

**CENTER FOR DRUG EVALUATION AND RESEARCH**

**APPLICATION NUMBER: 20763**

**BIOEQUIVALENCE REVIEW(S)**

JUN 24 1997

Naratriptan 2.5 mg tablets

Glaxo Wellcome Inc

NDA 20-763

Research Triangle Park, NC

Reviewer: Iftekhar Mahmood, Ph. D.

Submission Dates: December 4, 1996

Indication: Antimigraine

February 7, 1997

COMPILED  
AT  
JUN 25 1997

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## INTRODUCTION

Naratriptan (GR85548) is a potent and selective agonist for vascular 5-HT<sub>1</sub> receptors. Experimental data from animal studies suggest that naratriptan acts as 5HT<sub>1</sub> receptors on peripheral and central terminals of the trigeminal nerve to inhibit trigeminal nerve activity. This action may lead to antimigraine activity in humans.

The chemical name of naratriptan is N-methyl-3-(1-methyl-4-piperidiny)-1H-indole-5-ethanesulfonamide hydrochloride. Molecular formula of naratriptan is C<sub>17</sub>H<sub>25</sub>N<sub>3</sub>O<sub>2</sub>S.HCl with a molecular weight of 372. Naratriptan is a pale yellow microcrystalline solid and its solubility as hydrochloride salt in water at 25°C is 35 mg/mL. The pK<sub>a</sub> of naratriptan HCl is about 9.7. Naratriptan possesses no chiral centers.

Naratriptan is absorbed with a T<sub>max</sub> of approximately 3 hours. The absolute bioavailability is about 75% in females and 64% in males. Following a 2.5 mg oral dose of naratriptan, the C<sub>max</sub> is about 12 ng/mL. Food has no effect on the pharmacokinetics of naratriptan. The apparent volume of distribution at steady state (V<sub>SS</sub>) following 1.5 mg IV infusion over 15 minutes was 170 L. Naratriptan is 29% bound to human plasma proteins. Naratriptan is not extensively metabolized. The fraction of dose excreted unchanged (5 mg oral dose) in urine is 30% in males and 44% in females. The main metabolic pathway of naratriptan appears to be N-oxide and a piperidineone metabolite. The metabolic disposition of radiolabelled naratriptan indicated that 70% of the dose is excreted as unchanged naratriptan and 30% is metabolized. The systemic clearance of naratriptan is 6.6 mL/min/kg. Renal clearance represents 49% of systemic clearance in men and 60% in women. The elimination half-life of naratriptan is approximately 6 hours.

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Total number of studies submitted in this NDA was 50. Total number of studies reviewed were 22. There were 2 pre-clinical studies and 6 safety related clinical studies. Three in-vitro metabolism and 4 protein binding studies were merged as one study each. There were 15 irrelevant studies.

## SUMMARY

### **Bioavailability:**

The absolute bioavailability was evaluated in 12 healthy male and 12 healthy female subjects, with 5mg oral tablet and 1.5mg intravenous infusion over 15minutes. The estimated bioavailability was 75% and 64% in females and males, respectively (Study #1). The relative bioavailability of 10mg naratriptan tablets compared to naratriptan hydrochloride oral solution in 6 healthy male subjects was 100% (Study #2).

### **Absorption:**

Absorption of naratriptan is rapid and peak concentrations (13 ng/mL in females and 8 ng/mL in males) are reached within 2 hours following a single 2.5 mg oral dose (Studies #3 & 4).

### **Distribution:**

The apparent volume of distribution at steady state ( $V_{SS}$ ) following 1.5 mg IV infusion over 15 minutes was comparable (170 liters) in males and females (Study #1). In-vitro plasma protein binding ranged from over the concentration range of 50 to 1000 ng/mL (Study #19). The binding is non-specific. The blood to plasma ratio of radioactivity was 1.21 (Study #19).

### **Metabolism in vivo:**

The metabolic disposition of radiolabelled naratriptan was determined after intravenous and oral administration. In each study two healthy male subjects received radiolabelled naratriptan and blood, urine and feces samples were collected up to 96 hours after dosing. Plasma levels of total radioactive drug related material after IV infusion declined with an half-life of approximately 6 hours. In human plasma, the major components were unchanged naratriptan, the N-oxide, and a piperidineone metabolite. Three or four other metabolites were also detected, including hydroxylated piperidineones. The metabolites of naratriptan are inactive. Urine contained the same components and additional  $\alpha$ -hydroxy compound. After oral administration naratriptan was completely eliminated (97%) within 96 hours and urinary excretion is the main route of elimination (77%) with only 20% in the feces. About 70% of the dose was excreted as unchanged naratriptan and 30% was metabolised (Study #8).

### **Metabolism in-vitro:**

The enzymes responsible for naratriptan metabolism have been studied *in vitro* with male and female human liver microsomes and specific inhibitors of cytochrome P450 isoenzymes. *In vitro*, the metabolism of naratriptan is inhibited along a variety of pathways (CYP1A2, CYP2C8/9, CYP2D6, CYP2E1 and CYP3A), suggesting that no single isozyme is responsible for its metabolism. The potential for naratriptan to inhibit the metabolism of concomitant medication has been studied *in vitro* with human liver microsomes and specific substrates of cytochrome P450 isozymes. Naratriptan at concentrations up to 100µg/mL did not inhibit CYP1A1/2, CYP2A6, CYP3A, CYP2C8/9/10, CYP2C19 and CYP2E isoenzymes. An inhibitory effect (26%) on CYP2D6 was produced in microsomes from female subjects, at naratriptan concentrations of 100ng/mL to 100µg/mL much higher than concentrations observed after a therapeutic dose of 2.5mg (Study #18).

The potential for naratriptan to interact with the monoamine oxidase A and B (MAO) enzyme system was investigated *in vitro* using male and female human liver microsomes. The results demonstrated that naratriptan does not interact with the monoamine oxidase enzyme system *in vitro* using male and female human liver microsomes (Study #18).

### **Elimination:**

Following IV administration, the mean total plasma clearance of naratriptan was 471 mL/min (range: ) in males and 376 mL/min (range: ) in females. Following 5 mg oral administration, the mean total plasma clearance of naratriptan was 790 mL/min (range: ) in males and 509 mL/min (415-625 mL/min) in females. Though the renal clearance (approximately 230 mL/min) was similar in both males and females the percent of dose excreted in urine was 30% for males and 44% for females. The elimination half-life of naratriptan was 6.5 hours (study #1).

### **Dose Proportionality:**

Pharmacokinetics of naratriptan in 23 females is linear from 2.5 to 10 mg dose (Study #3). Single oral doses of 1mg, 2.5mg, 5mg, 7.5mg and 10mg naratriptan were administered to 16 healthy male Japanese subjects (Study #4). The pharmacokinetics of naratriptan is linear over the dose range of 1 to 10mg.

**Food Effect:**

The pharmacokinetics of 2.5mg oral tablet naratriptan was not modified by food intake in 20 female subjects (Study #5). The effect of food evaluated on the pharmacokinetics after a 5mg naratriptan dose in 6 Japanese male subjects showed a 20% decrease in  $C_{max}$  and AUC and 26% increase in clearance (Study #4 ).

**Multiple Dose Kinetics:**

Naratriptan tablets were administered once daily to 12 healthy young female subjects (aged 23 to 53 years) for 5 consecutive days. Multiple dose administration of 5 or 10mg naratriptan tablets for 5 days did not result in drug accumulation or a loss of dose proportionality in naratriptan pharmacokinetic parameters (Study #7). Naratriptan 5mg tablets were also administered once daily for 5 consecutive days to 6 healthy Japanese male subjects. Pharmacokinetic parameters on day 1 were identical to parameters on day 5 and there was no drug accumulation.

**Divided Doses:**

Eight healthy young male subjects were given two naratriptan tablets separated by 4 hours. The doses were 5+5mg, 7.5+7.5 mg and 10+10mg. The results indicated that the pharmacokinetics of naratriptan are similar to those seen with a single dose (Study #6).

**SPECIAL POPULATION:****Hepatic Impairment:**

The pharmacokinetics of naratriptan tablets were investigated in an open single dose study in 8 subjects (4 males, 4 females) with hepatic impairment compared with 8 matching healthy subjects (matched for gender, age and weight). Impaired subjects in the study had mild, compensated liver disease as judged by Child-Pugh classification, which is based on albumin and total bilirubin blood levels, prothrombin time, ascites and encephalopathy. Hepatic microsomal function was assessed by caffeine clearance, which was 0.3 to 0.7mL/min/kg body weight in hepatic impaired subjects and was 0.9 to 4.9mL/min/kg body weight in healthy subjects. Hepatic impairment was associated with a 41% increase in naratriptan half-life, an increase in the AUC by 48% and a decrease of 33% in naratriptan clearance. The renal clearance in patients with hepatic impairment decreased by 50%. The  $C_{max}$  and  $T_{max}$  remained unaffected by the liver impairment (Study #11).

**Renal Impairment:**

The pharmacokinetics of naratriptan tablets were investigated in an open single dose study in 15 (9 male and 6 female) subjects with renal impairment and compared with 8 (6M, 2F) healthy subjects. Healthy subjects received 5 mg naratriptan tablets while subjects with renal impairment received either 5 mg or 2.5 mg naratriptan tablets depending on the extent of impairment. The creatinine clearance ranged from 18 to 144 mL/min. Renal impairment was associated with an increase in naratriptan half-life by up to 50% and a 50% decrease in clearance. The renal clearance of naratriptan decreased by almost 3 fold in moderate renally impaired (GFR 15-39 mL/min) patients than in normals (GFR > 75 mL/min) (Study #10).

**Age:**

Twelve healthy elderly subjects (aged 65-77 years; 6 male and 6 female) and twelve healthy young subjects (aged 24-44 years; 6 male and 6 female) received two doses of 1 and 2.5mg or placebo separated by 4 hours. For 2.5 mg dose, the clearance decreased by 26% in elderly subjects compared to the young subjects. There was a 35% decrease in clearance for elderly women than young women, whereas clearance decreased by 13% in elderly men than young men. Overall, renal clearance decreased in elderly subjects by 29%. Renal clearance decreased by 28% in elderly females and by 35% in elderly males compared to young. The elimination half-life and  $C_{max}$  remained unaffected between elderly and young (Study #9).

**Gender:**

Females appear to have greater exposure to naratriptan than males. Following a 5 mg oral dose, females have 12% higher bioavailability than males. Apparent oral clearance decreased in females by 30% compared to males (8.8 ml/min/kg in females and 11.1 ml/min/kg in males). Though the renal clearance (approximately 230 mL/min) was similar in both males and females the percent of dose excreted in urine was 30% for males and 44% for females. The elimination half-life of naratriptan was similar in both males and females (6 hours) (Study #1).

**Race:**

No systemic study was done to evaluate the effect of race on the pharmacokinetics of naratriptan (Study #16).

## **Drug Interactions:**

### **Interaction with oral ergotamine:**

The potential pharmacokinetic interaction of concomitant administration of naratriptan tablets (2.5mg) and ergotamine (Ercaf; 2mg ergotamine/200mg caffeine) was investigated in 12 healthy female subjects. There were no statistically significant differences in the naratriptan parameters  $AUC(0-\infty)$ ,  $C_{max}$  and  $T_{max}$  with concomitant ergotamine administration compared to naratriptan tablets alone. Small but statistically significant increase in  $T_{1/2}$  of less than one hour with concomitant ergotamine administration was considered unlikely to be of clinical significance (Study #14).

### **Effect of dihydroergotamine (DHE) on oral naratriptan:**

No significant interaction between naratriptan and DHE was observed.  $AUC_{0-\infty}$  and  $C_{max}$  values for naratriptan were 15% and 20% lower, respectively, after concomitant administration of DHE and naratriptan, than after administration of naratriptan alone (Study #13).

### **Effect of subcutaneous sumatriptan on oral naratriptan:**

There was no significant difference in the pharmacokinetic parameters of sumatriptan, between subjects given sumatriptan alone and subjects given naratriptan + sumatriptan, except that there was a 22% increase in the mean elimination half-life of sumatriptan in the presence of naratriptan. This difference, although significant using standard statistical methods, is unlikely to be clinically relevant (Study #12).

### **Effect of alcohol:**

The potential interaction between alcohol and naratriptan was assessed in a double-blind, randomised, placebo-controlled, two-way crossover study in 16 healthy female subjects. Each subject received ethanol (0.6g/kg) followed by 5 mg naratriptan tablets 30 minutes later on one occasion, and ethanol placebo 30 minutes later followed by 5 mg naratriptan tablets on a separate occasion. There were no differences in pharmacokinetic parameters of naratriptan given alone or with alcohol (Study #15).

## **Pharmacokinetics-Pharmacodynamics:**

### **Pharmacokinetics/pain relief relationship in patients population:**

A population pharmacokinetics/pharmacodynamics (PK/PD) study was conducted to compare naratriptan pharmacokinetics during a migraine attack and during a non-migraine period, in patients with a history of at least 1 year of migraine. There were 2 parts of this

study. Part 1 was an open, 2 period, cross-over study in which 15 female migraine patients received naratriptan tablets 2.5mg during a migraine attack; and again 3-7 days later, during a non-migraine period. Fourteen blood samples were collected over 24 hours in both occasions. Part 2 was a double-blind, randomized, placebo controlled study in which 127 male and female subjects were treated with either placebo or Naratriptan Tablets 0.25mg, 1.0mg, or 2.5mg during a migraine attack. Subjects not responding to study medication were allowed to use rescue medications at 4 hours after the administration of study medication. During migraine attack, pain relief scores (5 points scale: 1 [no relief] to 5 [complete relief]) were collected over 24 hours post-dose. Headache severity was measured on a 4 point scale. A population modelling method was used to estimate parameters of a logistic model of probability of pain relief scores, with placebo effects, a saturable effect of time, a saturable ( $E_{max}$ ) effect of naratriptan concentration in an hypothetical effect compartment ( $C_e$ ), and additive inter-subject variability. Individual pharmacokinetic parameters determined separately using population modelling were used to predict naratriptan concentrations. The results of simultaneous analysis of pain relief data from part 1 and 2 show that the equilibration half-life between serum naratriptan concentration and effect site concentrations is approximately 0.5 hours, resulting in a delay of 1 and 2 hours between  $C_{max}$  and peak effect. Predictions based on the above model show that a dose of 0.25mg was not different from placebo, and 1mg and 2.5mg demonstrated efficacy. The onset of naratriptan effect was 1.5 hours post-dosing, and the maximum effect of naratriptan occurred 4 hours post-dosing (Study #16).

#### **Pharmacokinetics/blood pressure relationship:**

Blood pressure was collected during 4 hours post-dose, and serum naratriptan concentrations were predicted using the individual pharmacokinetic parameters. Migraine attack was associated with elevated blood pressure (+3mmHg) compared to a migraine free period. There was no relationship between predicted concentration and peak systolic and peak diastolic blood pressure over 4 hours post-dose (Study #16).

#### **Meta-analysis:**

To explore the effects of kinetic variability on systolic (SBP) and diastolic (DBP) blood pressure, a meta-analysis was used to estimate the parameters of the dose-concentration-response relationship in healthy subjects and non-migraine patients. Data from 250 subjects (148 females and 102 males) in 15 studies of the Clinical Pharmacology Programme were included in this analysis. Single, divided or repeated doses of 0.025mg up to 25mg naratriptan had been administered, by oral, intravenous or sub-cutaneous route.

Naratriptan data were collected in 238 subjects; placebo data were available from a total of 102 subjects. The individual relationship between concentration and blood pressure was best described by a sigmoid  $E_{max}$  model, which implies a gradual increase of blood pressure from a baseline, up to a maximum effect. In the absence of naratriptan, blood pressure was very variable, ranging from 75 to 175mmHg for SBP and 35 to 105mmHg for DBP. SBP increased with age and body weight. Systolic and diastolic blood pressure were higher in males than females, and with renal or hepatic impairment. Half the maximum effect on systolic blood pressure was obtained at concentrations ( $C_{50}$ ) of 7.4ng/mL in males and 13.1ng/mL in females; for diastolic blood pressure,  $C_{50}$  was 7.7ng/mL. Intersubject variability on  $C_{50}$  was large (around 100% CV). Age, weight or renal/hepatic impairment did not modify the sensitivity to naratriptan. The population average maximum increase ( $E_{max}$ ) in systolic blood pressure was 7.7mmHg and in diastolic was 6.1mmHg, with a large inter-subject variability (around 90% CV). Age, gender or renal/hepatic impairment had no effect on the maximum increase. After oral treatment with 2.5mg, average naratriptan  $C_{max}$  in males and females are lower than  $C_{50}$ , resulting in population increases of less than 5mmHg on SBP, and less than 3 mmHg on DBP (Study #17).

#### **Interaction with migraine prophylactic drugs:**

A population PK analysis was conducted in 127 patients during a migraine attack.. The interaction with migraine prophylactic drugs was investigated on pharmacokinetic parameters (apparent clearance and volume of distribution) by population modelling. Migraine prophylactic treatment by selective serotonin reuptake inhibitor (n=23), betablockers (n=8) and tricyclic antidepressant (n=15) had no effect on the clearance and volume of distribution of naratriptan (Study #16).

#### **Effect of smoking:**

Population modelling was used to estimate parameters from serum concentrations of 127 patients treated with oral naratriptan during an attack. The results showed an increase of clearance by 29% with tobacco use (n=19) (Study #16).

#### **Interaction with hormone contraceptives, hormone replacement therapy:**

Hormone contraceptives (n=15) were found to reduce naratriptan clearance by 32% and volume of distribution by 22%, resulting in slightly higher concentrations. Hormone replacement therapy (HRT) (n=25) had no effect on the pharmacokinetics of naratriptan in older female patients (Study #16).

**Analytical Method:**

**Dissolution:**

The Sponsor's proposed Dissolution Method and Specifications for naratriptan tablets are as follows:

Dosage Form:                    **Tablet**  
Strengths:                       **1mg and 2.5 mg (n =12)**  
Apparatus:  
Medium:  
Speed:  
Sampling Times:

**Sponsor's proposed Specifications: Q =            in 15 minutes**

**FDA's proposed Specifications: Q =            in 15 minutes**

## **Labeling of NARATRIPTAN**

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

### **Pharmacokinetics:**

The pharmacokinetics of naratriptan are linear over dose range of 2.5 to 10 mg. Repeat administration of naratriptan tablets (2.5 mg given 4 hours apart) does not result in drug accumulation.

**Absorption:** Naratriptan tablets are well absorbed, with 74% oral bioavailability in females and 63% in males. Following administration of a 2.5-mg tablet orally the absorption is rapid and peak concentrations are obtained in 2 to 3 hours. The  $C_{max}$  is approximately 8.3 ng/mL (6.5 to 10.5 ng/mL) in women and 5.4 ng/mL (4.7 to 6.1 ng/mL) in men. During a migraine attack, absorption was slower, with a  $T_{max}$  of 3 to 4 hours. Food does not affect the pharmacokinetics of naratriptan.

**Distribution:** The steady-state volume of distribution of naratriptan is 170 L. Plasma protein binding is low (25%).

**Metabolism:** Naratriptan is predominantly eliminated in urine, with 50% of the dose recovered unchanged and 30% as metabolites in urine. In vitro, naratriptan is metabolized by a wide range of cytochrome P450 isozymes into a number of inactive metabolites.

**Elimination:** The systemic clearance of naratriptan is 6.6 mL/min/kg. The renal clearance (220 mL/min) exceeds glomerular filtration rate, indicating active tubular secretion. The elimination half-life of naratriptan is 6 hours.

### **Special Populations:**

**Renal Impairment:** Renal excretion is the major route of elimination of naratriptan. A study was conducted to compare mild-to-moderate renally impaired subjects (n = 15;

creatinine clearance: 18 to 115 mL/min) to healthy subjects (n = 8; creatinine clearance: 78 to 144 mL/min). The study showed a mean decrease in oral clearance by 50% and renal clearance by 70% in moderate renally impaired patients as compared to healthy subjects. Decrease in clearances resulted in an increase of mean half-life from 6 hours (healthy) to 11 hours (range: 7 to 20 hours) in moderate renally impaired patients. The mean C<sub>max</sub> increased by approximately 40%. (See DOSAGE AND ADMINISTRATION).

**Hepatic Impairment:** Liver metabolism is a limited route of excretion for naratriptan. A study to compare moderately hepatically impaired subjects (n = 8) to healthy subjects (n = 8) showed a moderate decrease in oral clearance (by approximately 30%) and a 50% decrease in renal clearance resulting in approximately 40% increase in the half-life (range: 8 to 16 hours). (See DOSAGE AND ADMINISTRATION).

**Age:** A small decrease in clearance of approximately 26% was observed in healthy elderly subjects (65 to 77 years), resulting in slightly higher exposure.

**Race:** The effect of race on the pharmacokinetics of naratriptan has not been established.

**Drug Interactions:** In normal volunteers, coadministration of naratriptan tablets and ergotamine, dihydroergotamine, alcohol, or sumatriptan did not result in modification of naratriptan pharmacokinetic parameters.

Naratriptan does not inhibit monoamine oxidase (MAO) enzymes and is a poor inhibitor of P450, therefore metabolic interactions between naratriptan and drugs metabolized by P450 or MAO are unlikely.

From population pharmacokinetic study, it was found that contraceptives (n = 15) reduced clearance by 32% and volume of distribution by 22%, resulting in slightly higher

concentrations. Hormone replacement therapy (HRT) (n=25) had no effect on pharmacokinetics in older female patients.

From population pharmacokinetic study, it was found that smoking (n =19) increased the clearance of naratriptan by 30%.

In migraine patients, coadministration of naratriptan and migraine prophylactic drugs (fluoxetine (n =23), beta-blockers (n = 8), and tricyclic antidepressants ( n= 15)) did not affect the clearance of naratriptan.

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### Comments to the Medical Reviewer

The Sponsor has not conducted pharmacokinetic studies in severe renally and severe hepatic impaired patients. There may be a good number of migraine patients who may suffer from severe hepatic and renal impairment, therefore contraindication of naratriptan in such patients will deprive them from getting any medical benefit this drug has to offer. Therefore, it is suggested that some sort of adjustment in naratriptan dosing in these groups of patients could be recommended.

### Comments to the Sponsor

1. Since naratriptan

it is suggested that the Sponsor adopt the following dissolution specification:

Dosage Form: Tablet

Strengths:

Apparatus:

Medium:

Speed:

Sampling Times:

#### Recommendation:

From a pharmacokinetic point of view this NDA is acceptable to the Office of Clinical Pharmacology and Biopharmaceutics.

Please convey labeling Comments and Comment 1 to the Sponsor.

Iftexhar Mahmood, Ph.D. J. Mahmood 6/24/97

RD/FT initialed by Mohammad Hossain, Ph.D. M. Hossain 6/24/97

First draft prepared on: May 20, 1997, returned on May 28, 1997

Second draft prepared on: May 30, 1997, returned on June 2, 1997

**Division of Pharmaceutical Evaluation I  
Office of Clinical Pharmacology and Biopharmaceutics**

**CPB Briefing: June 17, 1997**

CC: NDA 20-763, HFD-120, HFD-860 (Mahmood, Hossain, Malinowski), HFD-340 (Viswanathan), CDR (Barbara Murphy) and FOI (HFD-19) files.

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