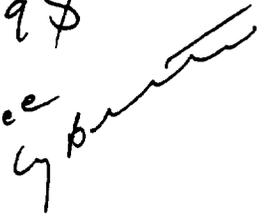
Calculation of Safety of Treatment Frequency

In the December 15, 1997 submission the sponsor indicates that the mean number of attacks per patient per month was 4.1 with 3.6 being the median. The sponsor indicates that this frequency was derived by first calculating the mean number of attacks treated per each individual patient per month and then obtaining summary statistics of these findings.

Summary:

The sponsor appears to have reasonably addressed concerns expressed in communications from the Agency so that an adequate safety profile for naratriptan can be described in labeling for safe use as described in the label.

 1/8/98
Michael J. Sevka, M.D.
HFD-120

1/8/98
I Agree


Safety Review of Clinical Data

Application Information:

NDA 20-763

Sponsor: Glaxo Wellcome Inc

Submission Date: December 4, 1996

Generic Name (Code Name): Naratriptan Hydrochloride (GR85548)

Proposed Trade Name: Unknown

Drug Characteristics:

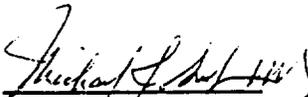
Pharmacologic Category: 5-hydroxytryptamine, (5-HT₁) receptor agonist

Proposed Indication: Acute treatment of migraine attacks

Dosage Form: Oral, green, D-shaped, 2.5mg tablets

Proposed Dosing: One 2.5mg tablet taken with fluids; repeated in 4 hours if headache returns for a maximum of 5mg in 24 hours.

Safety Review Conducted By:


Michael J. Sevka, M.D.

10/2/97


10/3/97

List of Reviewer Team Members For NDA 20-763:

- Efficacy.....Randy Levin, M.D.
- Safety.....Michael Sevka, M.D.
- Statistics.....Japobrata Choudhury, Ph.D.
- Pharmacology/Toxicology.....Robin Huff, Ph.D.
- Biopharmaceutics.....Iftexhar Mahmood, Ph.D.
- Chemistry.....Doris Bates, Ph.D.
- Consumer Safety Officer.....Lana Chen, R.Ph.

cc: Paul D. Leber, M.D., Director
Division of Neuropharmacological Drug Products

Summary of Naratriptan Safety Review

This review covers information submitted in the original NDA, the 4-month safety update, and all supplemental submissions submitted as of August 29, 1997. A list of these submissions can be found on page 60.

The sponsor is requesting approval to market naratriptan tablets for the treatment of acute migraine attacks and associated symptoms of migraine with and without aura in adults. The dosage proposed is 2.5mg with repeat of 2.5mg in 4 hours for recurrence, for a total daily dose of 5mg. According to the sponsor's counts (ISS Tables 7, 9 - Attachment 5) the ISS summarizes the safety experience from clinical migraine studies with naratriptan administration - orally (13,532 attacks treated by 3553 patients) and subcutaneously (1733 attacks treated by 814 patients) but the sponsor can not determine the exact number of patients that was exposed in more than one trial. The highest dose tested in oral clinical migraine studies was 10mg as a single administration and 2.5mg as repeated administration (2.5mg+2.5mg) in multiple attacks. The highest dose tested in subcutaneous clinical migraine studies is 10mg as a single administration and 5mg as repeated administration (5mg+5mg) in multiple attacks. In clinical pharmacology studies the highest dose tested was 25mg given orally to one healthy subject who experienced adverse events necessitating withdrawal. As of the 4-month safety update, for long-term exposure (Study Tables 13, 14 - Attachment 6), the sponsor indicates that 253 patients treated 2 or more attacks per month in 12 months with naratriptan 2.5mg (10376 attacks) or 2.5mg + 2.5mg (4842 attacks). According to my cumulative counts, across the NDA including the 4-month safety update, there were no deaths reported, 91 withdrawals due to adverse events, and 54 serious adverse events in 53 subjects; but patient accounting for the later two categories will need to be rechecked by the sponsor. The breakdown for the 91 adverse events resulting in withdrawal is: 36 from oral clinical migraine studies, 15 from the long-term oral clinical study, 24 from a subcutaneous clinical study, and 16 from clinical pharmacology studies. The breakdown for the 54 serious adverse events is: 19 from oral clinical migraine studies, 26 from the long-term oral clinical study, 7 from a subcutaneous clinical study and 2 from clinical pharmacology studies.

Across the NDA two body systems account for the majority of naratriptan's unintended effects - cardiovascular with increases in blood pressure and nervous with "characteristic sensations such as paresthesia, feeling of heaviness, warm/hot sensation." In clinical pharmacology studies, doses above 5 mg were associated with statistically significant increases in weighted mean and peak systolic and diastolic blood pressure but not change in heart rate. For example, in one trial (C92-055), the 20mg oral dose showed differences from placebo for 0-8hrs in weighted mean SBP/DBP (14/10mmHg) and peak SBP/DBP(12/9mmHg); and all doses of 5mg or greater also showed statistically significant differences from placebo but the magnitudes of blood pressure changes decreased as the dose decreased from 20mg to 5 mg. No statistically significant pressor effect was observed for the 2.5mg dose compared to placebo. No clear effect was noted on heart rate for any dose up to 15mg. A statistically significant dose response was observed for the 2.5mg-20mg dose range for weighted mean SBP and DBP (0-8hrs); but there appears to be the potential for considerable variability in the pressor response between individuals with similar systemic exposure. The pressor responses are similar during migraine periods compared to migraine-free periods (S2WA1007-Pt 1). Pressor responses are similar also in elderly compared to young when looking at magnitude of change from baseline since the elderly studied had higher baseline blood pressures compared to young (S2WB1002). Hypertensive patients had a similar or slightly exaggerated response compared to healthy subjects when looking at change from baseline compared to placebo but hypertensives had higher baseline values and there appeared to be a reduction in blood pressure for approximately the first 10 hours in hypertensives during placebo administration, presumably due to antihypertensive

medication (C94-036). In another study (S2WB3009), subcutaneous administration of 1.5mg also demonstrated naratriptan's ability to increase mean aortic pressure by approximately 8%, mean pulmonary artery blood pressure by 18% and to induce very small reductions in coronary artery lumen diameters. The most commonly reported adverse events in the clinical pharmacology trials are similar to those reported with sumatriptan and include headaches, drowsiness, dizziness, tingling, warm/hot sensation, feeling heaviness/tightness, and malaise and fatigue. In one trial one subject experienced a marked increase in BP (71/46mmHg), lightheadedness and loss of coordination after 25mg oral dose. In another trial, one experienced warm facial sensations, anxiety and vasovagal attack minutes after 5ug/kg IV requiring treatment with atropine and another experienced severe tingling and neck tension after 10ug/kg IV. Across clinical pharmacology studies, PR prolongation was noted in several subjects and QTc prolongation was noted in others prompting a request for statistical analyses of ECG intervals from serial ECGs obtained in clinical pharmacology studies where most serial measurements of ECG intervals were recorded. Review of these data is pending. Renal excretion is the main route of elimination and most likely predisposes to blood pressure elevation through increased systemic exposure. Patients with severe renal or hepatic impairment were not studied. No substantial drug interactions were detected.

In US placebo-controlled Phase III trials only drowsiness/sleepiness, tingling, warm/hot sensation, and malaise/fatigue occurred very slightly more frequently at doses of 2.5mg+2.5mg compared to placebo. In non-US placebo-controlled trials only paresthesia, malaise/fatigue and increased blood pressure appeared to occur at slightly higher rates at doses above 5 mg single doses; and only the following appeared at minimally higher rates in the 2.5mg dose groups compared to placebo: nausea, hyposalivation, pressure sensation, drowsiness/sleepiness, and malaise/fatigue. Events generally did not increase in the 2.5mg+2.5mg dose group compared to the 2.5mg single dose group. Although some laboratory data was collected during the long-term safety and efficacy trial, repeat laboratory determinations following completion of the trial was not required unless thought to be clinically indicated, resulting in the collection of limited laboratory data following long term exposure. Current human reproductive experience is limited to the birth of 5 healthy infants to women of poorly defined exposure but randomized to naratriptan during clinical trials.

In summary, naratriptan exposure rates can not be accurately determined by the sponsor but appear adequate. Naratriptan has a safety profile similar to that of sumatriptan, causing adverse events classed as "characteristic sensations" which are typical of 5HT agonists and pressor effects at oral doses of 5mg and above. Pressor effects are exerted on both the systemic circulation and the pulmonary artery following subcutaneous administration of 1.5mg. There were no deaths reported, 54 serious adverse events in 53 patients, and 91 withdrawals due to adverse events. Of the serious cases, 2 were severe chest pain occurring at the proposed dose which resolved spontaneously in 3-4 hours, one was heaviness and aching of all 4 limbs occurring after each of three 2.5mg doses administered in 24 hours, one was T-wave changes on ECG thought to be related to drug with a cause of coronary spasm 120 minutes following a 7.5mg dose, one was chest pressure lasting 12 hours after a 10mg dose, and one was general weakness and sweating 2-3 minutes following a 2.5mg subcutaneous dose. Review of ECG interval data is pending.

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Introduction

The sponsor seeks FDA approval to market naratriptan tablets for the treatment of acute migraine attacks and associated symptoms of migraine with and without aura; but does not seek approval for oral solution, subcutaneous, intravenous or intranasal formulations with which some clinical experience has been obtained and submitted for safety review. The sponsor's proposed labeling for naratriptan tablets specifically indicates that they are not for use in the management of hemiplegic or basilar migraine.

As of the time the 4-month safety update was submitted, approval had been granted in Sweden on March 10, 1997 for the 2.5mg tablet for use in adults 18-65 years of age with a recommended dose of 2.5mg followed by 2.5mg after 4 hours if needed, with a maximum 24 hour dose of 5mg. The European Union Mutual Recognition procedure is on-going with Sweden acting as the Reference Member State. Naratriptan is also under review in other countries which are not part of the mutual recognition procedure.

Overview of Development Program

According to the sponsor the development of naratriptan was undertaken because it is a potent, selective vascular 5-HT₁ (probably 5-HT_{1B/1D}) receptor agonist with similar pharmacologic properties to sumatriptan. The receptor subtype to which naratriptan binds is present on human cranial vessels (basilar artery and vasculature of the dura mater) so that naratriptan's antimigrainous effect is likely due to vasoconstriction of these arteries. Additionally, naratriptan is purported to act at 5-HT₁ receptors on the peripheral and central terminals of the trigeminal nerve which may contribute to its antimigrainous effect. The sponsor indicates that compared to sumatriptan, naratriptan has a longer half-life (6 hours versus 2 hours), greater bioavailability (60-70% versus 14%), greater lipophilicity and greater biologic potency (2-3 fold), and that these properties should provide therapeutic benefits which include longer duration of effect and lower incidence of headache recurrence. The sponsor also contends that the overall incidence of adverse events is lower with naratriptan than sumatriptan.

The naratriptan clinical development program began in the United Kingdom in November 29, 1990 with the administration of intravenous radiolabeled naratriptan and in May 10, 1993 with the administration of oral tablets. During the development program, clinical trials were conducted with two tablet formulations for the 2.5mg strength, a round white tablet and "D"-shaped green tablet; but the small differences in formulation are not viewed as having potential bioavailability consequences since dissolution profiles are so much alike¹.

Naratriptan does not have chiral centers or olefinic double bonds which would present a potential for optical isomerism or stereoisomerism; and there has been no evidence for polymorphic recrystallization.

The sponsor's Table 1 (Attachment 3) from the NDA summarizes the human clinical pharmacology and clinical trials and is attached as a photocopy along with a copy of proposed labeling. See the section, "Description of Naratriptan Clinical Development Program," below for more detail.

¹Verbal communication with the biopharmaceutics reviewer, Iftekhar Mahmood, Ph.D., on February 10, 1997.

Overview of Naratriptan Preclinical Experience

Receptor affinity: Naratriptan is a selective agonist for the 5-HT₁ receptor (probably 5-HT_{1B/1D}) with an affinity that is 3-6 times greater than that of sumatriptan. Preclinical studies have shown that naratriptan has low binding affinities for approximately 30 other receptor types including the following: alpha₁, alpha₂, beta₁, beta₂, dopamine₁, dopamine₂, muscarinic₁, muscarinic₂, nicotinic, central benzodiazepam, and opiate (delta, kappa, mu).

ADME: Absorption, distribution and excretion are reported to be similar in rats, mice, rabbits, dogs and human. The N-oxide metabolite is the major metabolite found in human urine. Following oral and IV administration to rat, drug related material is widely distributed throughout most tissues with low levels persisting in eye (presumably associated with melanin), testes, liver and kidney. In rat, drug related material can cross the placenta and can enter breast milk.

Animal Pharmacology Studies: In isolated coronary arteries from human and Cynomolgus monkey, naratriptan has caused contractions with a mean EC₅₀ of 170nM in humans and 30-47nM in Cynomolgus monkey. This effect is less (33±14% for humans and 25±6% for monkey) than the maximum contraction produced by 5HT.

In anesthetized dogs given IV naratriptan 1-1000ug/kg, dose-dependent carotid artery vasoconstriction lasting longer than 2 hours (following the highest dose) was observed with little change in systemic arterial blood pressure. Following IV administration to dogs at doses which cause carotid vasoconstriction, naratriptan causes small increases in vertebral and femoral vascular resistance. It also caused small increases in coronary vascular resistance (i.e. 33% compared to 184% for carotid artery) accompanied by a dose-dependent bradycardia; but injection directly into the coronary artery (0.03-300ug/kg) caused little or no acute effect on coronary blood flow, suggesting no direct coronary vasoconstrictor action.

In anesthetized dogs ECG changes were observed at ≥300ug/kg (slight increase in T wave amplitude) and at ≥30ug/kg (loss of P wave and ST segment shortening). These effects are reportedly slightly less than those observed following sumatriptan administration to dogs where doses of 10ug/kg caused some ECG change.

In anesthetized cat given IV naratriptan 10-100ug/kg, transient increases of 28-53mmHg in blood pressure were observed lasting 5-10 minutes with no effect on heart rate or ECG. The blood pressure increase was similar at 1000ug/kg IV.

In one of two conscious Cynomolgus monkeys, small decreases in arterial blood pressure after IV naratriptan 100-1000ug/kg and dosage-related decreases in heart rate were seen at 10-1000ug/kg, with increase in QT interval at 100-1000ug/kg. No significant effects on blood pressure or heart rate was observed in the other animal.

In conscious dog, oral and IV naratriptan induced tachycardia at systemic exposures about 4-5 times that seen in man after a 5mg oral dose.

Acute Animal Toxicity Studies: The maximum non-lethal dose was reported by the sponsor to be >1000mg/kg (oral) and ≈30-40mg/kg (IV) in mouse and ≈750mg/kg (oral) and ≈30-40mg/kg (IV) in rat. These oral doses were associated with signs of behavioral depression (prostrate posture) and effects on the

central nervous system (vocalization, aggression, unsteady gate and convulsions). Additionally, in rat, increase in testes weight, dilatation of the seminiferous tubules and changes in the head of the epididymies were observed following administration of oral doses of 340mg/kg with the sponsor declaring the no effect level for this finding at 170mg/kg.

Subchronic/Chronic Animal Toxicity Studies: In dogs, a 1 year (0-5mg/kg/day) oral gavage study reported clinical effects such as pupil dilation, corneal stippling, salivation, vocalization, aggressin and stiff hind legs. Also 2 dogs in the 5mg/kg/day group were reported to have repeated convulsive episodes and were killed on Days 270 and 290. Slightly prolonged QT interval developed in one male at 5mg/kg/day. Deep S waves were seen in one male in 5mg/kg/day group and deep Q-waves developed in 3 active treatment animals and 1 control animal.

In dogs, a 1 month (0-5mg/kg/day) oral gavage study showed similar clinical effects as the 1 year study but no convulsions were reported. Statistically significant increase in heart rate was noted at 2.25 and 5mg/kg/day levels. A statistically significant decrease (11%) in QT interval was reported in males with no abnormalities detected after recovery. In one male at the 2.25mg/kg level, a small, focal, monolateral corneal ulceration, microscopically characterized by diffuse keratitis was noted.

In rats, a 6 month (0-340mg/kg/day) oral gavage study showed similar clinical effects as the studies conducted in dogs with effects such as salivation, aggression, tenseness, and vocalization observed.

Special Animal Toxicity Studies: Tear film changes were observed in the dog which are thought to be pharmacologically mediated since these changes are blocked by administration of 5HT₁ antagonist and did not occur following direct instillation of naratriptan onto the cornea. Rabbit eye irritancy testing classified naratriptan as slightly irritant (Grade 2) to rabbit eye. Naratriptan demonstrated no antigenic potential in an active systemic anaphylaxis test and a homologous passive cutaneous anaphylaxis test in guinea pig. Naratriptan was shown to be low in skin sensitization potential and intact skin irritancy in guinea pig models.

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Safety Review Methods and Approach

The safety review was conducted relying predominantly on the paper version of the NDA with some reliance on the electronic Wordperfect^T version of the ISS and pivotal efficacy trials.

To evaluate accuracy of patient accounting and exposure, selected listings and tables of patients (e.g. randomization codes, safety population listing, withdrawal listings, serious adverse event listings) were compared to each other and to the information provided in the clinical study report (CSR) for several pivotal phase III trials and the ISS.

To evaluate the sponsor's adverse event (AE) coding, verbatim investigator terms were examined for mapping to subsumed preferred term and group term in the coding dictionary for the Integrated Summary of Safety (ISS) and clinical study report (CSR) for protocol S2WB3004 (long term safety protocol). Particular attention was focused on verbatims of AEs describing cardiovascular events, those generally associated with 5HT agonists, and those proposed for inclusion in labeling. Additionally, verbatim terms which denote potentially clinically important AEs not covered in the standard definition of serious were identified for further evaluation by the sponsor.

To evaluate the accuracy of the database, an audit was conducted to cross check selected data in the CRFs versus data presented in line listings and narratives for approximately 20% of the patients who withdrew due to AEs (i.e. patients for whom CRFs were already submitted). Additionally, an audit was conducted on the CRFs actually submitted versus those which are required to be submitted (i.e. deaths and withdrawals due to AEs) for omissions and patient identity.

Review Findings

General: Data is presented in the format of a standard NDA, with an ISE, ISS, and clinical study reports (CSRs) for each human clinical pharmacology and clinical migraine trial completed as of the data cut-off date. August 20, 1996. Study summaries are provided for ongoing clinical trials. In general information is provided in navigable format with tables of contents, abstracts/summaries, a body, and appended data tabulations - "Tables," "Appendices," "Attachments," and "Data Listings." Data tabulations presented in the body of the ISS are entitled "Charts" which are summations of data from "Tables" which are presented as attachments to the body of the ISS. Across clinical trials, presentation of addenda tend to appear in logical sequence but in some CSRs are difficult to locate because they are appended in very different sequences or data tabulations. Typographical errors are common. Some appended tabulations were not submitted and needed to be requested, while others were incorrect and needed to be replaced.

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Description of Naratriptan Clinical Development Program

The naratriptan clinical development program consisted of a total of 45 trials - 32 clinical pharmacology trials and 13 clinical trials in migraineurs. See the attached photocopy of Table 1 (Attachment 3) from the NDA which summarizes these 45 trials. The clinical development program has focused on only one indication, acute treatment of migraine attacks. All clinical trials were conducted in adult patients or healthy adult subjects except two:

- S2WA3012 (a completed trial in adolescent migraineurs which is reported as having failed to demonstrate efficacy); and
- S2WA1012 (a PK trial in adolescent migraineurs which is listed in the ISS as ongoing and which was prematurely terminated when the results of the adolescent efficacy trial failed to demonstrate efficacy).

Of the total 45 trials, 4 were ongoing or had not undergone data analysis at the time of data cut-off, August 20, 1996 and were not incorporated into the ISS but reported in the ISS as ongoing (2 clinical pharmacology - S2WA1012, S2WB3006; 2 clinical migraine - S2WB2005, S2WB3004). Of the 41 completed trials, the ISS incorporates data only from 39 completed US and non-US trials because the ISS excludes data from two completed Japanese PK tablet trials (total of 24 patients between the two trials). The sponsor indicates that these two Japanese PK trials were excluded because of database incompatibilities. The sponsor's Table 1 is attached listing all 45 trials and a brief description of each, completion status, and formulations used. One, 2-part clinical trial, S2WA1007, in migraineurs is listed as 2 separate trials because the trial designs for the two parts differ so much. Controlled and uncontrolled clinical trials in migraineurs are tabulated on pages 18-25 of Table 1 and clinical pharmacology trials are tabulated on pages 1-17 of Table 1. For protocol S2WA3003, Table 1 (page 18) omits the number of patients per treatment (randomized/treated at least once) in this placebo-controlled 4-way crossover clinical trial. This information is available in Table 43 of the CSR and is as follows: Randomization-740; Treated 0.25mg-593; 1mg-600; 2.5mg-590; placebo-606 with 514 patients listed as having treated 4 attacks.

Clinical Pharmacology Trials: The 30 completed clinical pharmacology trials incorporated in the ISS were conducted using the following formulations:

- nasal solution - 1 trial (dose range tested - 0.25mg-1.0mg);
- subcutaneous - 4 trials (dose range tested - 0.025mg-10mg);
- intravenous - 5 trials (dose range tested - 0.25 μ g/kg-1.5mg);
- oral solution or oral tablet - 24 trials (dose range tested - 0.5mg-25.0mg).

Two trials (C94-034 and C93-006) used both IV and oral formulations. Only 1 clinical pharmacology trial was conducted in the US (S2WA1003 - food effect on PK), with 3 conducted in Canada and almost all of the remainder in the United Kingdom.

Clinical Trials in Migraineurs: The trial designs of the 11 completed clinical trials in migraineurs incorporated in the ISS are summarized in the tables below. All these trials were conducted in multiple centers except S2WA1007 Pt-1 (#9 in the table below) which was conducted in one center as an open-label, cross-over, efficacy and PK trial in female migraineurs during a migraine attack and during a migraine-free period. These 11 trials were conducted using tablets - 9 trials, and subcutaneous injection - 2 trials. Of the 9 clinical trials using tablets, 7 are placebo-controlled with 2 trials also sumatriptan-controlled: 1 trial is only sumatriptan-controlled; and the remaining trial is open-label. Of these 7 placebo-controlled trials, 4 were conducted only in the US (S2WA1007 Pt-2; S2WA3001; S2WA3012; S2WA3003) testing doses ranging from 0.1mg to 2.5mg across trials and the remaining 3 non-US trials testing doses from 0.1mg to 10mg across trials. Of the 2 subcutaneous trials, both are placebo-controlled

and one is also 6.0mg SQ sumatriptan-controlled. The dose range of SQ naratriptan tested was 0.5mg-10mg across trials. None of the sumatriptan-controlled trials, oral or SQ, were conducted in the US.

Oral Naratriptan Clinical Migraine Studies						
1	S2WA1007 Pt-2	Single-Attack; Single Dose per Attack; Clinic-Based	DB	Parallel	PC	
2	S2WB2003	Single-Attack; Single Dose per Attack; Clinic-Based	DB	Parallel	PC	
3	S2WB2004	Single-Attack; Single Dose per Attack; Clinic-Based	DB	Parallel	PC	SC 100mg
4	S2WA3001	Single-Attack; Multi- Dose per Attack; Home-Based	DB	Parallel	PC	
5	S2WA3012	Single-Attack; Multi- Dose per Attack; Home-Based; Adolescents	DB	Parallel	PC	
6	S2WB3002	Multiple-Attack (x3); Multi- Dose per Attack; Home-Based	DB	Parallel	PC	SC 100mg
7	S2WA3003	Multiple-Attack (x4); Multi- Dose per Attack; Home-Based	DB	<u>Cross- Over</u>	PC	
8	S2WB3011	Multiple-Attack (x2); Multi-Dose per Attack; Home-Based	DB	<u>Cross- Over</u>		SC 100mg
9	S2WA1007 Pt-1	Single-Attack; Single-Dose per Attack; Clinic-Based; Cross-over to non-attack for PK	<u>Open Label</u>	<u>Cross- Over</u>		
Sub Q Naratriptan Clinical Migraine Studies						
1	S2WB2001	Single-Attack; Single-Dose per Attack; Clinic-Based	DB	Parallel	PC	SC 6mg
2	S2WB2002	Multiple-Attack (x3); Multi-Dose per Attack; Home-Based	DB	Parallel	PC	
<p>N.B.- Bolded Study Numbers Indicate Trials Conducted in the U.S. DB = Double-Blind PC = Placebo-Controlled SC = Sumatriptan-Controlled</p>						

Naratriptan Clinical Studies													
Naratriptan Doses Studied	0.1 mg	0.25 mg	0.5 mg	1.0 mg	2.5 mg	5.0 mg	7.5 mg	10.0 mg					
Oral Naratriptan Clinical Migraine Studies													
1	S2WA1007 Pt-2		0.25 mg		1.0 mg	2.5 mg				DB	Parallel	PC	
2	S2WB2003						5.0 mg		10.0 mg	DB	Parallel	PC	
3	S2WB2004				1.0 mg	2.5 mg	5.0 mg	7.5 mg	10.0 mg	DB	Parallel	PC	SC 100mg
4	S2WA3001	0.1 mg	0.25 mg		1.0 mg	2.5 mg				DB	Parallel	PC	
5	S2WA3012		0.25 mg		1.0 mg	2.5 mg				DB	Parallel	PC	
6	S2WB3002	0.1 mg	0.25 mg		1.0 mg	2.5 mg				DB	Parallel	PC	SC 100mg
7	S2WA3003		0.25 mg		1.0 mg	2.5 mg				DB	<u>Cross-Over</u>	PC	
8	S2WB3011					2.5 mg				DB	<u>Cross-Over</u>		SC 100mg
9	S2WA1007 Pt-1					2.5 mg				<u>Open Label</u>	<u>Cross-Over</u>		
Sub Q Naratriptan Clinical Migraine Studies													
1	S2WB2001			0.5 mg	1.0 mg	2.5 mg	5.0 mg		10.0 mg	DB	Parallel	PC	SC 6mg
2	S2WB2002					2.5 mg	5.0 mg			DB	Parallel	PC	

N.B. Bolded Study Numbers Indicate U.S. Trials: DB = Double-Blind; PC = Placebo-Controlled; SC = Sumatriptan-Controlled

Japanese Tablet PK Trials: Regarding the 2 Japanese tablet PK trials (548-01; 548-02) whose safety data were not incorporated into the ISS, only summary reports were submitted to the NDA. Trial 548-01 evaluated PK in 16 young healthy males (age 20-24) taking ascending single doses between 1-10mg or placebo. Trial 548-02 evaluated PK in 8 young healthy males taking placebo or naratriptan 5mg daily for 5 days. The English translations of the Japanese summary reports for each trial indicate that there were no apparent clinical problems for ECGs, clinical lab values and that there were no adverse events reported in naratriptan-treated patients. However, information from trial 548-01 indicates that a non-dose dependent, 10mmHg, statistically significant, elevation from baseline in systolic and diastolic blood pressure was considered attributable to drug at a dose of 5mg or higher. Information from trial 548-01 indicates also that no abnormalities were reported during optometric, slit lamp or fundoscopic testing.

Summary of Naratriptan Human Pharmacokinetics and Metabolism

Absorption: Absolute bioavailability in healthy subjects following 5mg tablet is 63% in men and

74% in women, with 34% and 35% lower AUC and C_{max}, respectively, in men compared to women (Protocol C94-034). Following a 5mg tablet, the C_{max} is 10.8ng/ml (95% CI: 9.4;12.3) in men and 16.6ng/ml (95% CI: 13.1; 21.0) in females with median T_{max} of 3.0 hours for both genders (Protocol C94-034). Absorption from tablets has been shown to be dose proportional from 2.5mg to 10mg in women (Protocol C93-070) and from 1mg to 10mg in Japanese men (Protocol 548-01). During a migraine attack the T_{max} is prolonged to 3.5 hours compared to 2.0 hours during the pain free period (Protocol S2WA1007 - Part 1). In elderly subjects (i.e. >65 years), naratriptan exposure, expressed as the mean AUC, following 2 doses of 2.5mg separated by 4 hours, is 32% greater than in young subjects (Protocol S2WB1002).

Metabolism: Following oral administration at least 5 metabolites have been detected in plasma and urine with an additional compound detected in urine (Report BDRR/96/0008/01). In vitro, using human liver microsome, naratriptan metabolism is inhibited by a variety of specific inhibitors of cytochrome P450 isoenzymes suggesting no single enzyme is responsible for its metabolism (Report GDM/95/113). Naratriptan does not inhibit a variety of cytochrome P450 isoenzymes at concentrations up to 100µg/ml (Report GDM/95/059) except for 26% inhibitory effect on CYP2D6 in microsomes from females at concentrations 100ng/ml to 100µg/ml, which are higher concentrations than those observed in plasma following a 2.5mg dose. Using male and female human liver microsomes, naratriptan does not interact in vitro with monamine oxidase A or B (Report GDM/95/128).

Distribution: In vitro binding to human plasma proteins ranges from 14.8%-26.3% at concentrations ranging from 50ng/ml to 1000ng/ml and is comparable between males and females (Report GDM/95/035).

Elimination: After oral administration approximately 30% of a dose is metabolized and approximately 70% of a dose is excreted as unchanged naratriptan (Protocol C94-007). Urinary excretion is the main route of elimination with 50% of a dose excreted as unchanged naratriptan in the urine (Protocol C94-007). The elimination half-life in normal healthy adults is approximately 6 hours (Protocol C94-034) and increases up to 20 hours (range 6.7-19.8) with mild to moderate renal impairment (Protocol C93-081) or up to 16 hours (range 7.6-15.9) with Child-Pugh class A or B hepatic impairment (Protocol C95-036). In elderly subjects, the mean half-life, following 2 doses of 2.5mg separated by 4 hours, is only 14% greater than in young subjects (Protocol S2WB1002). The half-life in adolescents is 4.9 hours (S2WA1012). There was no significant drug accumulation following daily administration for 5 consecutive days of 5mg or 10mg doses to females (Protocol C94-071) or 5mg doses to Japanese males (Protocol 548-02).

Pharmacokinetics Following Parenteral Administration: Following intravenous administration to healthy males, approximately 9% of the dose was eliminated in the feces and approximately 85% of the dose was eliminated in the urine with over 50% of the dose eliminated as unchanged naratriptan (Protocol W91-019). Following subcutaneous administration of single doses of 1mg-5mg to healthy male subjects, the T_{max} was 0.2 hours with a rapid decline over 2 hours during distribution and an approximate terminal elimination half-life of 4-6 hours with a range of 3.4-9.7 hours across doses (Protocol W91-013).

Range of Systemic Exposure: The table below shows the range, largest and smallest C_{max} and AUC of human exposure from across PK trials at the proposed maximum recommended daily dose (i.e. 5mg/day given as 2.5mg+2.5mg tablets 4 hours apart). It also shows the largest human exposure following administration of oral doses above 5mg per day and following parenteral administration.

Selected Naratriptan PK Parameters Expressed as the Geometric Mean in healthy subjects or migraineurs (Selected from Sponsor's Pharmacokinetic Tables 2-1 and 3-1)				
Protocol	Subjects	Dose	C _{max} (ng/ml)	AUC _{0-∞} (ng/ml.h)
S2WB1002	6M + 6F Young	2.5mg+2.5mg Tablet 4 hours apart	10.4	115.0
	6M + 6F Elderly	2.5mg+2.5mg Tablet 4 hours apart	11.9	152.3
S2WA1002	12M	2.5mg+2.5mg Tablet 2 hours apart	9.9	106.8
C93-081	6M + 2F	5mg Tablet	18.3	174.6
C93-070	23F	5mg Tablet	23.9	200.0
C94-034	12M	5mg Tablet	10.8	108.2
	12F	5mg Tablet	16.6	163.6
C92-055	6M	5mg Oral Solution	16.7	169.5
	6M	10mg Oral Solution	35.8	292.8
	5M	15mg Oral Solution	47.9	448.5
C93-060 * C _{max} for 2nd dose	8M	5mg+5mg Tablet 4 hours apart	18.6*	223.8
	8M	7.5mg+7.5mg Tablet 4 hours apart	28.9*	317.2
	8M	10mg+10mg Tablet 4 hours apart	33.1*	398.7
C93-006	3M	1.5mg IV Infusion	40.8	55.6
C94-034	11M	1.5mg IV Infusion	41.8	53.1
	12F	1.5mg IV Infusion	38.2	66.4
W91-013	6M	1mg Subcutaneous	10.1	29.7
	6M	2.5mg Subcutaneous	34.9	97.4
	6M	5mg Subcutaneous	43.1	120.0
W91-023	6M	10mg Subcutaneous	135.4	442.0
S2WB2001 ** AUC _{last}	8F	1mg Subcutaneous	13.8	31.5**
	7F	2.5mg Subcutaneous	35.5	74.2**
	4F	5mg Subcutaneous	82.4	181**
	6F	10mg Subcutaneous	207.1	324.6**

For contrast, the package insert for sumatriptan indicates that the mean Cmax concentrations are 51ng/ml following a 100mg oral dose and 75ng/ml following a 6mg subcutaneous dose.

Description of the ISS Population and Extent of Exposure

The ISS population is summarized in the NDA in (See attached photocopies):

Table 2 - Oral Demographics

Table 3 - SubQ Demographics

Table 6 - Extent of Exposure - All Naratriptan

Table 7 - Extent of Exposure - Oral Naratriptan in Clinical Migraine Studies

Table 8 - Extent of Exposure - Oral Naratriptan in Clinical Migraine Studies - By Dose

Table 9 - Extent of Exposure - Subcutaneous Naratriptan

Table 10- Extent of Exposure - Subcutaneous Naratriptan - By Dose

Population Size: From ISS Table 7, as of the data cut-off date for the NDA, the ISS population consisted of 3553 patient-exposures (including double-exposures) to various doses (range 0.1mg to 10mg) of oral naratriptan in oral clinical migraine studies.

Single Attack, Single-Dose, Placebo-Controlled, Clinic-Based, Migraine Studies-----	624
(S2WA1007- pt 2; S2WB2003; S2WB2004)	
Multiple Attack, Single-Dose, Placebo-Controlled, Home-Based Migraine Studies -----	717
(S2WA3001; S2WA3012)	
Multiple Attack, Multiple Dose, Placebo-Controlled, Home-Based Migraine Studies--	1544
(S2WB3002; S2WA3003)	
Sumatriptan-Controlled Migraine Studies -----	239
(S2WB3011)	
Uncontrolled Open-Label Migraine Studies -----	429
(S2WB3004; S2WA1007- pt 1)	
	Total-----3553

Sponsor-Acknowledged Double-Exposures From July 25, 1997 Submission-----77

Total Estimate of Unique Subjects Exposed From Clinical Migraineur Studies--3476

It is not clear how the sponsor handled double-exposures in computing exposure rates, AE rates, and other descriptors of the ISS population.

Double-Exposures of Patients Across Oral Clinical Trials in Migraineurs

On June 27, 1997 and July 14, 1997, the sponsor was asked to map and enumerate the numbers of patients who participated in more than one clinical trial with naratriptan. The sponsor's responses dated July 3, 1997 and July 25, 1997 indicated that patients who participated in more than one clinical study had a different subject number assigned for each study in which they participated. The sponsor's examination of their databases (comparing birth date, race, sex and patient initials for US trials and comparing patients initials, birth date, sex, country and investigator for non-US trials) identified 37 (US) and 40 (non-US) subjects, as being exposed to naratriptan in more than one oral clinical trial in migraineurs, not including subjects who had exposures to placebo in the second trial. The sponsor indicates that the true number of patients exposed for second time in S2WB2004 can not be accurately determined because the occurrence of previous naratriptan exposure was not documented on the case report forms for that trial. The sponsor's ability to document 4 double exposures in S2WB2004 stems from investigators electing to document prior exposure in the "comments" section of the CRFs. The CSR for S2WB2004 shows that a total of 454

subjects were randomized to treatment with various doses of naratriptan, 91 others to placebo and 98 others to sumatriptan. If all subjects in trial S2WB2004 were exposed to naratriptan in more than one trial then the smallest estimate for unique subjects exposed to oral naratriptan would be 3099. The sponsor has not addressed the question of double-exposures in subcutaneous clinical trials. The sponsor did not comment on double exposures across formulations (e.g. SubQ to oral).

According to ISS Table 8 (Attachment 5), the number of patients exposed to doses higher than 2.5mg during oral clinical migraine studies are: 5mg (122), 7.5mg (93), and 10mg (129). The numbers exposed to one or more doses of 1mg and 2.5mg are condensed into the table below and is not adjusted for known double exposures. Table 8 also lists the sumatriptan exposure as 271 but the CSR lists 241.

Extent of Oral Naratriptan Exposure During Clinical Migraine Studies (condensed from Table 8 of the ISS)		
Study Type	1mg dose (# patients) (total # doses)	2.5mg dose (# patients) (total # doses)
Single Attack/ Single Dose	124 124	122 122
Single Attack/ Multi-Dose	195 247	197 236
Multi-Attack/ Multi-Dose	822 1492	802 1413
Controlled with Only Sumatriptan	0 0	239 340
Uncontrolled	5 27	429 10354
Totals	1146 1890	1789 12465

Duration of Exposure to Naratriptan in Oral Clinical Pharmacology and Clinical Migraine Studies:

Long term intermittent exposure to naratriptan is limited to 1 study population - trial S2WB3004 with 417 patients who treated multiple attacks over varying periods of time up to 1 year. As of the date of NDA submission, the sponsor indicated that 276 patients treated ≥ 2 attacks per month over a 6 month period with oral naratriptan 2.5mg (+2.5mg). (See Table 5 from S2WB3004 - Attachment 6).

In the 4-month safety update the sponsor also reports in study Table 13 (Patient Exposure to Oral Naratriptan) that **253 patients treated 2 or more attacks per month in 12 months with naratriptan 2.5mg** and that 185 patients treated more than 36 attacks in 12 months with oral naratriptan 2.5mg. See attached photocopy of Table 13 (Attachment 6). It is not clear why Table 13 lists only 407 patients as the total number of patients treated with 2.5mg naratriptan during a 12 month period when the safety population is declared to be 417. To describe exposure the sponsor prepared the table reproduced below from page 31 of the final study report. The sponsor states that included in the extent of exposure and the safety analysis, are 266 treated attacks in 97 patients which occurred beyond the protocol's definition of 12 months.

Treatment	Number of patients treated with oral naratriptan	Number of attacks treated with oral naratriptan during the 12 months defined for this study and beyond
Oral Naratriptan 2.5mg	409	10376
Oral Naratriptan 2.5mg +2.5mg	360	4842
Oral Naratriptan 1.0mg	10	66
Oral Naratriptan 1.0mg +1.0mg	6	17
Total*	417*	15301

* A patient may be counted under more than one dose, but an attack is counted only once

**Details for this table were obtained from Tables 1, 14 and 19 of protocol S2WB3004

Please see the review of the 4-month safety up-date for patient accounting for study S2WB3004.

Consecutive day exposure is limited to 3 study populations:

- Protocol C94-071, 12 females received 5mg naratriptan for 5 consecutive days and 11 of these females also received 10mg naratriptan for 5 consecutive days with at least 5 day washout between periods;
- Protocol 548-02, 6 Japanese males exposed to 5mg naratriptan daily for 5 consecutive days;
- Protocol 548-01, 12 Japanese males exposed to 3 courses of naratriptan daily for 5 consecutive days in dose range from 1mg to 10mg with at least 1 week washout between periods.

Age: Of the patients/subjects in the ISS, 300 were adolescents in protocol S2WA3012 with the remainder older than 18 years up to:

- 66 years in oral placebo-controlled migraine trials
- 65 years in subcutaneous placebo-controlled migraine trials
- a few up to 77 years in a clinical pharmacology trial in elderly
- a few up to 69 years in a clinical pharmacology trial of cardiac hemodynamics.

Gender: 54-94% female across oral placebo-controlled migraine trials and 86-87% across subcutaneous placebo-controlled migraine trials

Race: approximately 95% Caucasian in oral placebo-controlled migraine studies and approximately 97% Caucasian in subcutaneous placebo-controlled migraine trials.

Migraine Type: approximately 80% without aura in oral placebo-controlled migraine studies and approximately 85% without aura in subcutaneous placebo-controlled migraine trials.

General Exclusion/ Inclusion Criteria Across Clinical Trials: In general, the ISS population with which clinical experience has been obtained consisted of healthy adult subjects and adolescent and adult migraineurs none of whom was to have significant cardiovascular disease. Participants were generally **excluded** from clinical migraine trials if they had conditions or situations described as the following:

- history of ischemic heart disease (i.e. angina, MI, silent ischemia on ECG)
- Prinzmetals angina
- ECG evidence of ischemic heart disease
- symptoms consistent with ischemic heart disease
- history of coronary vasospasm

- atherosclerotic disease
- peripheral vascular disease
- Raynauds disease
- hypertension, BP $\geq 165/\geq 95$ mmHg, whose definition was later changed to BP $\geq 140/\geq 90$ mmHg
- evidence of severe hypertension (i.e. fundus changes)
- use of certain concomitant meds: ergotamine, DHE, methysergide, sumatriptan, SSRIs, lithium and MAO inhibitors
- renal or hepatic impairment
- epilepsy or brain lesions
- some protocols also excluded congenital heart disease and arrhythmia requiring medication

Participants were generally included if the frequency of their migraine attacks was 1-6 attacks per month for the previous 2 or 6 months.

Audit Findings

The audit findings of the paper version for patient exposures (randomization, exposure, withdrawals) across oral clinical migraine studies generally showed close agreement between declared numbers of exposed patients in the body of the clinical study report and the addenda (tables or appendices or data listings) for the clinical study reports but could be discrepant by a patient or two. Additionally, in comparing the patient accounting and exposure estimates in the CSR to those in Table 7 (Extent of Exposure to Oral Naratriptan) there appears to be a discrepancy of only a few patients in Table 7. In comparing ISS Tables for discontinuations due to adverse events and serious adverse events there appear to be several patients that are poorly accounted for across tables (e.g. appear on one Table but not another where they would be expected to appear) and that merit further examination by the sponsor. The number of patients exposed to naratriptan used as the denominator for Table 69 (Proposed Treatment Emergent AE Table for Labeling) were confirmed by adding the number of patients listed in the exposure tables from the 4 component placebo-controlled clinical migraineur trials but it is unclear why AE data from study S2WA1007-Pt are not included in this table since its design is similar to the other 4 trials combined in the table.

CRFs for 3 subjects who appear to have been withdrawn due to AEs have not been submitted. Audit of agreement between the content of the case report forms (CRFs) and the database for 20 subjects who were withdrawn due to a serious adverse event showed no substantive discrepancies between the content of the narratives and the CRFs.

Examination of the mapping of the adverse events in the adverse event coding dictionary (Appendix 1 of ISS) showed that the sponsor should re-examine some of the mapped verbatim terms and reexamine AE rates for these terms (See Section on AE mapping).

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Deaths

Overall, the sponsor reports no deaths associated with this NDA. Please see also the section below discussing dropouts regarding follow-up of patient dropouts.

Dropouts/ Withdrawals

Accurate accounting of patient withdrawals is complex. Table 75 of the ISS lists a total of 80 subjects as having been withdrawn due to adverse events from across clinical and clinical pharmacology studies; but CRFs for 84 subjects were submitted with the additional 4 CRFs for 4 additional patients (C93-070 - Subjects #07 and #22; WHP:9006 - Subjects #03 and 04) from clinical pharmacology studies. These 4 subjects were omitted from Table 75. Of the 84 subjects who withdrew due to an AE, 45 came from oral clinical migraine studies. 15 came from clinical pharmacology studies and 24 were from protocol S2WB2002 in which subjects were given subcutaneous naratriptan.

Table 11 (Attachment 7) in the ISS displays patient disposition and discontinuation from individual oral studies across the ISS. It presents the numbers of patients and percentages of withdrawn treated patients under three reasons for withdrawal: "adverse event," "lack of efficacy" or "other." 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%). It is not clear what these dropouts listed under "other" represent across trials. Additionally, for those "other" dropouts which may be classified as "lost to follow-up" or "failed to return to clinic," it is not certain 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 are not responsible for patient discontinuation. Similar to Table 11 is Table 12 (Attachment 7) for patients exposed to subcutaneous naratriptan, which shows similar uncertainty for study S2WB2002.

Table 74 in the ISS lists patients who experienced serious adverse events. Several subjects did not have their correct subject identifying number listed but rather treatment number. Two of these subjects are S2WB3004-05007 (corrected ID number-4094) and S2WB3004-04008 (corrected ID number-4078). These two subjects are listed as having discontinued study drug on Table 74 but are not listed in Table 75 as a withdrawal if in fact they discontinued study drug due to an adverse event and have no case report forms submitted. It is not clear what their withdrawal status is.

Narratives for patients who discontinued due to adverse events are presented in Appendix 2 of the ISS. The sponsor has provided narratives for only those patients who discontinued due to serious adverse events and not for all 84 patients who discontinued.

In the ISS the sponsor provides Charts 19-21 (summarized from Table 7 of the ISS) which list dropouts from oral clinical pharmacology and clinical trials whose reason for withdrawal was considered by the investigator to be drug-related but the sponsor provides no chart of all dropouts regardless of ascribed drug-relatedness nor a summary or discussion 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.

Adverse Event Collection Methods

In general, adverse events were collected in single dose clinic-based studies from spontaneous reporting and by querying the patient. In two of the multiple-attack home-based studies and the long term study, patients were to record AEs on their diary cards. In the remaining oral naratriptan multiple-attack home-based study, AEs were collected at each clinic visit and patients were phoned every 1-2 weeks for AE collection. For the analysis of AEs, the only AEs counted were those 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 study drug administration may not be true AEs. Additional analyses of AE rates using a definition of an AE such as an event which occurred within 48 hours of study drug administration is not provided.

Adverse Event Mapping

The sponsor indicates that serious adverse event narratives (Appendix 2 of ISS) and serious adverse event listings (Table 74 of ISS - photocopy attached) were created from data frozen as of August 20, 1996 in the sponsor's Worldwide Product Safety and Pharmacovigilance Department (WPSP). Adverse event incidence tables and other patient listings in the ISS were produced from separate databases created from case report form data frozen as of August 20, 1996. Since the WPSP data base is continually updated with follow-up information, the sponsor indicates that data discrepancies in details of events may exist between the WPSP database and the case report form database. Additionally, the sponsor indicates that slight variations in the presentation of adverse event data may exist due to differences in the coding dictionaries used in the two databases. The databases created from the case report forms were coded using two coding dictionaries, MIDAS and SYMPKEY, which are Glaxo Wellcome developed dictionaries. MIDAS and SYMPKEY were later linked by mapping SYMPKEY-coded adverse events to MIDAS so that the final adverse event reporting in the ISS is considered MIDAS by the sponsor. **All oral clinical studies in migraineurs were coded in MIDAS. The two clinical subcutaneous studies were coded in SYMPKEY; and clinical pharmacology studies were coded in either MIDAS OR SYMPKEY with subsequent mapping of SYMPKEY-coded studies to MIDAS.**

Both the MIDAS and SYMPKEY dictionaries that were actually used for naratriptan trials were modifications of the MIDAS and SYMPKEY dictionaries to account for a new body system category, "Characteristic Sensations," which includes adverse events which occur more frequently with 5HT₁ agonists. These adverse events include warm/hot sensation (including facial flushing), paresthesia, tingling, cold sensation, pressure sensation, feeling of tightness, feeling of heaviness, numbness, feeling strange, burning/stinging sensation, tight feeling in the head, prickling sensation, hot and cold sensation, and dysesthesia.

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 below.

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 sedation 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"

The sponsor indicates in a submission dated August 29, 1997 that the AE coding dictionary submitted in the original paper version of the ISS (Appendix 1 - Volume 194) is specific for only naratriptan studies and that for each investigator's text term listed there is at least one patient, and possibly more than one, in

naratriptan studies with that AE reported. 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.

"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"

Serious Adverse Events

The sponsor summarizes serious adverse events in Chart 18 which summarizes Table 74 (Attachment 8) of the ISS and reports 42 serious adverse events from oral and subcutaneous trials. Ten serious AEs are listed as resulting in patient withdrawal. Fourteen cases were from long-term trial S2WB3004 (n.b. 12 additional cases from this trial were submitted in the 4-month safety update and reviewed there). One case is from S2WB3009, an open label trial at doses of 1.5mg subcutaneous naratriptan.

Number of serious cases treated only with sumatriptan: 3
 Number of serious cases treated only with placebo: 2
 Number of serious cases treated with naratriptan and sumatriptan: 1
 Number of serious cases treated with naratriptan alone or naratriptan/placebo: 36
 Number of serious cases by gender: 36 females; 6 males
 Number of serious cases by age in years: 1- <20; 1- ≥20<30; 12- ≥30<40; 17- ≥40<50; 11- ≥50

Causality was rated as probable, possible or almost certain in 10 cases (1 was on sumatriptan), unlikely or unrelated in 30, and unknown in 2. The sponsor states they are in agreement the investigator's assessment of all serious adverse events except one, patient #1525 in S2WB2002, who experienced extrasystoles, chest pressure, heat sensation and dyspnea one month after completing the trial.

Number of Serious Cases Involving Specific Naratriptan Doses (From Chart 18 of ISS)										
Naratriptan dose in mg (oral and subcutaneous)	0.1	0.25	1	1+ 2.5	1.5	2.5	3.75	5	7.5	10
total # of cases (# which are Sub Q cases)	1	2	5	1	1 (1 SQ)	18 (3 SQ)	1	5 (4 SQ)	1	2
total # of cases causally related by investigator (# which are Sub Q cases)					1 (1 SQ)	2 (1 SQ)	1	3 (2 SQ)	1	1

While comparing Chart 18 (Serious AEs) to Table 74 (Serious AEs) to Table 75 (Withdrawals Due to AEs) in the ISS, it was noted that 10, 11, and 13 patients, respectively, were listed as discontinuing study treatment or withdrawing due to serious AEs.

Summaries of Narratives for Serious AEs

The narratives for the 42 serious adverse events are summarized below and 10 cases of pregnancy are summarized in the section on human reproductive experience. From the narratives of the 37 patients with serious AEs exposed to naratriptan or naratriptan/placebo or naratriptan/sumatriptan, it was noted that 5 patients experienced events for which no other condition is listed which could be responsible for the event. These 5 cases might be considered cardiovascular in origin or chest discomfort associated with 5HT agonist use. Two cases occurred following doses greater than 5mg (i.e. 7.5mg; 10mg); and one case of general weakness and sweating occurred within a few minutes of 2.5mg subcutaneous naratriptan. The numbers preceding each case description below represent the sequence of the narrative in Appendix 2 of the ISS.

Associated events for which no other condition is listed which can be viewed as causal (5 Patients)

9-- (ID-B0904) 40 yo symptomless female had ECG showing variable T-wave flattening (Lead II) at 120 minutes after naratriptan 7.5mg dose and borderline ST segment sagging (Lateral Leads) with increased heart rate to 100 bpm at about 240 minutes post-treatment; pre-treatment ECG showed T-wave inversion (Lead III); hospitalized for investigation and for unresolved migraine; ECG was still abnormal the following morning and in the afternoon 2 days post treatment; cardiac enzymes remained normal; follow-up stress test normal; evaluation of ECG results by independent cardiologist considered T-wave changes related to drug with a likely cause of coronary spasm (Case: B0004718).

10-- (ID-B1182) minutes after 10mg dose, 54 yo female experienced mild chest pressure lasting 12 hours; hospitalized; ECG had no signs of ischemia and cardiac enzymes were normal (Case: B0005966).

24-- (ID-3882) 30 hours after treating third attack with second dose of naratriptan 2.5mg, during an open-label study, 46 yo female had moderately severe chest pain radiating down her arm which resolved after 3 hours without treatment; ECG 7 days later and CPK were normal; pre-study and post study use of sumatriptan without problems (Case: B0013081).

28-- (ID-4078) 2 days after the last dose, during an open-label study, 49 yo female hospitalized for severe chest pain which resolved spontaneously within 4 hours; both ECG and enzymes were normal (Case: B0038459).

36-- (ID-1429) 51 yo female with a history of chest pain during attacks, was hospitalized for general weakness and sweating 2-3 minutes after the 1st dose of subcutaneous 2.5mg of naratriptan; ECG and cardiac enzymes were normal (Case: B0001978).

Associated with neoplasms (3 patients):

- 2-- (ID-96) 48 yo female with pre-existing melanoma (Case: A0040262).
18-- (ID-03282) 43 yo male hospitalized 3 days after treating second attack for excision of hypercalcemia-inducing benign parathyroid adenoma (Case: B0035830).
40-- (ID-1801) 47 yo female with breast cancer diagnosed weeks after experiencing AEs after treating her first attack (AEs: dysphagia, sore neck, lightheadedness, weakness, lethargy and increased sensitivity of the head eyes and hearing). The narrative indicates the condition was unresolved but it is unclear if the narrative refers to breast cancer or AEs (Case: B0001879).

Associated with hospitalizations for surgery (6 patients):

- 16-- (ID-03012) 30 days after last naratriptan dose, 32 y.o. female hospitalized for ovarian cyst surgery (Case: B0035693).
22-- (ID-3758) 41 yo female after treating 8 attacks, hospitalized for repair of umbilical eventration (Case: B0038444).
26-- (ID-4044) 3 days after last naratriptan dose, 39 y.o. female hospitalized with peritonitis and hemorrhaged ovarian cysts for hysterectomy and bilateral oophorectomy (Case: B0034647).
29-- (ID-4089) 4 days after last naratriptan dose, 35 y.o. female hospitalized for hysterectomy and bilateral oophorectomy to reduce the number and severity of menstrual migraines (Case: B0036854).
35-- (ID-1025) 4 months after last naratriptan dose, 34 y.o. female hospitalized for cholecystitis and cholecystectomy (Case: B0002718).
37-- (ID-1515) 2 months after last naratriptan dose, 39 y.o. female hospitalized for dilatation and curettage for pre-existing menorrhagia (Case: B0006564).

Associated with hospitalizations for other conditions (7 patients)

- 4-- (ID-407) 5 days after last naratriptan dose, 27 y.o. female patient with paraplegia due to spina bifida had UTI, nausea, and vomiting treated with oral antibiotics, 6 days later hospitalized for IV antibiotics for pyelonephritis (Case: A0039656).
6-- (ID-3352) 13 days after last naratriptan dose, 17 y.o. female hospitalized with vomiting and dehydration, elevated white count, malar rash, urinalysis showing hematuria/ proteinuria/ bacteria, later diagnosed with lupus nephritis (Case: A0039646).
7-- (ID-S0015) 26 hours after exposure to naratriptan, 43 yo male, with history of iritis reported severely painful left eye, diagnosed and treated for flare-up of iritis, subsequently hospitalized (Case: B0012593).
11-- (ID-01692) 3 hours after 0.25mg for second attack, 35 yo female had severe neck pain and vomiting; 8 hours later developed fever following second naratriptan dose; hospitalized and treated with diazepam and alizapride with resolution in 3 days; event attributed to viral infection (Case: B0017063).
23-- (ID-3879) following unstated quantity of naratriptan exposure, during an open-label study, 33 yo female was hospitalized for severe depression, but continued in the study (Case: B0039480).
25-- (ID-4038) 4 days after last naratriptan dose, 56 y.o. male hospitalized for flue-like illness, cellulitis of leg, malaise, nausea and treated with antibiotics (Case: B0038244).
33-- (ID-3757) 57 yo female, during an open-label study, was hospitalized for increased depression with insomnia and asthenia after treating one attack (Case: B0014312).

Associated with severe migraine (4 patients)

- 5-- (ID-615) 1-5 days after a dose (0.1mg - 2.5mg) of naratriptan, 38 yo female hospitalized on 3 occasions for migraine exacerbation unresponsive to outpatient therapy (Case: A0017299).
27-- (ID-4061) 52 yo female, during an open-label study, hospitalized after 5th and 9th attack for severe migraine and treated with pethidine each time, but continued in the study (Case: B0036499).

34-- (ID-3858) 41 yo female, during an open-label study, was hospitalized for migraine crisis when she vomited the second dose of naratriptan while treating an attack (Case: B0035686).

39-- (ID-1743) 51 yo female hospitalized for severe exacerbation of migraine with nausea and vomiting after treating 2nd attack with placebo + 5mg subcutaneous; symptoms resolved in 4 days; withdrawn from study (Case: B0001241).

Associated with other possible conditions (5 patients)

8-- (ID-B0328) 1 day after naratriptan, 31 yo female developed a severe infection in her lower lip from where test samples of unspecified variety had been taken; treated with cefuroxime with resolution (Case: B0008352).

20-- (ID-04382) 40 yo female with history of right eyelid drooping with migraines, treated St. attack with sumatriptan and second with naratriptan; after naratriptan noticed residual right sided facial numbness and drooping right eyelid; on hospitalization had normal CT of brain and orbits, carotid ultrasound, EMG and Tensilon test; diagnosed as 7th nerve palsy 16 days after 2nd attack; ptosis noted to increase and numbness to recur with migraine attacks (Case: B0037060).

21-- (ID-03727) following unstated quantity of naratriptan exposure, during an open-label study, 42 yo female was hospitalized for 5 days for anxiety attributed to increased work pressure, but continued in the study (Case: B0040598).

30-- (ID-4094) 50 yo male, during an open-label study, during an accident fractured right wrist 8 hours after treating 36th attack and the left wrist during a second accident after treating 38th attack; nature of accidents not described (Case: B0039576).

42-- (ID-01417) 51 yo female non-patient volunteer, with suspected coronary artery disease, undergoing angiographic testing to monitor coronary artery diameter following 1.5 subcutaneous naratriptan, was hospitalized for severe headache attributed by the investigator to the "stress of having an angiogram" (Case: B0036321).

Association remote from active drug exposure (4 patients):

1-- (ID-760) 18 days after last naratriptan dose, 46 y.o. female hospitalized with palpitations, chest pain, shortness of breath, dizziness, pulmonary congestion and bradycardia thought to be due to nadolol (Case: A0011682).

3-- (ID-2589) 15 days after last naratriptan dose, 35 y.o. female hospitalized with vomiting, fever, dehydration, weakness and swollen right parotid gland, thought to be due to viral infection (Case: A0039667).

19-- (ID-03348) 48 days after last naratriptan dose, 31 y.o. male hospitalized and diagnosed with small bowel obstruction and gastric ulcer (Case: B0036234).

38-- (ID-1525) one month after study completion, 53 yo female reported chest pressure, light dyspnea, and tachycardia occurring several times per day and only at rest; ECG revealed trigeminal extrasystoles with repeat ECG 2 months later normal; no exercise stress test performed; chemistry, CBC and thyroid tests were normal; symptoms attributed by cardiologist to work stress and menopause (Case: B0003679).

Associated with Overdose But Total Daily Dose Less Than 5mg (2 patients)

31-- (ID-4114) 47 yo female, reported as an overdose during an open-label study because of taking 3.75mg instead of 2.5mg, and experienced "stronger" drowsiness which resolved in 12 hours (Case: B0035691).

32-- (ID-4167) 49 yo female, reported as an overdose during an open-label study because of taking 3 separate doses of 3.75mg, 5mg, 5mg on 3 separate days instead of 2.5mg, and experienced "weird dreams," drowsiness, and lightheadedness/drowsiness on each of the days (Case: B0036920).

Associated with failure of event recurrence following rechallenge (1 patient)

41-- (ID-1833) 47 yo female experienced being "out of the world" and "problems to wake her up" 30 minutes after 1st dose of 5mg subcutaneous naratriptan; but 2nd dose without the same symptoms (Case: B0000414).

Overall Adverse Events

The sponsor indicates that the adverse event profile of naratriptan was compiled from only those AEs which occurred at any time after exposure to study drug. Each subject was counted only once regardless of experiencing one or multiple events and each subject was counted once for each type of event.

For trials where 2 doses were permitted to treat an attack, a "total dose" analysis was used in preparing AE tables. This analysis presents data in 2 columns per dose level (2.5mg; 2.5mg+2.5mg) where the first column shows AE rates for subjects who took only one dose and the second column shows the rate for subjects who used 2 doses regardless if the event took place after the first or second dose. However, at the request of the FDA, Tables 30-32 in the ISS (AEs in all oral placebo-controlled trials) have an additional column for AE rate for all subjects randomized and received any dose, regardless of whether one or two doses were taken.

The sponsor proposes the use of AEs listed in ISS Tables 69-73 for labeling:

Table 69 (Treatment Emergent Adverse Events in Placebo-Controlled Trials - at least 1% in naratriptan and greater than placebo);

Table 70 (AEs Equal or More Common in Placebo);

Tables 71-73 (Frequent, Infrequent, Rare Adverse Events in all oral clinical trials).

For these tables the sponsor submitted replacement tables on June 26, 1997 to reflect "total dose" analysis along with revised portions of proposed labeling. According to the sponsor, Tables 69-73 originally submitted to the NDA reflected a "Dose-at-Event" analysis which the sponsor says was the analysis used in NDA 20-626 for Imitrex[®] (sumatriptan) Nasal Spray. According to the sponsor, "Total Dose Analysis" is what was used in the NDA for naratriptan. Revised Tables 69-73 and accompanying letter are attached (Attachment 10).

Tables 69 and 70 include AEs from 4 pivotal placebo-controlled oral clinical trials in adults (S2WB2004; S2WA3001; S2WB3002; S2WA3003). AEs from S2WA1007- Part 2 were not included in these tables although it is a placebo-controlled trial at 1mg and 2.5mg doses.

For the revised version of Table 69 the sponsor has removed 2 events, "nasal signs and symptoms" and "throat and tonsil signs and symptoms" indicating that these categories are too general and clearly not related to study drug administration.

Table 70 (AEs Equal or More Common in Placebo) has only one AE listed, "vomiting" - placebo - 9.0%; placebo-placebo - 6.2%; 1mg - 4.1%; 1mg+1mg - 8.1%; 2.5mg - 4.9%; 2.5mg+2.5mg - 6.6%.

Tables 71-73 provided AE rates for labeling frequent, infrequent and rare AEs. Initial versions were compiled from only placebo-controlled trials and compares placebo rates versus rates for all naratriptan doses as a group. Revised versions of Tables 71-73 include adverse events from all oral clinical trials (controlled and uncontrolled; adult and adolescent) regardless of naratriptan dose. This raises the extent of patient exposure only for naratriptan from 2885 to 3557 and not placebo exposure.

I have examined the revised portion of the proposed label and note that all the AEs listed in these tables were included in the proposed labeling except those which the sponsor has elected to exclude because they were already included in Table 69, were too general to be informative, were not reasonably associated with the drug, were repetitious, or occurred only with placebo. None of the sponsor's deletions appeared to be unreasonable. A photocopy of the sponsor's letter listing the deletions is attached to Tables 69-73 (Attachment 10).

The table below is condensed from Table 31 in the ISS which looked at adverse events in all oral placebo-controlled trials to show only the doses listed and only those events which occurred at a rate of 1% or greater in any of the active treatment columns. The 4 shaded events appear to occur at slightly greater rates in active treatments compared to placebo rates. Of the AEs in the table below, malaise & fatigue occurred at a higher rate in both (1mg; 2.5mg) the active treatment groups compared to placebo. Hyposalivation, drowsiness & sleepiness, and musculoskeletal pain occurred at very slightly higher rates in the 2.5mg dose groups compared to placebo. Tingling may have occurred at very slightly higher absolute numbers in both active treatment groups (i.e. 12 patients in each vs only 3 patients in placebo), although the percentages barely reflect this.

Naratriptan Adverse Events ≥1% in Any Active Treatment Column - All Oral Placebo-Controlled Clinical Trials Note: Total Dose Analysis Trials - S2WA1007 Pt2: S2WA3001; S2WA3003; S2WA3012 S2WB2003; S2WB2004; S2WB3002 (Condensed from Table 31 in ISS)									
	Placebo Taken	Placebo +Placebo Taken	Placebo +Placebo Randomized	1mg Taken	1mg + 1mg Taken	1mg + 1mg Randomized	2.5mg Taken	2.5mg + 2.5mg Taken	2.5mg + 2.5mg Randomized
Number of Patients Who Took ≥ 1 Dose	846	187	930	910	314	1141	919	267	1121
Nausea	49 (6%)	9 (5%)	56 (6%)	47 (5%)	25(8%)	69 (6%)	56 (6%)	12(4%)	68 (6%)
Vomiting	77 (9%)	11 (6%)	81 (9%)	51 (6%)	18 (6%)	69 (6%)	51 (6%)	18(7%)	69(6%)
Hyposalivation	3 (<1%)	0	3 (<1%)	3 (<1%)	2 (<1%)	5 (<1%)	10(1%)	0	10(<1%)
Dizziness	15(2%)	1(<1%)	10(1%)	10(1%)	1 (<1%)	11 (<1%)	21(2%)	4(1%)	25(2%)
Migraines	21(2%)	2(1%)	23(2%)	21(2%)	5(2%)	26(2%)	18(2%)	1 (<1%)	19(2%)
Drowsiness & Sleepiness	8 (<1%)	0	7 (<1%)	6 (<1%)	3 (<1%)	9 (<1%)	15(2%)	3 (1%)	18(2%)
Warm/hot Sensation	8 (<1%)	1 (<1%)	4 (<1%)	8 (<1%)	1 (<1%)	9 (<1%)	10 (1%)	4 (1%)	14 (1%)
Tingling	2 (<1%)	1 (<1%)	2 (<1%)	7 (<1%)	5(2%)	12 (1%)	9 (<1%)	3 (1%)	12 (1%)
Malaise & Fatigue	8 (<1%)	0	7 (<1%)	11 (1%)	6(2%)	16 (1%)	23 (3%)	3 (1%)	26(2%)
Sensitivity to Noises	14(2%)	0	14(2%)	9 (<1%)	3 (<1%)	12 (1%)	6 (<1%)	4 (1%)	10 (<1%)

Ear Nose & Throat infections	9 (1%)	0	9 (<1%)	13 (1%)	2 (<1%)	15 (1%)	8 (<1%)	1 (<1%)	9 (<1%)
Musculoskeletal Pain	6 (<1%)	1 (<1%)	6 (<1%)	5 (<1%)	4 (1%)	8 (<1%)	10(1%)	3 (1%)	13 (1%)
Photophobia	18 (2%)	0	18 (2%)	6 (<1%)	4 (1%)	10 (<1%)	13 (1%)	2 (<1%)	15 (1%)

The table below is condensed from Table 34 in the ISS which looked at adverse events in oral U.S. placebo-controlled trials to show only the doses shown and to show only those events which occurred at a rate of 1% or greater in any of the active treatment columns. The 4 shaded events appear to occur at slightly greater rates in active treatments compared to placebo rates.

Naratriptan Adverse Events ≥ 1% in Any Active Treatment Column - Oral <u>U.S.</u> Placebo-Controlled Clinical Trials Note: Total Dose Analysis; Contains Adolescent Data Trials - S2WA1007 Pt2; S2WA3001; S2WA3003; S2WA3012 (Condensed from Table 34 in ISS)						
	Placebo	Placebo +Placebo	1mg	1mg +1mg	2.5mg	2.5mg +2.5mg
Number of Patients	633	187	626	208	634	188
Vomiting	68(11%)	11(6%)	48(8%)	16(8%)	46(7%)	14(7%)
Nausea	45(7%)	9(5%)	38(6%)	21(10%)	42(7%)	11(6%)
Noise Sensitivity	14(2%)	0	7(1%)	3(1%)	6(<1%)	4(2%)
ENT Infections	9(1%)	0	10(2%)	2(<1%)	8(1%)	1(<1%)
Migraines	20(3%)	2(1%)	19(3%)	5(2%)	17(3%)	1(<1%)
Dizziness	7(1%)	1(<1%)	3(<1%)	1(<1%)	16(3%)	2(1%)
Drowsiness/Sleepiness	5(<1%)	0	4(<1%)	1(<1%)	8(1%)	3(2%)
Tingling	1(<1%)	1(<1%)	6(<1%)	4(2%)	7(1%)	3(2%)
Warm/Hot Sensation	0	1(<1%)	4(<1%)	1(<1%)	4(<1%)	3(2%)
Malaise/Fatigue	1(<1%)	0	3(<1%)	1(<1%)	10(2%)	1(<1%)
Temperature Regulation Disturbances	1(<1%)	0	0	2(<1%)	2(<1%)	2(1%)
Photophobia	18(3%)	0	4(<1%)	4(2%)	12(2%)	2(1%)

The table below is condensed from Table 37 in the ISS which looked at adverse events in oral non-U.S. placebo-controlled trials to show only the doses listed and to show only those events which occurred at a rate of 2% or greater in any of the active treatment columns. The non-U.S. placebo-controlled trials tested doses above 5mg per day. The shaded events appear to occur at slightly greater rates across active treatments compared to placebo rates. A dose response is noted for doses greater than 5mg in 24 hours for the following AEs (underlined below): a) paresthesia, b) malaise and fatigue, c) increased blood pressure

and possibly a slight dose response for d) tingling, e) muscle pain f) throat & tonsil discomfort/pain, g) abnormal ECG, and h) chest pressure/heaviness.

Naratriptan Adverse Events ≥2% in Any Active Treatment Column - Oral <u>Non-U.S.</u> Placebo-Controlled Clinical Trials Note: Total Dose Analysis Trials - S2WB2003; S2WB2004; S2WB3002 (Condensed from Table 37 in ISS)								
	Placebo	1mg	1mg +1mg	2.5mg	2.5mg +2.5mg	5mg	7.5mg	10mg
Number of Patients	213	284	106	285	79	122	93	129
Nausea	4(2%)	9(3%)	4(4%)	14(5%)	1(1%)	5(4%)	4(4%)	5(4%)
Vomiting	9(4%)	3(1%)	2(2%)	5(2%)	4(5%)	3(2%)	1(1%)	2(2%)
Hyposalivation	0	1(<1%)	1(<1%)	5(2%)	0	2(2%)	2(2%)	3(2%)
GI Discomfort/ pain	1(<1%)	0	0	1(<1%)	2(3%)	1(<1%)	1(1%)	1(<1%)
Diarrhea	3(1%)	4(1%)	2(2%)	1(<1%)	0	1(<1%)	0	0
Abdominal Discomfort/ pain	1(<1%)	2(<1%)	2(2%)	3(1%)	0	1(<1%)	0	0
Warm/ hot Sensation	8(4%)	4(1%)	0	6(2%)	1(1%)	4(3%)	2(2%)	2(2%)
Paresthesia	3(1%)	1(<1%)	0	2(<1%)	0	2(2%)	5(5%)	2(2%)
Cold Sensation	1(<1%)	2(<1%)	1(<1%)	1(<1%)	1(1%)	0	2(2%)	0
Pressure Sensation	2(<1%)	3(1%)	1(<1%)	5(2%)	0	2(2%)	0	4(3%)
Feeling of Heaviness	2(<1%)	2(<1%)	1(<1%)	3(1%)	1(1%)	2(2%)	0	3(2%)
Numbness	2(<1%)	3(1%)	2(2%)	0	0	1(<1%)	0	2(2%)
Tingling	1(<1%)	1(<1%)	1(<1%)	2(<1%)	0	1(<1%)	1(1%)	2(2%)
Feeling of Tightness	0	1(<1%)	0	1(<1%)	1(1%)	2(2%)	0	1(<1%)
Burning/ Stinging Sensation	0	1(<1%)	0	0	0	2(2%)	1(1%)	0
Dizziness	8(4%)	7(2%)	0	5(2%)	2(3%)	2(2%)	2(2%)	7(5%)
Headaches	3(1%)	3(1%)	0	4(1%)	1(1%)	4(3%)	1(1%)	1(<1%)
Vertigo	2(<1%)	4(1%)	2(2%)	3(1%)	1(1%)	2(2%)	1(1%)	4(3%)
Drowsiness & Sleepiness	3(1%)	2(<1%)	2(2%)	7(2%)	0	2(2%)	1(1%)	4(3%)
Tremors	2(<1%)	1(<1%)	2(2%)	1(<1%)	1(1%)	0	1(1%)	1(<1%)
Migraines	1(<1%)	2(<1%)	0	1(<1%)	0	2(2%)	0	0
Malaise & Fatigue	7(3%)	8(3%)	5(5%)	13(5%)	2(3%)	5(4%)	10(11%)	13(10%)
Disturbance of odor and taste	0	1(<1%)	0	2(<1%)	0	0	0	2(2%)
Musculoskeletal Pain	4(2%)	3(1%)	3(3%)	7(2%)	2(3%)	3(2%)	1(1%)	2(2%)

Muscle Stiffness Tightness & Rigidity	0	0	1(<1%)	3(1%)	2(3%)	1(<1%)	0	1(<1%)
Muscle Pain	0	0	0	1(<1%)	0	0	1(1%)	2(2%)
Viral Ear Nose & Throat Infections	1(<1%)	1(<1%)	2(2%)	2(<1%)	0	1(<1%)	0	0
Throat & Tonsil Signs and Symptoms	1(<1%)	0	0	1(<1%)	2(3%)	0	1(1%)	1(<1%)
Throat/Tonsil Discomf. & Pain	0	0	1(<1%)	0	0	1(<1%)	0	2(2%)
Palpitations	3(1%)	2(<1%)	2(2%)	1(<1%)	0	0	0	2(2%)
Increased Blood Pressure	1(<1%)	1(<1%)	0	1(<1%)	0	1(<1%)	3(3%)	2(2%)
Abnormal ECG	0	0	0	1(<1%)	0	0	2(2%)	1(<1%)
Viral Respiratory Infections	2(<1%)	6(2%)	0	3(1%)	0	0	0	1(<1%)
Chest Pressure/Heaviness	4(2%)	0	1(<1%)	1(<1%)	1(1%)	0	0	5(4%)
Skin Rashes	0	0	2(2%)	0	0	0	0	0

AEs by Demographics

Tables 96-105 of the ISS present overall incidence of AE rates and percent of patients experiencing a particular AE in all placebo-controlled oral clinical trials (all adult and adolescent) by subgroup analysis for age, gender, and ethnic origin. Attached is Table 96 (Attachment 11) from the ISS [Occurrence of AEs (subgroup analysis) All Placebo-Controlled Studies - Oral Naratriptan]

Age (12-17; 18-30; 31-40; 41-50; 51-65): slight trend for a decrease in AEs with increase in age in double-dose active treatment groups.

Gender: female patients appear to have slightly higher rates of overall AEs compared to males which might be explained by pharmacokinetic differences (i.e AUC 34% and C_{max} 35% greater; Clearance 51% lower in females).

Ethnic origin: no meaningful conclusion can be derived because so few non-Caucasian patients enrolled in any trial; no more than 26 non-Caucasian patients were observed in any one treatment cell. No discussion of patients experiencing a particular AE by subgroups is presented although the sponsor prepared Tables 98 and 101 for age and gender respectively, to compare these subgroups.

Overall incidence of AE rates is also presented in Table 96 for weight (< or ≥ 75 Kg), pre-treatment headache duration (≤ or >4 hours), presence of aura, prophylaxis medication use, oral contraceptive use, and smoking habits (current, ex-smoker, non-smoker).

Overall the sponsor concludes that age, weight, headache duration, presence or absence of aura, prophylaxis use, and tobacco use do not appear to affect the overall incidence of AEs in naratriptan treated patients. A slightly lower rate of AEs was reported in 2 dose treatment groups who did not use oral contraceptives perhaps due to lower naratriptan clearance in oral contraceptive users. Female patients appear to report a slightly higher incidence rate than males; and no meaningful conclusion can be derived for influence of ethnic origin.

AEs by Duration of Use

For incidence of AEs over "time" please see review for Protocol S2WB3004, the only long-term safety study, in the review of the 4 month safety update.

AEs by Disease State

Hepatic Failure (S2WB1004) - an open-label, single-dose, parallel group study was conducted in 8 hepatically impaired (6- Child-Pugh A; 2 -Child-Pugh B) and 8 healthy subjects who each received 2.5mg of naratriptan. Eight post treatment AEs were reported by 4 subjects. All reported AEs were considered mild or moderate and no serious AEs were reported. One healthy subject is reported to have developed paroxysmal atrial fibrillation with aberrant ventricular conduction on the ECG 4 hours post dosing and a single ventricular extrasystole 30 minutes post dosing with additional ventricular extrasystoles at 29 hours post dosing. One hepatically impaired subject had leucocytosis attributed to pancreatitis along with hypokalemia. No clinically significant deviations in laboratory measurements or ECGs were attributed to naratriptan by the investigator. Increases in weighted mean systolic and diastolic blood pressures were observed in both groups and viewed as not clinically significant by the investigator. Examination of individual blood pressure responses (Appendix 5 of the study report) showed that 2 impaired patients had the following peak responses from baseline: subject 5 - 127/77 to 157/92mmHg at 4hrs; subject 16 - 121/77 to 156/94mmHg at 6hrs.

Renal Failure (C93-081) - an open-label, single-dose, parallel group study was conducted in 15 renally impaired (8- mild- GFR 40-75ml/min; 7 moderate - GFR 15-39ml/min) and 8 healthy subjects who each received one dose of 5mg (healthy and mild impairment) or 2.5mg (moderate impairment) of naratriptan. No serious AEs were reported. A total of 5 mild AEs were reported in 4 subjects only in the mild impairment group - dry mouth, diarrhoea, nausea and vomiting. No clinically significant deviations in laboratory measurements were attributed to naratriptan by the investigator. Clinically significant asymptomatic changes in blood pressure without changes in ECGs were noted by the investigator in 3 subjects with mild impairment -

subject #5 - 149/92 to 168/108mmHg (AUC-185; Cmax-16.9ng/ml; T_{1/2}-7.6hrs);

subject #10 - 137/95 to 158/108mmHg (AUC-640; Cmax-76.8ng/ml; T_{1/2}-12.1hrs);

subject #22 - 141/86 to 180/115mmHg (AUC-446; Cmax-27.8ng/ml; T_{1/2}-10.6hrs).

No statistical analysis was conducted of the blood pressure data but compared to the healthy group, the mild impairment group which had greater exposure (5mg - geometric mean AUC: healthy-173; mild-335) appeared to have greater increases in blood pressure. Peak increase in systolic blood pressure above baseline for 0-4hrs was 4-13mmHg in healthy vs 0-36mmHg in mild impairment.

Hypertension - Please refer to the section for summary of special studies.

Adverse Events and Concomitant SSRI Use

The sponsor did not conduct clinical trials to specifically look for serotonin syndrome-like symptoms but did examine part of the database for patients taking SSRIs and having serotonin syndrome-like symptoms. The entire clinical database was not examined. According to Table 106 all oral clinical trials were examined except S2WA1007 (Part 1) and neither of the clinical subcutaneous trials appear to be examined. From the database that was examined, the sponsor shows in Table 106 that, of the SSRI-user patients 27% (60/225) on naratriptan and 29% (37/127) on placebo had any adverse event compared to non-SSRI-user patients (31%-naratriptan; 27%-placebo). Appendix 11 (attached) lists 8 subjects who had any one of serotonin syndrome-like symptoms and footnotes the following symptoms as characteristic of the syndrome: mental confusion, euphoria, agitation, sedation, difficulties in concentration, dysarthria,

myoclonus, chills, shivering, dystonia, muscle cramping and weakness, diarrhea, sweating, malaise and fatigue, cognitive function disorder, fever. The footnote also refers to a citation for serotonin syndrome-like symptoms, Cephalgia 1996;16:323-7, which lists the following symptoms: mental status and behavioral changes (agitation, excitement, hypomania, obtundation), motor system involvement (myoclonus, hemiballismus, tremor, hyperreflexia, motor weakness, dysarthria, ataxia) and autonomic symptoms (fever, chill, diarrhea). Of these 8 patients, 3 patients had been on placebo, and 2 other patients had all events which occurred 3 days or more after naratriptan exposure. The remaining 3 subjects experienced the following AE code (AE text):

- mild muscle atrophy weakness & tiredness (legs weak) and mild cold sensation (cold sweats) at 4.5 hours after 2.5mg for the same attack;
- mild cold sensation (body felt cold) and mild malaise & fatigue (fatigue) at 55 minutes after 1mg for the same attack;
- severe malaise & fatigue (fatigue) at 30 minutes and mild muscle cramps and spasms (leg cramps) at 29 days after 2.5mg for different attacks.

Of these 6 events in these 3 patients, the first 5 might be considered syndrome-like events, with the last being distant from drug exposure but it is difficult to clearly relate these events to concomitancy with SSRIs.

Adverse Events Following Subcutaneous Administration

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. Each of these tables will need to be condensed from the multiple dosing regimens to show the incidence of only those adverse events which occur more frequently in naratriptan than placebo and at rates greater than or equal to 1% for doses of naratriptan which equal or exceed the bioequivalent oral doses.

Changes in ECGs Associated With Naratriptan Use

Charts 24-27 in the ISS present ECG changes considered significant in all clinical pharmacology and clinical studies.

From these charts, for doses of 5mg or less (1mg to 5mg doses) of oral naratriptan, these charts show the following ECG changes (# of patients): PR prolongation (3); QT/QTc prolongation (5); atrial fibrillation (1); atrial ectopy (1); atrial flutter (1); sinus bradycardia (2); conduction abnormalities/RBBB (2); ventricular ectopy (2); ST segment depression (1); T-wave inversion/T-wave flattening(2).

From these charts, for oral doses above 5mg, the following are reported: sinus extrasystoles (1); PR prolongation (4); QT/QTc prolongation (3); sinus bradycardia (2); ventricular ectopy (2); ST/T wave changes (4); arrhythmia (1).

For doses of 5mg or less (2.5mg and 5mg doses) of subcutaneous naratriptan these charts show the following ECG changes: PR prolongation (2); atrial bigeminy (1); sinus bradycardia (1); sinus arrhythmia (1); AV nodal rhythm(3); RBBB (1); ventricular ectopy (5); poor R-wave progression (1).

From clinical pharmacology studies with IV and SubQ formulations, one case each of bradyarrhythmia and PR prolongation are reported.

The sponsor identified the following notable cases across clinical pharmacology and clinical trials involving ECG changes.

Protocol S2WB2004 - subject 0904 - ECG-related event reported as a serious event at a dose 7.5mg oral naratriptan and thought to represent coronary spasm. It is described in greater detail under "serious AEs."

Protocol S2WB2004 - subject 1076 - 53 yo female in the 2.5mg dose group experienced "horizontal ST S1 in leads V4 and V5" at 4320minutes (72hrs) post-dose; this patient also had blood pressure changes from 130/80mmHg to 90/60mmHg, 90/55mmHg, and 100/50mmHg at 120, 180 and 240 minutes post-dose.

Protocol S2WB1004 - subject 0010 - 43 yo female in the 2.5mg dose group showed an isolated ventricular extrasystole 30 minutes post-dose and developed paroxysmal atrial fibrillation with aberrant ventricular conduction 4 hours post-dose and ventricular extrasystoles 29 hours post-dose; ECG performed 3 months later was normal.

Protocol C94-036 - subject 0014 - 47 yo male had 2 asymptomatic episodes of ventricular tachycardia lasting 8 and 10 seconds, approximately 4.5 and 9.5 hours after a placebo and 8 days after 1mg + 1mg naratriptan and was withdrawn from trial prior to breaking the randomization code; further investigation of arrhythmias including Holter showed supraventricular tachycardia, ventricular extrasystoles, and non-sustained VT during sinus bradycardia; echocardiogram and stress test were normal.

Across all doses of naratriptan in clinical pharmacology and clinical trials subjects were noted to have altered ECG intervals which were listed as significant in Charts 24-27 in the ISS. Increases in PR interval were noted for 8 subjects and an AV nodal rhythm was noted in 3 others, with all these subjects listed on active treatment with naratriptan and only one other QTc prolongation on placebo. For example, subject #2 in protocol C94-007 was noted to have increased PR interval length for multiple time points after a 10mg oral dose which did not normalize for 6 hours. In protocol WHP-9006, subjects #6 and #14 were each noted to have multiple QTc prolongations (>460msec) which appeared at greater frequency on the highest of the 3 doses each received but not while on placebo. Further, ventricular tachycardia or ventricular ectopy were listed in 9 patients on naratriptan and 2 in placebo.

In a number of clinical pharmacology trials, including trials which used parenteral administration, actual ECG interval measurements were recorded on the case report forms for PR, QRS and QTc; but no statistical analysis of this data was conducted. Noting the observations mentioned above in some subjects during the clinical development program, it seems reasonable to analyze available data from selected trials for which these data have already been collected. The sponsor has recently submitted analyses of their ECG data which are under review.

Changes in Vital Signs Associated With Naratriptan Use

To assess the naratriptan's effect on vital signs, the sponsor performed an outlier analysis on all clinical pharmacology and clinical migraine studies which collected pre-dose and post-dose vital signs. In addition to studying blood pressure responses in several clinical pharmacology trials in volunteers, they studied blood pressure responses in migraineurs during an attack and a migraine free period (S2WA1007-Part 1), in elderly versus young (S2WB1002) and in hypertensives (C94-036- reviewed under the section of special studies). Finally they conducted a meta-analysis of blood-pressure concentration relationships in 250 patients in Phase I trials which has been reviewed by the biopharmaceutics reviewer.

Outliers were defined by the sponsor as shown in the table below. Outlier definitions for the adolescent

study were defined by criteria from the "Fifth Report of the Joint National Committee on Detection, Evaluation, and Treatment of High Blood Pressure, NIH, March 1994."

Vital Sign	Adult Vital Signs Outlier Definition
Systolic Blood Pressure	≥ 180mmHg and at least 20mmHg increase ≤ 90mmHg and at least 20mmHg decrease
Diastolic Blood Pressure	≥ 105mmHg and at least 15mmHg increase ≤ 50mmHg and at least 15mmHg decrease
Heart Rate	≥ 120bpm and at least 15bpm increase ≤ 50bpm and at least 15bpm decrease

Percent of outliers for migraine clinical trials is summarized in the table on the next page. In clinic-based, single-attack studies vital signs were collected for 4 hours to 24 hours post-dose (oral) and for 2 hours post dose (subcutaneous). In home-based studies vital signs might have been obtained several days to weeks post-treatment which may account in part for the lower outlier frequencies observed in these trials compared to clinic-based. In both the oral and subcutaneous clinic-based studies the majority of outliers were decreases in blood pressure and heart rate and appeared to occur at similar frequency to placebo.

The following subjects were considered notable for changes in vital signs by the sponsor:

In the oral clinic-based studies all from S2WB2004- 6 subjects; one was a decrease in blood pressure with ECG changes (subject 1076 - 2.5mg) described further under the section for ECGs. For the others the following were observed:

- subject 0515 (10mg) - 150/98mmHg at baseline to 204/144mmHg at 225 minutes post-dose necessitating treatment with atenolol;

The others had changes from pre-dose to highest post-dose (mmHg):

- subject 1261 (7.5mg) - 160/90 to 200/100 at 120 minutes (3 other high readings);
- subject 1413 (2.5mg) - 152/90 to 184/102 at 60 minutes (3 other high readings);
- subject 0477 (5mg) - 135/85 to 157/105 at 290 minutes;
- subject 1584 (5mg) - 125/85 to 165/105 at 120 minutes (several other high readings).

In oral home-based, multiple attack, multi-dose studies:

- S2WA3003- subject 0884 (0.25mg + placebo) - 142/85 to 173/107 at 29.5 hours post-dose after treating 2nd attack; withdrawn from study and started on losartan (Cozaar); event resolved in 7 days.

In the subcutaneous clinical trials 3 additional subjects were noted to have the following pre-treatment to highest value (mmHg):

- S2WB2001 subject 0451 (2.5mg) - 160/105 to 180/115 and 180/110 at 30 and 60 minutes;
- S2WB2002 subject 1515 (2.5mg+2.5mg) - 150/90 to 180/100 at final visit;
- S2WB2002 subject 1598 (2.5mg+2.5mg) - 140/70 to 180/100 at final visit, 2 days after treating 3rd attack.

In clinical pharmacology trials these additional subjects had notable changes listed below (mmHg). Those

from the renal impairment trial are discussed in that part of the review.

- C92-055 subject 0006 (25mg oral) - 120/67 to 191/113, 5.5 hours post-dose returning to near baseline in 8 hours and also experienced lightheadedness, tension in the neck, tiredness, and loss of coordination;

-C94-071 subject 007 (5 mg oral) - 130/62 to 158/84 at 10 hours post-dose;

- S2WB3009 subject 1414 (placebo/ 1.5mg Sub Q) - 169/89 to 216/110 after placebo but 158/89 at follow-up visit;

- S2WB3009 subject 1420 (placebo/ 1.5mg Sub Q) - 150/80 to 180/90, 20 minutes after naratriptan;

- S2WB3009 subject 1421 (placebo/ 1.5mg Sub Q) - 180/70 to 204/88, 20 minutes after naratriptan.

Percent of Outliers Across Clinical Migraine Naratriptan Studies- Number of Patients with Baseline and at Least One Post-Baseline Measurement (% of Patients with an Outlier Change in One or More Vital Sign)										
(Condensed from Tables 90-95 in ISS)										
Study Type	Placebo	0.1mg	0.25mg	0.5mg	1.0mg	2.5mg	5.0mg	7.5mg	10mg	Placebo + Nara. (0.25/ 1 /2.5mg) crossover
Clinic-Based; Single Attack; Single Dose: Oral	128 (10%)		34 (3%)		124 (5%)	122 (7%)	121 (7%)	93 (11%)	129 (8%)	
Home-Based: Single Attack; Multi-Dose: Oral	194 (1%)	128 (2%)	197 (2%)		191 (2%)	197 (<1%)				
Home-Based: Multi-Attack; Multi-Dose: Oral	76 (0%)	205 (0%)	214 (<1%)		208 (<1%)	200 (0%)				668 (3%)
Home-Based: Multi-Attack; Multi-Dose: Oral	No Placebo					68 (3%)				
Clinic-Based: Single Attack; Single Dose: Subcutaneous	63 (5%)			60 (3%)	55 (4%)	42 (5%)	34 (6%)		34 (0%)	
	Placebo + 2.5mg	Placebo +5mg	2.5mg +Placebo	2.5mg +2.5mg	5mg +Placebo	5mg +5mg				
Home-Based: Multi-Attack; Multi-Dose: Subcutaneous	55 (2%)	55 (2%)	63 (2%)	175 (2%)	56 (0%)	170 (2%)				

In study S2WA1007-Part 1, fifteen migraineurs were studied during an attack period and a migraine-free period, taking a single dose of 2.5mg naratriptan during each period. There were small increases in mean SBP during an attack at 8hrs and 12 hrs (114.1 and 114.9mmHg) compared to non-migraine period (112.2 and 112.0mmHg). There was also a small pre-dose increase in DBP (78.7 vs.75.3mmHg) and in pulse (74.7 vs 71.6 bpm) during an attack with these differences tending to persist over 24 hours. Within each period the mean SBP, DBP and pulse tended to remain constant. No statistical analysis was conducted.

In a study (S2WB1002) of elderly (12 subjects) versus young (12 subjects), each subject was treated in crossover fashion with 1mg+1mg, 2.5mg+2.5mg and placebo+placebo, doses separated by 4 hours. The sponsor reports that in elderly the greatest increase was in SBP of 12mmHg as difference from placebo 4-8 hours after 2.5mg+2.5mg. There was a statistically significant difference between elderly and young only for the 4-8 hour weighted mean and peak SBP of 8 and 10mmHg difference (respective 95% CI 3,13; 4,16). However, the analyses were conducted on difference from baseline; and at baseline the elderly had higher mean SBP and DBP compared to the young across all treatment periods. Examination of Figures 1 and 2 show that there is a tendency maintain these baseline differences between the young and the elderly across all doses for the 24 hours of observation. Tables 15 and 16 of the study show the highest absolute mean SBP was 147mmHg (2.5mg+2.5mg period) and DBP was 84mmHg (1mg+1mg period) for the elderly were observed 6 hours post-dose.

In (C92-055), 18 healthy volunteers were randomized to placebo and 2-3 single doses of naratriptan in ascending dose order (dose range 0.5 - 25mg). The blood pressure response for the 20mg oral dose showed statistically significant differences from placebo for 0-8hrs in weighted mean SBP/DBP (14/10mmHg) and peak SBP/DBP(12/9mmHg); and all doses of 5mg or greater also showed statistically significant differences from placebo but the magnitudes of blood pressure changes were decreased as the dose decreased from 20mg to 5 mg. The 2.5mg dose showed no such statistically significant effect. No effect was noted on heart rate for any dose. The sponsor argues that a dose response is not observed for the dose levels of 5mg to 15mg but a statistically significant dose response is reported for the 2.5mg-20mg dose range for weighted mean SBP/DBP (0-8hrs). Additionally, the sponsor includes 4 scatter plots with regression lines showing correlation between weighted mean SBP and plasma AUC (doses 0.5mg-5mg) and peak SBP and plasma Cmax (doses 0.5mg-25mg). These plots show considerable variability in individual blood pressure response in relation to plasma concentration. Finally, from patient. line listings (Appx 8 Vol-106) it is noted that for Subject 006 whose peak plasma concentration of 83ng/ml after a 25mg oral dose experienced a maximum increase from 120/67 to 191/113 at 329 minutes and AEs (lightheadedness, tension in the neck, tiredness and loss of coordination) resulting in withdrawal. However, Subject 008 who also had a peak plasma concentration 83ng/ml after 20mg oral dose experienced only a maximal increase from 121/78 to 134/93 at 240 minutes.

Changes in Laboratory Parameters Associated With Naratriptan Use

The sponsor presents results from laboratory data only as outlier analyses, examining frequencies in change from baseline to any time after start of treatment between the placebo and active treatment groups at various dose levels of naratriptan. Data analysis is not presented as shift tables or change from baseline to post-treatment means for each clinical laboratory analyte. Outlier comparisons are presented in Tables 76-85 of the ISS showing overall incidences of laboratory data, incidences within laboratory categories (clinical chemistry, renal function, hepatic function, hematology, and urinalysis) and incidences for each individual laboratory variable. Outliers were pre-defined by the sponsor. Data from similar trials are grouped together according to the following:

A) clinical pharmacology trials -

Tables 76-79 are grouped by formulation (IV, oral, subcutaneous, nasal);

B) oral clinical migraineur trials -

Table 80 - clinic-based, placebo-controlled, single dose, single attack (S2WA1007-Pt2; S2WB2003; S2WB2004);

Table 81 - home-based, placebo-controlled, multi-dose, single attack (S2WA3001);

- S2WB3012);
Table 82 - home-based, placebo-controlled, multi-dose, multi-attack (S2WA3003;
S2WB3002);
Table 83 - long-term home-based, uncontrolled, multi-dose, multi-attack (S2WA3004);
C) subcutaneous migraineur trials -
Table 84 - clinic-based, placebo-controlled, single dose, single attack (S2WB2001);
Table 85 - home-based, placebo-controlled, multi-dose, multi-attack (S2WB2002).

The sponsor concludes that there were no apparent treatment-related or dose-related trends in clinical laboratory data in naratriptan clinical pharmacology or clinical trials; but the sponsor does point out that the incidences of clinically significant abnormalities were not similar within individual categories for "hepatic function" (2-9% vs 2% for placebo in S2WB2001- Table 84 with no dose-response relationship) and "hematology" (0-4% in the 5mg/day groups vs 8-10% in the 2.5mg/day groups in S2WB2002-Table 85). Examination of these outlier Tables 76-85 as presented in the ISS does not show any obvious trends in increasing outlier frequency across treatments or dose levels of naratriptan.

However there are limitations to the interpretation of these tables. The sponsor does not indicate if the same outlier definitions were used across all 45 clinical trials in the NDA. Further, the tables for clinical studies indicate that some labs were measured in only a few patients. For example GGT was measured in fewer than 30 patients in Table 82, in 15 in Table 83 and not listed at all in Table 81. In some trials, WBC differentials were conducted only if the WBC was abnormal; therefore, only about one-half to one quarter of patients in S2WB2001 had differential data. Additionally, trials conducted post-exposure measurements at different times. Trials (S2WA1007-part 1; S2WB2003) required post-exposure collection at 24 hours while others did not obtain post-exposure laboratory data until 1-7 days after exposure. Trials (S2WB3004; S2WB3011; S2WB3002) did not require post-treatment collection of laboratory data unless deemed necessary by the investigator, resulting in limited numbers of post-exposure sample collections. Thus Table 83, which provides the only long-term exposure of patients from S2WA3004 (i.e. 1 year) to drug, had one or more a post-treatment exposure lab values for only 21 patients with some lab variables displaying as few as 5 patient observations for a particular variable. Little more data is available for S2WB3004 in the 4-month safety update.

The sponsor reports no changes in laboratory tests were listed as adverse events for any subject in the clinical pharmacology studies and reports laboratory changes for only one subject (#3352 in S2WA3012) who was withdrawn and hospitalized, and later diagnosed with lupus (See narrative summary in "Serious AEs").

APPEARS THIS WAY
ON ORIGINAL