CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-016

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW

NDA:	21-016	SUBMISSION DATES:	June 27, 2002 November 7/20/27, 2002
DRUG NAME:	Eletriptan HBr (Relpax™)		
DOSAGE STRENGTH:	Immediate release tablets (20, 40, 80 mg)		
APPLICANT:	Pfizer Eastern Point Road, Groton, CT 06340		
REVIEWER:	John Duan, Ph.D.		
TEAM LEADERS:	Ramana Uppoor, Ph.D., Joga Gobburu, Ph.D.		
TYPE OF SUBMISSION:	NDA resubmission		

I. Executive Summary

Eletriptan is an oral $5HT_{1B/1D}$ receptor agonist for the treatment of acute migraine. Its approvability is contingent on the results of the coronary safety study because eletriptan levels are increased in the presence of CYP3A4 inhibitors, and because drugs in its class may cause coronary artery constriction. An approvable letter for Relpax was issued on 12/1/00, in which the applicant was requested to conduct a placebo-controlled study to assess the potential of eletriptan to constrict coronary arteries at eletriptan plasma concentrations (Cp) comparable to exposures seen with CYP3A4 inhibition. The applicant was also requested to include an active control (another triptan) in the study.

The Clinical Pharmacology and Biopharmaceutics (hpbio) section of the current submission includes Study A160-1045, which is a pharmacokinetic study to investigate the effects of ketoconazole on the pharmacokinetics of a single dose of eletriptan, and two bioequivalence studies A160-1063 and A160-1069. These studies were reviewed previously by Dr. Rae Yuan and Dr. Maria Sunzel in the original and subsequent submissions. The bioequivalence studies are not relevant to the issue regarding the coronary safety. Therefore, they are not included in the current review. Although not in the hpbio section, the applicant submitted a concentration effect (measured changes in the mid left anterior descending coronary diameter) analysis in the summary section as an appendix. This study used mixed effects modeling to investigate the relationship between the observed arterial eletriptan concentrations and the measured changes in the mid left anterior descending coronary diameter (mid-LAD). The observed decrease in the mid-LAD over time in the placebo data was described using a model with two different slopes ($0.502\%\cdot min^{-1}$ constriction from baseline between 0 to 15 minute time period and $0.278\%\cdot min^{-1}$ constriction from baseline between 15 and 40 minute time period). The additional concentration (treatment) effect was characterized by a linear relationship. The estimated slope of the treatment effect $-7.77 \times 10^{-3}\%\cdot(ng/ml)^{-1}$ approximates to a 1.5% constriction per 80mg dose increment. However, the analysis did not use the last time points (50 min), at which in most cases the effect of constriction was continually increased. The PK-PD relationship shows a hysteresis, indicating that a delay exists between PK and PD. Therefore, the modeling does not support the conclusion regarding the coronary safety. Study 1072 had sumatriptan treatment arm as an active control. Most of the subjects in this arm showed the similar trend with eletriptan treatment group. At every time point, these two arms showed no statistical differences. Whether they are clinically similar is subject to medical review. It should be noted that the maximum decreases and the time course of mid-LAD diameter returning to baseline are unknown. Without this information, interpretation of the submitted data is not possible. On the other hand, the concentrations after

two doses of eletriptan separated by 2 hours in the presence of ketoconazole were predicted from a single dose study. This prediction is based on an assumption that the pharmacokinetics of eletriptan are linear. However, the pharmacokinetics of eletriptan are more than dose proportional. The applicant provided a justification to show that while the pharmacokinetics of eletriptan increases slightly more than predicted over a low dose range, there is evidence to indicate the pharmacokinetics of eletriptan are proportional with higher doses (>40mg). Further, based on the in vitro metabolism data there are theoretical reasons to believe that the pharmacokinetics should be linear. The applicant also provided a study (A1601087) to justify the differences in the concentration measurements between studies A1601045 (venous concentration) and A1601072 (artery concentration). The study showed that venous and arterial AUC_t, C_{max} and T_{max} were very similar. There were no clinically significant differences between the arterial and venous plasma eletriptan concentrations over time following administration of eletriptan 80mg in the presence of CYP3A4 inhibitor (ketoconazole).

Recommendations

The following comments should be sent to the applicant.

1. The proposed concentration effect (mid-LAD diameter) model is not appropriate for describing the data due to the following reasons.

   - The last time point (50 min post infusion, 10 min post end of infusion) was not used in the proposed model.

   - By taking the last time point into consideration, a hysteresis effect exists.

2. The accuracy and precision of the assay for eletriptan in study A1601087 for low QC are out of the acceptable range. The applicant should check the method and properly validate the assay in future if low concentrations are expected.

Comments to the medical officer

1. The concentration effect (mid-LAD diameter) model is not appropriate for describing the data because the last time point (50 min, 10 min post end of infusion) was not used in the proposed model. When this time point was taken into consideration, a hysteresis effect for the relationship between concentration and mid-LAD diameter was observed.

2. The maximum decreases at the given doses and the time course of mid-LAD diameter returning to baseline are unknown. Without this information, interpretation of the submitted data is not possible.

3. The concentrations after two doses of eletriptan separated by 2 hours in the presence of ketoconazole were predicted from a single dose study. This prediction is based on an assumption that the pharmacokinetics of eletriptan are linear. However, the pharmacokinetics of eletriptan are more than dose proportional. The applicant provided a justification to show that while the pharmacokinetics of eletriptan increase slightly more than predicted over a low dose range, there is evidence to indicate the pharmacokinetics of eletriptan are proportional

with higher doses (>40mg). Further, based on the in vitro metabolism data there are theoretical reasons to believe that the pharmacokinetics should be linear.

4. There were two concentration targets for the coronary safety study: CMAX1 and CMAX2. CMAX1 was taken from the mean observed C_{max} (491 ng/mL) in Study A1601045. The concentration time data from the eletriptan plus ketoconazole treatment period in study A1601045 was modeled. The expected individual C_{max} (CMAX2) following administration of 2 doses of 80mg of eletriptan separated by 2 hours and concomitantly administered with ketoconazole were subsequently estimated by simulation using the individual pharmacokinetic parameters and the original A1601045 sampling scheme. The mean estimate of CMAX2 was calculated from the predicted individual CMAX2 values. Further, the C_{max} was reduced by 32.7% when eletriptan was administered during a migraine attack from Study 160101. The CMAX1M and CMAX2M were calculated by correcting CMAX1and CMAX2 for this effect. The mean arterial C_{max} of 660ng/ml exceeds that predicted for two oral eletriptan 80mg doses separated by two hours in the presence of a potent CYP3A4 inhibitor (ketoconazole) during a migraine attack (predicted as 598ng/ml).

5. The applicant provided a study (A1601087) to justify the inconsistency in the concentration measurements between studies A1601045 (venous concentration) and A1601072 (artery concentration). The study showed that venous and arterial AUC_t, C_{max} and T_{max} were very similar. There were no clinically significant differences between the arterial and venous plasma eletriptan concentrations over time following administration of eletriptan 80mg in the presence of CYP3A4 inhibitor (ketoconazole).

Draft Labeling

1 page(s) of revised draft labeling has been redacted from this portion of the review.

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CC: NDA 21016 original
HFD-120 Division File
HFD-860 MMehta, CSahajwalla, RUppoor, JGobburu, JDuan
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II. Table of Contents

III. Summary of Clinical Pharmacology and Biopharmaceutics Findings

Eletriptan is an oral $5HT_{1B/1D}$ receptor agonist for the treatment of acute migraine. The relevant pharmacokinetics of eletriptan were described in the reviews of original submission of NDA 21-016 dated August 9, 1999, by Dr. Rae Yuan and subsequent submission dated Jun. 1, Aug 9, and Oct. 13, 19 and 24, 2000 by Dr. Maria Sunzel as follows.

- Fast and relatively complete absorption —— with moderate 1st pass extraction and an absolute bioavailability (F) of 50% (t_{max} 1-2 hr, F=34% in males, F=64% in females)
- Moderate plasma protein binding (approx. 85%) for both parent drug and active metabolite with a large volume of distribution after i.v. dosing (138 L; 125 L in males, 143 L in females)
- Metabolized by CYP3A4 to an equi-potent active metabolite, UK-135,800, which appears in the plasma at an exposure of <20% of the parent drug, and has a t½ of 13 h
- Minor metabolism by CYP1A and CYP2D6 (not considered as important routes of metabolism)
- Mostly metabolized with approximately 10% of renal excretion attributed to the parent drug elimination (CL_{iv}=36 L/h, Cl_R=3.9 L/h, estimated in male subjects)
- Secreted into nursing milk (0.02%)
- AUC and C_{max} are not dose proportional from 20-80mg
- A terminal half-life of about 4 hours
- No effect on eletriptan PK after oral doses was found for age, gender, menstrual cycle, moderate to severe renal impairment, and CYP2D6 polymorphic status
- Effects on eletriptan PK after oral dosing were found for race, the onset of the disease (reduction in C_{max} and AUC, t_{max} prolonged), food intake (C_{max} and AUC +20-30%), mild to moderate hepatic impairment (30% decrease in CL), propranolol co-administration (AUC +30%), and erythromycin co-administration (AUC +357%)
- It was shown that the C_{max} and AUC of eletriptan
  - Increased 2.7-fold and 5.9-fold, respectively, during co-administration of eletriptan and ketoconazole
  - Increased 2.2-fold and 2.7-fold, respectively, during co-administration of eletriptan and verapamil
  - Increased 1.4-fold and 2-fold, respectively, during co-administration of eletriptan and fluconazole
  - Were not influenced by concomitant intake of oral contraceptives
- An *in vitro-in vivo* correlation between the interaction potential of CYP3A4 inhibitors on the pharmacokinetics of eletriptan was not established. For example, both verapamil and fluconazole co-administration *in vivo* showed increases in C_{max} and AUC of eletriptan, but the interaction potentials were not detected in the *in vitro* system.

- The maximum increase of DBP elicited by eletriptan was determined to be approximately 12 mmHg and 50% of the maximal DBP increase was reached at eletriptan plasma concentrations of about 130 ng/mL.

In the current submission, the applicant submitted a study to address the coronary safety. The approvability of eletriptan is contingent on the results of the coronary safety study because eletriptan levels are increased in the presence of CYP3A4 inhibitors, and because drugs in its class may cause coronary artery constriction. An approvable letter for Relpax was issued on 12/1/00, in which the applicant was requested to conduct a placebo-controlled study to assess the potential of eletriptan to constrict coronary arteries at eletriptan plasma concentrations (Cp) comparable to exposures seen with CYP3A4 inhibition. The applicant was also requested to include an active control (another triptan) in the study.

This study included a concentration effect analysis which used mixed effects modeling to investigate the relationship between the observed arterial eletriptan concentrations and the measured changes in the mid left anterior descending coronary diameter (mid-LAD) from Study A1601072. The observed decrease in the mid-LAD over time in the placebo data was described using a model with two different slopes (0.502 $\%\cdot min^{-1}$ constriction from baseline between 0 to 15 minute time period and 0.278 $\%\cdot min^{-1}$ constriction from baseline between 15 and 40 minute time period). The additional concentration (treatment) effect was characterized by a linear relationship. The estimated slope of the treatment effect $-7.77 \times 10^{-3}\%\cdot(ng/ml)^{-1}$ approximates to a 1.5% constriction per 80mg dose increment. However, the analysis did not use the last time points (50 min), at which in most cases the effect of constriction was continually increased. The current review can be summarized as follows.

- The concentration effect (baseline subtracted mid-LAD) data showed a hysteresis. The applicant's model did not account for the delay between PK and PD. Further, the data collected do not allow for reliable characterization of the concentration-effect relationship. In other words, the effect seems to continue to increase. The maximum decrease and the time course of mid-LAD returning to baseline are unknown. Without this information, interpretation of the submitted data is not possible. Therefore, the modeling does not support the conclusion regarding the coronary safety.

- The concentrations after two doses of eletriptan separated by 2 hours in the presence of ketoconazole were predicted from a single dose study. This prediction is based on an assumption that the pharmacokinetics of eletriptan are linear. However, the pharmacokinetics of eletriptan are more than dose proportional. The applicant provided a justification to show that while the pharmacokinetics of eletriptan increase slightly more than predicted over a low dose range, there is evidence to indicate the pharmacokinetics of eletriptan are proportional with higher doses (>40mg). Further, based on the in vitro metabolism data there are theoretical reasons to believe that the pharmacokinetics should be linear.

- Study 1072 had sumatriptan treatment arm as an active control. Most of the subjects in this arm showed the similar trend with eletriptan treatment group. At every time point, these two arms showed statistical similarities. However, the maximum decreases and the time course of mid-LAD diameter returning to baseline are unknown. Without this information, interpretation of the submitted data is not possible.

- There is an inconsistency in the concentration measurements between studies A1601045 (venous concentration) and A1601072 (artery concentration). The applicant provided a study to justify the inconsistency which showed that venous and arterial AUC_t, C_{max} and T_{max} were very similar. There were no clinically significant differences between the arterial and venous plasma eletriptan concentrations over time following administration of eletriptan 80mg in the presence of CYP3A4 inhibitor (ketoconazole).

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IV. Question Based Review

1. What is this submission about?

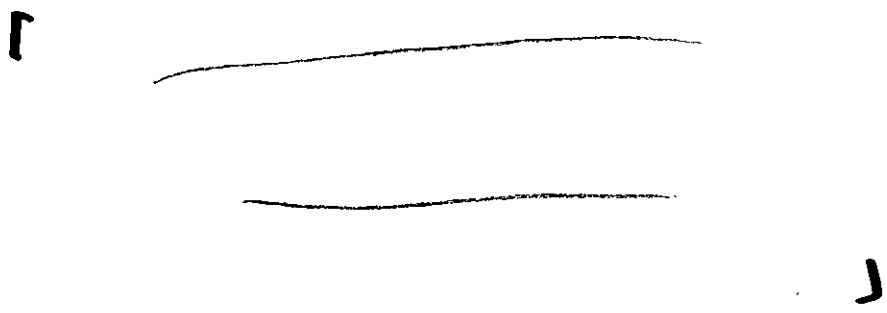
Eletriptan is an oral 5HT1B/1D receptor agonist for the treatment of acute migraine. Its approvability is contingent on the results of the coronary safety study because eletriptan levels are increased in the presence of CYP3A4 inhibitors, and because drugs in its class may cause coronary artery constriction. In the approvable letter for Relpax issued on 12/1/00, the applicant was requested to conduct a placebo-controlled study to address this issue. The current submission provides information in this regard.

2. What was the additional information that was requested in the approvable letter? What information was provided?

Following are the requests for additional information from the approvable letter relevant to Clinical Pharmacology and Biopharmaceutics.

> "You will need to conduct a placebo-controlled study designed to assess the potential of eletriptan to constrict coronary arteries at eletriptan concentrations that are higher than those achieved in Study 211 and that are comparable to exposures seen with CYP3A4 inhibition. The study should include several active controls of available triptans. The subjects studied should be those with suspected coronary artery disease who have been selected for diagnostic coronary angiography. We will be happy to discuss the design of the study with you."

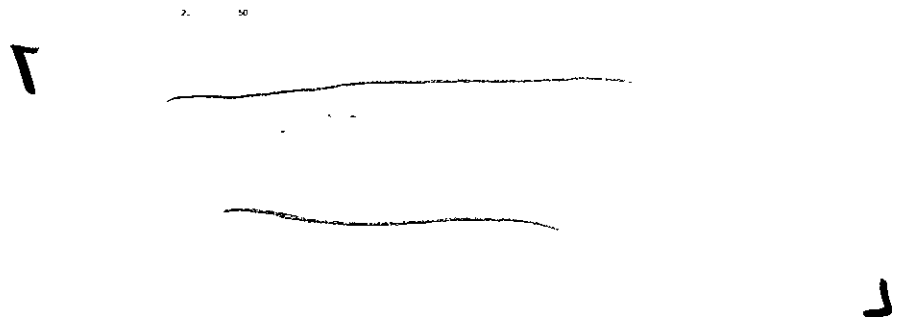
In the current submission, the applicant provided a concentration effect analysis to address this issue. This study used mixed effects modeling to investigate the relationship between the observed arterial eletriptan concentrations and the measured changes in the mid left anterior descending coronary diameter (mid-LAD) from Study A1601072. The observed decrease in the mid-LAD over time in the placebo data was described using a model with two different slopes (0.502 $\%\cdot min^{-1}$ constriction from baseline between 0 to 15 minute time period and 0.278%$\cdot min^{-1}$ constriction from baseline between 15 and 40 minute time period). The concentration (the treatment) effect was characterized by a linear relationship. The estimated slope of the treatment effect $-7.77 \times 10^{-3}\%\cdot(ng/ml)^{-1}$ approximates to a 1.5% constriction per 80mg dose increment. Following figure shows some examples for the mid-LAD diameter- and concentration-time profiles (left panel) and the relationship between concentration and effect (mid-LAD diameter, right panel).



3. Is the concentration effect analysis study acceptable?

No. The concentration effect model is not appropriate for describing the data due to the following reasons.

- The last time point (50 min post infusion, 10 min post end of infusion) was not used in the proposed model.
- A delay exists between concentration and mid-LAD constriction. The model did not account for this delay. The following figure shows the mid-LAD diameter- and concentration-time profiles (left panel) and the relationship between concentration and effect (mid-LAD diameter, right panel) for the same examples as last figure with the last time point included.



- Most importantly, the maximum decrease and the time course of mid-LAD diameter returning to baseline are unknown. Without this information, interpretation of the submitted data is not possible. Therefore, the modeling does not support the conclusion regarding the coronary safety.

4. What is the result for the sumatriptan arm as an active control?

The mid-LAD constriction effect profiles for the sumatriptan treatment arm are not statistically different from that for the eletriptan treatment arm at every time point. However, the maximum decreases and the time course of mid-LAD diameter returning to baseline are unknown. Without this information, interpretation of the submitted data is not possible.

5. Is the prediction of concentrations for two 80 mg doses of eletriptan separated by 2 hours in the presence of ketoconazole appropriate?

Yes. This prediction is based on a simulation from a model built from single 80mg dose of eletriptan coadministered with ketoconazole. The simulation is contingent on the linearity of eletriptan pharmacokinetics. However, the pharmacokinetics of eletriptan are more than dose proportional. The applicant made a justification as follows.

In the formal dose proportionality study (160-228) dose corrected C_{max} and AUC values for doses from across the clinical dose range (20, 40 and 80 mg) were compared. The ratios for the dose normalized values and 90% confidence interval (CI) for these comparisons are shown below. These data indicate that the pharmacokinetics are essentially dose proportional above 40mg.

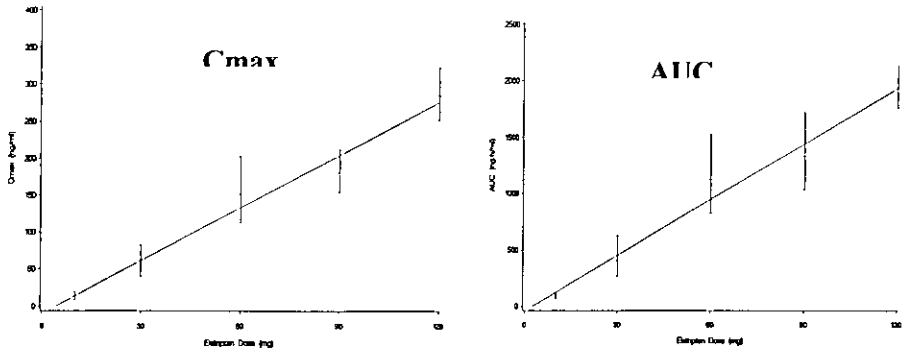
Cmax

Comparison:	*Ratio Between Geometric Means (%)*	*90% Confidence Intervals (%)*	*P*
40mg/20mg	112.2	99.1, 126.9	0.13
80mg/40mg	108.4	95.8, 122.7	0.28

AUC

Comparison:	*Ratio Between Geometric Means (%)*	*90% Confidence Intervals*	*P*
40mg/20mg	120.0	109.7, 131.3	<0.05
80mg/40mg	105.9	96.8, 115 8	0.29

These results are supported by the data from study 160-001. Although this study was not designed to investigate dose proportionality, data from across a wider dose range (10 to 120 mg) is available. The data indicates that the PK are dose proportional over this wider dose range (see figure below).



Points are the Geometric means, Intervals are the 90%CI's, lines show the linear regressions

The applicant also provided supportive information with the in vitro data on the metabolism of eletriptan by CYP3A4. In vitro studies have demonstrated that the in vitro biotransformation of eletriptan by human liver microsomes is consistent with Michaelis-Menten kinetics, having an apparent Km value of 144 µM.

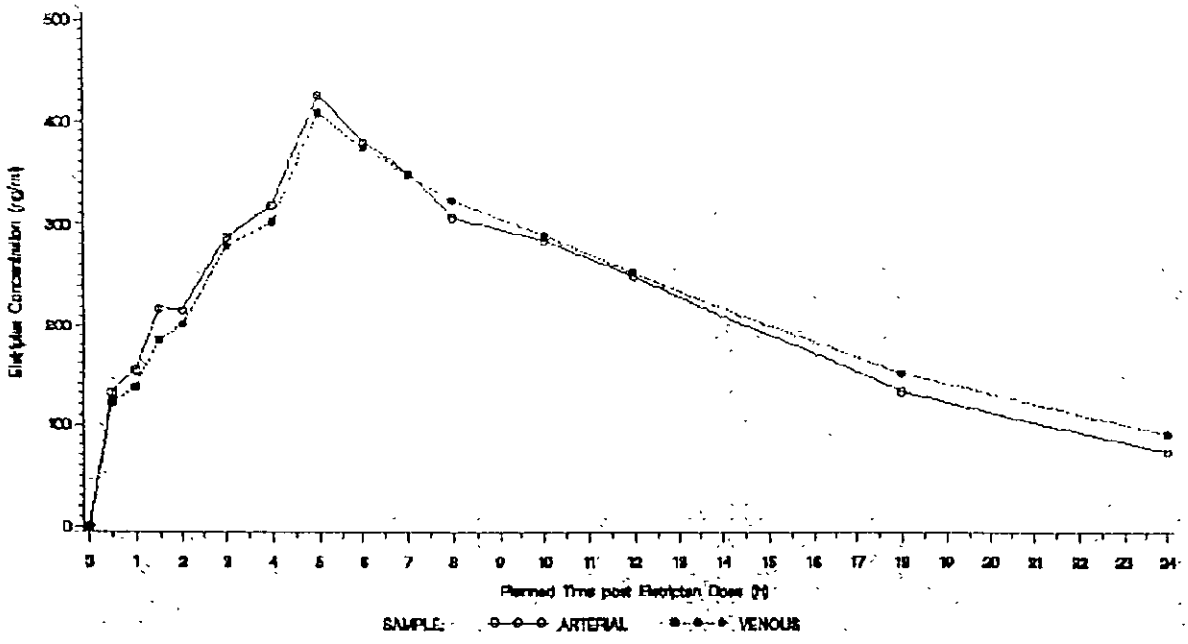
The Km value of 144 µM is equivalent to 55 µg/ml (55,000 ng/ml). The relation of Km to anticipated in vivo plasma concentrations of eletriptan (designated as [S]) provides an estimate of the probability of kinetic nonlinearity due to saturable metabolism. Cmax values after 80 mg doses of eletriptan average approximately 190 ng/ml (0.5 µM). When a single dose of 80 mg eletriptan is administered with ketoconazole the mean C_{max} value is 491 ng/ml (1.29 µM). Even

when two doses of 80mg eletriptan separated by two hours are administered with ketoconazole to a migraineur the mean C_{max} value is 598 ng/ml (1.57 μM). Thus even in extreme cases, eletriptan plasma levels do not approach Km, and the maximum ratio of plasma level divided by Km ([S]/Km ratio) would not exceed 0 01.

Therefore, while the pharmacokinetics of eletriptan increases slightly more than predicted over a low dose range, there is evidence to indicate the pharmacokinetics of eletriptan are proportional with higher doses (>40mg). Based on the in vitro metabolism data there are theoretical reasons to believe that the pharmacokinetics should be linear in the case of predicting from one dose of 80mg in presence of ketoconazole to two doses of 80mg separated by two hours in the presence of ketoconazole.

6. There is an inconsistency in the concentration measurements between studies A1601045 (venous concentration) and A1601072 (artery concentration). Is the artery concentration similar to venous concentration?

Yes. The applicant provided a study (protocol #1601087) to justify the inconsistency in the concentration measurements between studies A1601045 (venous concentration) and A1601072 (artery concentration). The study showed that venous and arterial AUC_t, C_{max} and T_{max} were very similar. There were no clinically significant differences between the arterial and venous plasma eletriptan concentrations over time following administration of eletriptan 80mg in the presence of CYP3A4 inhibitor (ketoconazole) as shown in the following figure (See Appendix III for details).



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APPENDIX II. PHARMACOMETRIC REVIEW

Pharmacometrics Review

NDA:	21-016
Drug name:	Eletriptan HBr (Relpax™)
Dosage strength:	Immediate release tablets (20, 40, 80 mg)
Submission date:	June 27, 2002
Applicant:	Pfizer Eastern Point Road, Groton, CT 06340
Reviewer:	John Duan, Ph.D.
Team Leader:	Joga Gobburu, Ph.D.

Background:

Eletriptan is an oral $5HT_{1B/1D}$ receptor agonist for the treatment of acute migraine. Its approvability is contingent on the results of the coronary safety study because eletriptan levels are increased in the presence of CYP3A4 inhibitors, and because drugs in its class may cause coronary artery constriction. An approvable letter for Relpax was issued on 12/1/00, in which the applicant was requested to conduct a placebo-controlled study to assess the potential of eletriptan to constrict coronary arteries at eletriptan plasma concentrations (Cp) comparable to exposures seen with CYP3A4 inhibition. The applicant was also requested to include an active control (another triptan) in the study. In the current submission, the applicant submitted a concentration effect analysis to support the coronary safety of the drug. The current review evaluates the PK-PD analysis.

Objectives:

To investigate the relationship between the observed arterial eletriptan concentrations and the measured changes in the mid left anterior descending coronary diameter (mid-LAD diameter) from Study A1601072 and to use the resultant model to predict the typical mid-LAD diameter change associated with the mean Cmax following for one 80mg dose of eletriptan in the presence of ketoconazole (CMAX1) or two doses of 80mg eletriptan separated by 2 hours and concomitantly administered with ketoconazole during a migraine (CMAX2M).

Design

Data:

Study A1601072

This study was an acute, double blind, placebo-controlled, parallel group study of coronary vascular responsiveness during administration of the $5HT_{1B/1D}$-receptor agonists, eletriptan (IV) or sumatriptan (SC), as determined using quantitative coronary angiography. Subjects received study drug as a 40 minutes IV infusion or a sc injection. Eletriptan hydrobromide supplied in IV solution (2mg/ml) was delivered as an 18, 26 or 36ml infusion, for the 36, 52 and 72mg eletriptan dose, respectively. For the 36mg dose, investigators infused eletriptan solution at 0.325ml/min (0.65mg/min) for 20 minutes to administer the first 13mg of eletriptan followed by 0.575ml/min (1.15mg/min) for the next 20 minutes to administer the remaining 23mg of

eletriptan. For the 52mg dose, investigators infused eletriptan solution at 0.475ml/min (0.95mg/min) for 20 minutes to administer the first 19mg of eletriptan followed by 0.825ml/min (1.65mg/min) for the next 20 minutes to administer the remaining 33mg of eletriptan. For the 72mg dose, investigators then infused eletriptan solution at 0.650ml/min (1.30mg/min) for 20 minutes to administer the first 26mg of eletriptan followed by 1.150ml/min (2.30mg/min) for the next 20 minutes to administer the remaining 46mg of eletriptan. The commercially available sumatriptan succinate for sc administration was used as Imitrex®, STATdose® SYSTEM Kits comprising two cartridges each containing 6mg of sumatriptan in 0.5ml of solution and administered sc. Investigators performed quantitative arterial coronary angiography (QCA) at two coronary artery regions and took blood samples for pharmacokinetic analysis at 5, 15, 40 and 50 minutes after the start of the infusion. All subjects randomized to either eletriptan or placebo were included in the concentration effect analysis. 154 observations from 42 subjects, measured at set time points during the 40-minute infusion of eletriptan or placebo were included in the analysis. Seventy-two of the observations were available from 18 subjects randomized to placebo. The mid-LAD segment diameters measured only at 0, 5, 15 and 40 minutes during the infusion were used in the analysis. The planned time was used for all observations except the 40 minutes observation for Subject 50, where the actual observed time of 25 minutes was utilized. Missing, non-reportable and post start of infusion BLQ pharmacokinetic observations were excluded from the analysis. Points where the mid-LAD diameter observations were missing were also excluded from the analysis.

Other Studies

Study 1601045 was an open randomized, placebo controlled, two-period crossover study to investigate the effects of ketoconazole on the pharmacokinetics, safety and toleration of a single oral dose of eletriptan (80mg) in 18 subjects. Plasma samples were taken at 0, 0.5, 1, 1.5, 2, 3, 4, 6, 8. 12, 18, 24, 36, and 48 hours after an 80mg eletriptan IR dose on Day 3, in subjects who were taking ketoconazole 400mg on Day's 1 to 4.

Study 160101 investigated the pharmacokinetics of eletriptan in the presence and absence of a migraine attack. The ratio of geometric mean Cmax values was 67.3%, indicating that Cmax was reduced by 32.7% when eletriptan was administered during a migraine attack.

Methods:

The mean observed C_{max} (CMAX1) was taken from Study A1601045. The concentration time data from the eletriptan plus ketoconazole treatment period in this study was modeled and individual estimates of the expected C_{max} following administration of 2 doses of 80mg of eletriptan separated by 2 hours and concomitantly administered with ketoconazole (CMAX2) were subsequently estimated by simulation using the individual pharmacokinetic parameters and the original A1601045 sampling scheme. The mean estimate of CMAX2 was calculated from the predicted individual CMAX2 values.

The C_{max} was reduced by 32.7% when eletriptan was administered during a migraine attack from Study 160101. The CMAX1M and CMAX2M were calculated by correcting CMAX1and CMAX2 for this effect.

Analysis of the relationship between concentration and mid-LAD diameter was performed using the mixed effects modeling approach in NONMEM, version V. The mixed effect model estimates the means of parameters, the interindividual variability components and the residual variability The FOCE (first order conditional estimation) method was used throughout this analysis

The constriction associated with the mean observed CMAX1 and CMAX2 were predicted using the mid-LAD diameter concentration effect model.

Data Checking

The reviewer plotted the concentration and mid-LAD diameter against time to check the data distribution. The placebo group (without concentration data) and the eletriptan group are plotted in different panels.

Models

Structural Model

Linear models for placebo and treatment effects were used to estimate the proportional change from the pre-dose baseline value.

Random Variance Models

An additive residual error model was utilized: $Y=F+\varepsilon$ (in NONMEM notation), where Y represents the observation, F the individual concentration prediction and ε is a symmetrically distributed, zero-mean random variable with a variance term that is estimated as part of the population model fitting process.
Interindividual variability terms were included on all the structural parameters of the model where supported by the data. Exponential models were used to account for interindividual variability such that the value of a parameter value in an individual (Pi) was a function of the parameter value in the typical individual (Ppop) and an individual deviation represented by η_i: $Pi=Ppop*\exp(\eta_i)$. The η's in the population are symmetrically distributed, zero-mean random variables with a variance that is estimated as part of the model.

Model Selection

The objective function values were used to select models. However, the detailed information was not submitted.

Software

The softwares used include NONMEM (version V level 1.1) [redacted] for modeling and simulation.

Results and Discussion

Data Checking

The reviewer plotted the concentration and mid-LAD diameter against time to check the data distribution. The placebo group (without concentration data) and the eletriptan group (with concentration data) are plotted in different panels. The upper three panels show the mid-LAD diameter time profile for placebo group and the lower four panels show the concentration-time

profile and mid-LAD diameter time profile for the treatment group. It was noted that at time point of 50 min (10 min after the end of infusion), the concentrations of eletriptan were decreased (compared to the end of infusion, time point 40 min) in most of the cases. However, the mid-LAD diameters were continuously decreased from the end of infusion in most cases. Therefore, the proposed model is not appropriate to describe the relationship between eletriptan concentration and mid-LAD diameter. In the lower four panels, the blue line represents the concentrations of eletriptan and the red line for the mid-LAD diameters.

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Model and Model Selection

A total of 154 mid-LAD diameter observations from 42 subjects were utilized in the analysis, with the 18 placebo subjects providing 72 observations. The mid-LAD diameter decreased over the time of the infusion in the placebo group. A model using two different slopes (0 502 %•min^{-1} constriction from baseline between 0 to 15 minute time period and 0.278 %•min^{-1} constriction from baseline between 15 and 40 minute time period) was used to account for this placebo effect since a single slope model over predicted the mid-LAD diameter at 40 minutes. The concentration (treatment) effect model was characterized by a linear relationship. The applicant concluded that there was no evidence that a more complex model was required to describe the data.

Interindividual variability was estimated on baseline and the combination of placebo and treatment effects. Separate interindividual variability terms on the placebo and treatment effects could not be supported by the data. Residual variability was estimated to have a standard deviation of 0.08 mm.

Table 1 shows the mean and variability estimates for the final model. Observed mid-LAD diameter versus the population and individual predictions for subjects randomized to eletriptan or placebo are shown in Figure 2. The estimated slope of the treatment effect is -7.77 x10^{-3}%•(ng/ml)$^{-1}$.

Table 1. Parameter estimates for the final model.

Parameter		Placebo effect		Treatment effect
	Baseline (mm)	Slope (t0-t15) (%.min^{-1})	Slope (t15-t40) (%.min^{-1})	Slope (%.(ml. ng)$^{-1}$)
Fixed Effect	2.35	-5.02 x10^{-1}	-2.78 x10^{-1}	-7.77 x10^{-3}
RSE (%)	5%	15%	11%	24%
	Baseline	Combined (placebo/treatment effect)	Covariance (baseline and combined effect)	
IIV(%CV)	28%	6%	3%	
RSE(%)	18%	38%	>100%	
Residual Error (mm)	0.08			
RSE(%)	24%			

RSE – relative standard error (SE/ESTIMATE *100)
IIV – Interindividual variability

The data from Study A1601045 were fit to a two compartment model with first order absorption and an absorption lag. The mean observed C_{max} (CMAX1) was 491ng/ml with 29% CV and a range of 338 - 904 ng/ml. Plots of the population and individual predictions versus observed concentration for the fit are shown in Figure 3. Based on this model, a simulation was conducted to get the individual pharmacokinetic parameters for two doses of 80mg of eletriptan separated by 2 hours and concomitantly administered with ketoconazole. Figure 4 shows the predicted individual concentration time profiles based on these parameters. The mean predicted C_{max} (CMAX2) was 889ng/ml.

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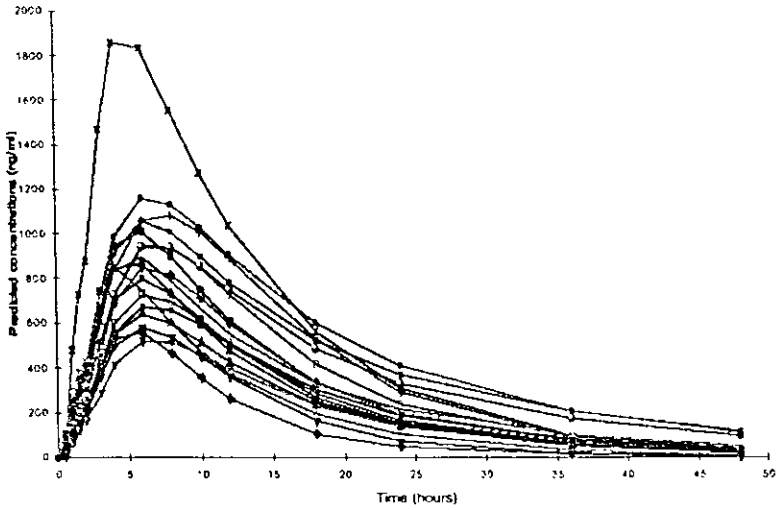
Fig 4. Simulated plasma concentration time profiles for two doses of 80 mg eletriptan separated by 2 hours in the presence of ketoconazole.



After accounting for the effect of migraine the resulting mean predicted CMAX1M and CMAX2M were 330ng/ml and 598ng/ml, respectively. Figure 5 shows the observed 40 minute (end of infusion) concentration for subjects from Study A101072 along with the target concentration, the observed CMAX1 data and the predicted CMAX2M. The observed mean 40 min concentration of 660ng/ml exceeds the predicted mean CMAX2M.

Fig 5. The observed concentrations for subjects from study 1072 and 1045 (CMAX1) and predicted C_{max} for two doses of eletriptan separated by 2 hours in the presence of ke0toconazole and migraine (CMAX2M).

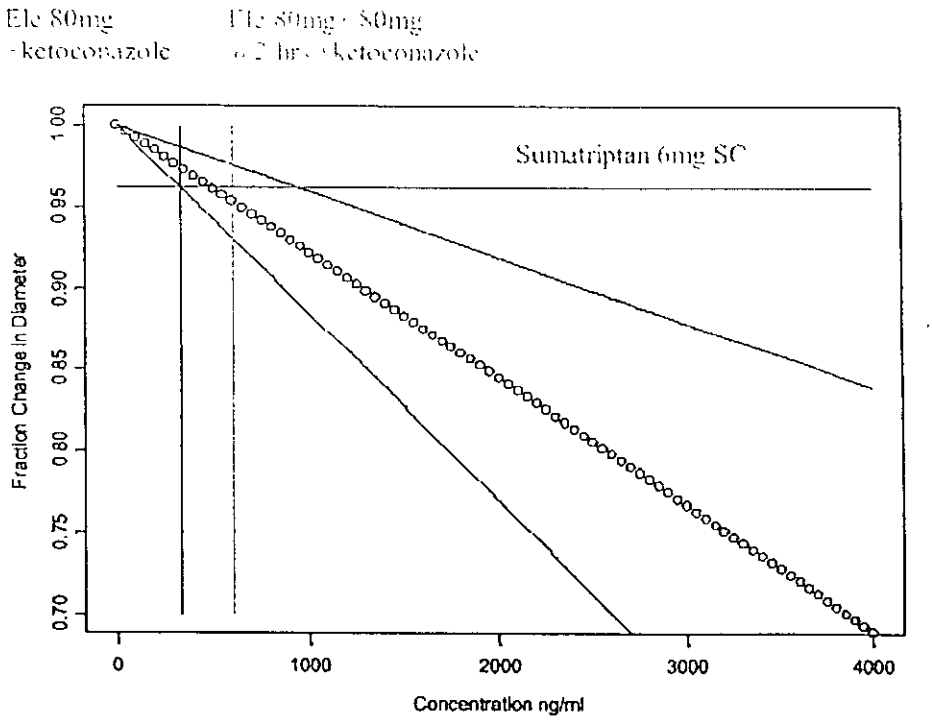
Table 2 shows the predicted mean percentage mid-LAD diameter constrictions based on the observed mean CMAX1, the predicted mean CMAX2, the predicted mean CMAX1M and the predicted mean CMAX2M. Figures 6 shows the mid-LAD diameter constriction predictions for mean CMAX1 and mean CMAX2M along with the extrapolated model predictions. The maximum observed constriction for Sumatriptan 6mg SC from Study A1601072 is also shown.

Table 2. Predicated Mid-LAD constrictions for CMAX1, CMAX2, CMAX1M, and CMAX2M.

	80mg + Keto		80mg + 80mg @ 2hr +Keto	
	Mean C_{max} (ng/ml)	Mean constriction (%)	Mean C_{max} (ng/ml)	Mean constriction (%)
Absence of Migraine	491*	3.8%#	889**	6.9%##
Presence of Migraine	330***	2.6%###	598****	4.6%####

*** The observed mean CMAX1, **The predicted mean CMAX2, ***The predicted mean CMAX1M, ****The predicted mean CMAX2M, # Predicted mean constriction based on the observed mean CMAX1, ## Predicted mean constriction based on the predicted mean CMAX2, ### Predicted mean constriction based on the predicted mean CMAX1M, #### Predicted mean constriction based on the predicted mean CMAX2M**

Fig 6. The simulated Mid-LAD diameter constrictions associated with CMAX1, and CMAX2M (the dotted and solid diagonal lines represent the prediction and its 95% confidence interval of the constriction, respectively).



Discussion

The validity of the results

1 There is an inconsistency for the concentration measurement between the studies. The venous concentrations of the drug were measured in Study A1601045 and arterial concentrations of the drug were measured in study A1601072. Protocol 1601087 entitled "Arterial and venous pharmacokinetics of a single oral dose of eletriptan 80 mg in healthy subjects in the presence of ketoconazole" has been completed and submitted, which showed that the arterial and venous pharmacokinetics of eletriptan are comparable.

2. The concentration time data from the single dose of eletriptan plus ketoconazole treatment period in Study A1601045 was modeled and based on the model, the concentrations after two doses of eletriptan separated by 2 hours were predicted. This simulation is contingent on an assumption that the pharmacokinetics of eletriptan are linear. However, the pharmacokinetics of eletriptan are more than dose proportional over the clinical dose range. Per request, the applicant made proper justification, which is acceptable.

3. The analysis did not employ the last time point (50 min). As shown in the plot of Fig 1, although the concentration at 50 min (10 min post of end of infusion) was decreased compared to the concentration at the end of infusion (at 40 min time point), the constriction effect was still increasing (the mid-LAD diameter kept decreasing). In order to visualize the differenece between using the last time point versus not using it, two sets of plots of effect versus concentration were made. Fig 7 uses the last time point and Fig 8 does not. As can be seen, in most subjects of Fig 8, a linear relationship is obvious. However, in most cases of Fig 7, a hysterresis is seen. Therefore, the model proposed in the submission is not appropriate.

This hysteresis effect may be caused by several factors: including active metabolite, disequilibrium between plasma and biophase, and indirect effect. It is uncertain if the data collected covers the peak effect. For this reason, it is difficult to make effort to correctly interpretate these data with or without modeling.

Due to these reasons, the model selected is not qualified for the data and the modeling does not support the conclusions regarding the coronary safety.

On the other hand, study 1072 had sumatriptan arm as an active control. In order to compare eletriptan arm with this arm, plots of effect against concentration are generated for sumatriptan arm as shown in Fig 9. Most of the subjects showed the similar trend with eletriptan treatment group. The table below (Table 3) provides the mid-LAD diameter and the changes from the baseline at different time points for placebo and treatment (eletriptan and sumatriptan) groups. Fig 10 provides a comparison between the two treatment groups. Table 4 shows the comparisons of the baseline corrected effect of eletriptan IV, at 5, 15 and 40 minutes post-start of infusion and 10 minutes post-end of infusion, and the time of maximum sumatriptan 6mg sc effect (at mean concentration 67.9ng/ml) on the mid-LAD diameter.

Fig 10 and Table 4 indicated that at every observed time point, the baseline corrected effects are not significantly different between eletriptan and sumatriptan.

Table 3. The mid-LAD diameters and the changes from the baseline at different time points for eletriptan, sumatriptan and placebo groups.

Eletriptan

Time(min)	N	Mean±SD	Range	Change from baseline	
				Mean±SD	Range
0	20	2 2882±0.64063			
5	20	2.1352±0 62288		-0 1530±0 12807	-
15	19	2.0998±0.65049		-0 2209±0 11397	-
40	19	1.9228±0 58142		-0.3991±0.23873	-
50	19	1.8593±0.60938		-0.4626±0.17098	-

Sumatriptan

Time (min)	N	Mean±SD	Range	Change from baseline	
				Mean±SD	Range
0	18	2.5343±0.75681			
5	18	2 3917±0 73606		-0.1426±0.10512	
15	17	2.2431±0.70883		-0 2376±0 13597	
40	18	2 1841±0.71117		-0.3502±0 18848	
50	18	2 0604±0 68690		-0.4739±0 16698	

Placebo

Time (min)	N	Mean±SD	Range	Change from baseline	
				Mean±SD	Range
0	18	2.5407±0.76263			
5	18	2.4472±0.75662		-0 0935±0.12557	
15	18	2.3050±0.70922		-0.2357±0 18687	
40	18	2.2280±0.70846		-0 3128±0.19940	
50	18	2 1620±0.73577		-0.3787±0.20822	

Table 4. The comparisons of the baseline corrected effect of eletriptan IV and the time of maximum sumatriptan 6mg sc effect on the mid-LAD diameter.

Drug	Time	Geometric mean mid-LAD diameter ratio[a]	Ratio[b]	95% CI
Eletriptan	5 mins post-start of infusion	0 96	1.00	0.96 to 1.05
Sumatriptan		0.96		
Eletriptan	15 mins post-start of infusion	0.99	1 02	0.98 to 1.07
Sumatriptan		0.96		
Eletriptan	40 mins post-start of infusion	0.95	0.98	0.93 to 1.04
Sumatriptan		0.96		
Eletriptan	10 mins post- end of infusion	0.95	0.98	0.94 to 1.03
Sumatriptan		0.96		

[a]antilog of the mean log(minimum mid-LAD diameter post-start of infusion / baseline mid-LAD diameter).
[b]the ratio of the geometric means eletriptan iv:sumatriptan 6mg sc;

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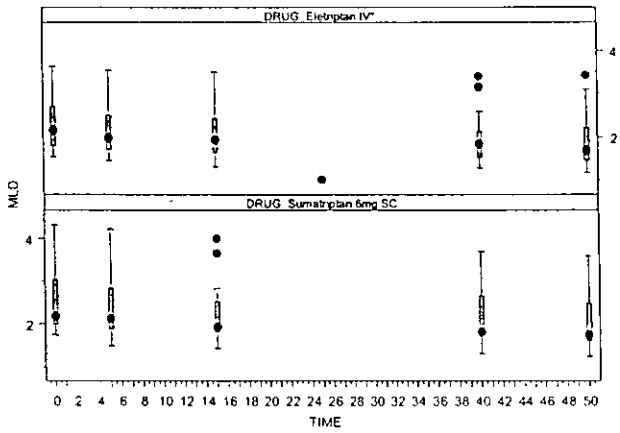
Fig 10. The time courses of mid-LAD diameters by treatment group.



The significance of the results

The concentration effect model presented in the submission is not qualified and is therefore not supportive for the conclusion regarding the coronary safety.

The comparison among the different arms showed similarity. The clinical singnificance of this similarity is subject to medical review.

Conclusions and Recommendations

Conclusions

1. The proposed concentration-effect model is not appropriate to describe the data due to the following reasons.

- The last time point (50 min post infusion, 10 min post end of infusion) was not used in the proposed model.
- The hysteresis effect is not accounted.
- The maximum decrease and the time course of mid-LAD returning to baseline are unknown. Without this information, interpretation of the submitted data is not possible.

2. The concentrations after two doses of eletriptan separated by 2 hours were predicted from a model. This model was built from concentration time data in Study A1601045 for the single dose of eletriptan plus ketoconazole treatment arm. This simulation is contingent on an assumption that the pharmacokinetics of eletriptan are linear. However, the pharmacokinetics of eletriptan are more than dose proportional over the clinical dose range. The applicant made proper justification, which is acceptable.

Recommendations

1. The data collected are inadequate to reliably characterize the complete effect of eletriptan on mid-LAD diameter. Data over the full time course of effect is required.

2 Due to the non-linearity of the eletriptan pharmacokinetics, the concentrations for two doses of eletriptan separated by 2 hours were under-predicted. The applicant made proper justifications to address this issue, which is acceptable.

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Appendix

Population Pharmacodynamics Model Control Stream

```
$PROB  eletriptan 1072 PK/PD
,,Basic Model
;;;;
$INPUT ID TIME DV PAT CONC
$DATA  C:\nonmempc\N21-016\1072.csv
$PRED

BASE=THETA(1)*EXP(ETA(1))
IF(TIME.LT.20) THEN
PLAC= (1+THETA(2)*TIME**THETA(4));  THETA 4 is fixed to 1
ELSE
PLAC= (1+THETA(5)*TIME**THETA(4));  THETA 4 is fixed to 1
ENDIF
DEFF= (1+THETA(3)*CONC)
IND=0
IF(TIME.GT.0) IND=1
F=BASE*(1-IND)+BASE*PLAC*DEFF*IND*EXP(ETA(2))
IPRE=F
Y=F+ERR(1)

$THETA (0,2) (-0.008) (-0.0005) (1,FIXED) (-0.008)

$OMEGA BLOCK(2) 0.1 0.01 0.1

$SIGMA 1
$ESTIMATION MAXEVALS=3000 SIG=4 PRINT=10 METHOD=CONDITIONAL
$TABLE ID TIME PAT CONC ETA1 ETA2 IPRE NOPRINT ONEHEADER FILE=sdtab521
$COV
```

Appendix III Study A1601087

Study title: Arterial and venous pharmacokinetics of a single oral dose of eletriptan 80mg in healthy subjects in the presence of ketoconazole (A1601087)

Investigator: William B. Smith

Study period: 8 August 2002 to 26 August 2002

Study Objectives: The objective was to determine and compare the arterial and venous pharmacokinetics of eletriptan in the presence of ketoconazole.

Study Design: This was an open-label study of a single dose of eletriptan in the presence of ketoconazole. There was a screening visit, one study visit lasting four days and four nights and a follow up phone call two to four days later.

During the study visit, subjects received ketoconazole 400mg on Days 1, 2 and 3 and eletriptan 80mg on Day 3. On Day 3, subjects had an arterial (radial artery hep-lock) and venous (peripheral arm vein) catheter fitted for pharmacokinetic blood sampling. Subjects received ketoconazole 400mg under the same conditions as on Days 1 and 2 (except that the times of lunch and dinner were specified as four and ten hours post-dose, respectively) followed by eletriptan 80mg. Pharmacokinetic blood samples and blood pressure and pulse rate pre-dose were measured and at specified times up to 24 hours post-dose.

The maximum observed venous plasma eletriptan concentration (VC_{max}), maximum arterial plasma eletriptan concentration (AC_{max}), the time to first occurrence of the maximum observed venous eletriptan plasma concentration (VT_{max}) and the time to first occurrence of maximum arterial eletriptan plasma concentration (AT_{max}) were obtained directly from the data. The area under the venous plasma eletriptan concentration-time curve ($VAUC_t$) and the area under the arterial plasma eletriptan concentration-time curve ($AAUC_t$) were calculated using the linear trapezoidal method.

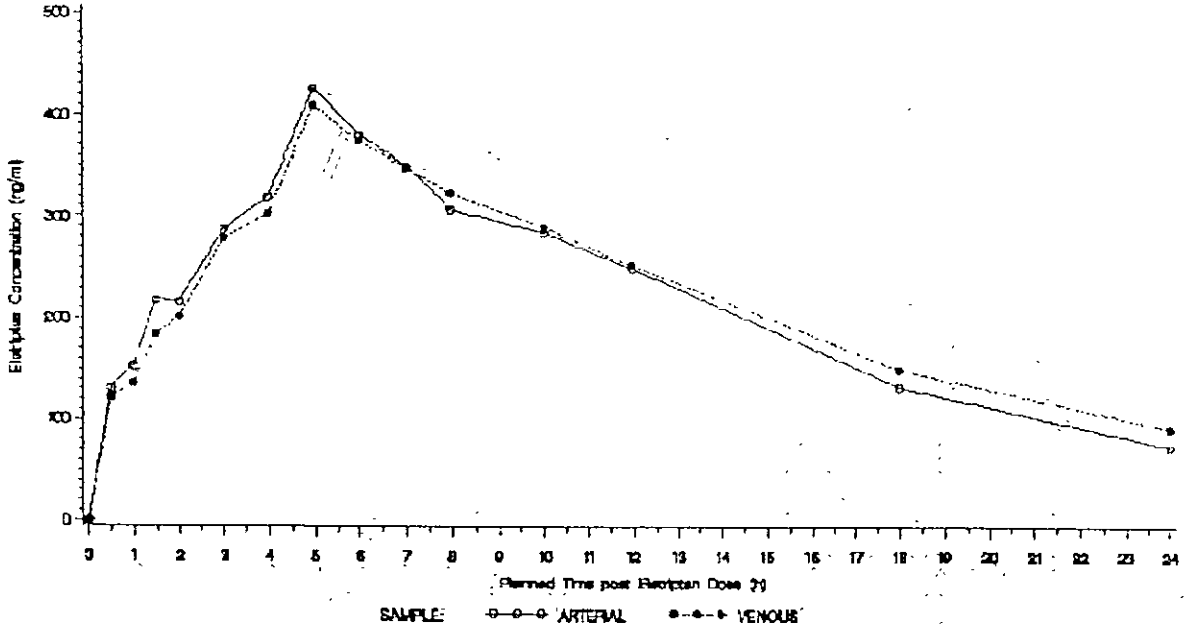
The mean and individual plasma eletriptan concentrations over time and AUC_t and T_{max} for arterial and venous samples and arterial concentrations at the venous eletriptan T_{max} were tabulated. The log transformed concentrations for arterial and venous samples at the time of C_{max} for the venous samples were analyzed using a paired t-test. The mean difference between the log transformed concentrations for arterial and venous samples at venous C_{max}, the standard error associated with this difference and 95% CIs for the difference were presented as were the anti-logged mean difference and the anti-logged CIs.

Pharmacokinetics:

The pharmacokinetic results showed that the mean arterial concentration at VT_{max} was 8% (95% CI: 3 to 14%) higher than the venous concentration and that the arterial and venous concentrations are very similar over the 24 hours time course. In addition, venous and arterial AUC_t, C_{max} and T_{max} were very similar as shown in the following tables.

	Venous	Corresponding arterial	Geometric mean ratio (%)	95% CI
C_{max} (ng/ml)	383	415	108	103, 114
AUC (ng•h/mL)	4863	4699	-	-
T_{max} (h)	5.1	5.1	-	-

The figure below shows the arterial and venous mean plasma eletriptan concentrations up to 24 hours post-dose.



Comments:

1. This study showed that venous and arterial AUC_t, C_{max} and T_{max} were very similar. There were no clinically significant differences between the arterial and venous plasma eletriptan concentrations over time following administration of eletriptan 80mg in the presence of CYP3A4 inhibitor (ketoconazole).

2. The accuracy and precision of the assay for eletriptan at the low QC —— are out of the acceptable range. Although for this study this is not a concern since the lowest concentrations observed are —— . the applicant should check the method and properly validate the assay in future if lower concentrations are expected.

Appendix IV

Office of Clinical Pharmacology and Biopharmaceutics

New Drug Application Filing and Review Form

General Information About the Submission

	Information		Information
NDA Number	21-016	Brand Name	Relpax
OCPB Division (I, II, III)	I	Generic Name	Eletriptan
Medical Division	Neurology Drug Products	Drug Class	Anti migraine
OCPB Reviewer	John Duan	Indication(s)	Migraine
OCPB Team Leader	Ramana Uppoor	Dosage Form	Tablets
	Joga Gobburu	Dosing Regimen	20, 40, 80 mg
Date of Submission	6/27/20/02	Route of Administration	Oral
Estimated Due Date of OCPB Review	11/1//02	Applicant	Pfizer
PDUFA Due Date	12/27/02	Priority Classification	3S
Division Due Date	12/27/02		

Clin. Pharm. and Biopharm. Information

	"X" if included at filing	Number of studies submitted	Number of studies reviewed	Critical Comments if any
STUDY TYPE				
Table of Contents present and sufficient to locate reports, tables, data, etc.	X			
Tabular Listing of All Human Studies	X			
HPK Summary				
Labeling	X			
Reference Bioanalytical and Analytical Methods				
I. Clinical Pharmacology				
Mass balance:				
Isozyme characterization:				
Blood/plasma ratio:				
Plasma protein binding:				
Pharmacokinetics (e.g., Phase I) -				
Healthy Volunteers-				
acute dose:				
chronic dose:				
Patients-				
acute dose:				
chronic dose:				
Dose proportionality -				
Fasting / non-fasting acute dose:				
Fasting / non-fasting chronic dose:				
Drug-drug interaction studies -				
In-vivo effects on primary drug:	x	1	1	
In-vivo effects of primary drug:				
In-vitro:				
Subpopulation studies -				
Ethnicity:				
Gender:				
Pediatrics:				
Geriatrics:				
renal impairment:				
hepatic impairment:				
PD:				
Phase 2:				
Phase 3:				
PK/PD:				

Phase 1 and/or 2, proof of concept	X	1	1	
Phase 3 clinical trial				
Population Analyses -				
Data rich				
Data sparse				
II Biopharmaceutics				
Absolute bioavailability:				
Relative bioavailability -				
solution as reference:				
Alternate formulation as reference.				
Bioequivalence studies -				
Traditional design, acute / multi dose:	X	2		
Replicate design; acute / multi dose:				
Food-drug interaction studies:				
Dissolution:				
(IVIVC):				
Bio-wavier request based on BCS				
BCS class				
III Other CPB Studies				
Genotype/phenotype studies:				
Chronopharmacokinetics				
Pediatric development plan				
Literature References				
Total Number of Studies		4	2	

Filability and QBR comments

	"X" if yes	*Comments*
Application filable ?	X	Reasons if the application is not filable (or an attachment if applicable) For example, is clinical formulation the same as the to-be-marketed one?
Comments sent to firm ?	N/A	Comments have been sent to firm (or attachment included) FDA letter date if applicable.
QBR questions (key issues to be considered)	**1. Is the modeling supportive to address the issue raised in the approvable letter?**	
Other comments or information not included above		
Primary reviewer Signature and Date	**John Duan 10/1/02**	
Secondary reviewer Signature and Date	**Ramana Uppoor 10/1/02**	

CC: NDA 21-016, HFD-850 (Electronic Entry or Lee), HFD-120 (CSO), HFD-860 (Uppoor, Mehta), CDR

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

John Duan
12/11/02 01:04:32 PM
BIOPHARMACEUTICS

Jogarao Gobburu
12/12/02 09:26:28 AM
BIOPHARMACEUTICS

Ramana S. Uppoor
12/12/02 11:39:51 AM
BIOPHARMACEUTICS

COMPLETED NOV 20 2000

NOV 20 2000

OFFICE OF CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW

Eletriptan HBr (Relpax™)
Immediate release tablets (20, 40, 80 mg)
NDA 21-016

Pfizer Inc.
Eastern Point Road, Groton, CT 06340

Submission Dates:	Jun. 1, Aug. 9, and Oct. 13, 19 and 24, 2000
Primary Reviewer:	Maria Sunzel, Ph.D.
Indication:	Migraine
Submission Type:	Resubmission, Class I (Amendment to NDA 21-016)

EXECUTIVE SUMMARY

An approvable letter was issued on 11/27/99 for Relpax™ (eletriptan HBr), for treatment of acute migraine attacks with or without aura in adults. The 80 mg tablet was not included in the approvable action, due to inconclusive data regarding the safety and lack of improved efficacy above a 40 mg dose. The approvable letter contained label revisions with a contraindication section for all concomitant use of eletriptan and CYP3A4 inhibitors. The major safety concern is related to the coronary artery vasoconstricting effects of eletriptan at therapeutic doses. The pharmacologically elicited vasoconstriction appears to be related to peak plasma concentrations (C_{max}) rather than exposure (AUC) of eletriptan.

The Clinical Pharmacology and Biopharmaceutics section of this Class I resubmission contains *in vitro* inhibition studies and study reports where the interaction between eletriptan and ketoconazole, verapamil, and fluconazole respectively, were investigated in healthy volunteers. The two latter CYP3A4 inhibitors were considered to have intermediate interaction potential, and not show large *in vivo* effects. The sponsor also submitted a meta-analysis of the blood pressure / plasma concentration relationship of eletriptan.

The issue regarding this submission is;

- Can an *in vitro-in vivo* correlation of the interaction potential of CYP3A4 inhibitors on the pharmacokinetics of eletriptan be established, and be used in a predictive manner?

It was shown that the C_{max} and AUC of eletriptan

1. Increased 2.7-fold and 5.9-fold, respectively, during co-administration of eletriptan and ketoconazole
2. Increased 2.2-fold and 2.7-fold, respectively, during co-administration of eletriptan and verapamil
3. Increased 1.4-fold and 2-fold, respectively, during co-administration of eletriptan and fluconazole
4. Were not influenced by concomitant intake of oral contraceptives

An *in vitro-in vivo* correlation between the interaction potential of CYP3A4 inhibitors on the pharmacokinetics of eletriptan was not established.

The maximum increase of DBP elicited by eletriptan was determined to be approximately 12 mmHg and 50% of the maximal DBP increase was reached at eletriptan plasma concentrations of about 130 ng/mL.

In conclusion, the pharmacokinetics of eletriptan is susceptible to concomitant administration of CYP3A4 inhibitors, where *in vitro* predictions have not been of use. Minor revisions of the previously proposed label by FDA and revisions of the currently proposed label by the sponsor are recommended.

BACKGROUND

An approvable letter was issued on October 27, 1999 for Relpax™ (eletriptan HBr), for treatment of acute migraine attacks with or without aura in adults. The 80 mg tablet was not included in the approvable action, due to inconclusive data regarding the safety and lack of improved efficacy above a 40 mg dose. On the contrary, indications of increased adverse events, where chest pain is of major concern, in relation to higher doses were observed. In the original NDA submission (10/27/98), eletriptan was shown to interact with cytochrome P450 3A4 inhibitors. Co-administration of erythromycin increased eletriptan peak plasma concentrations (C_{max}) and exposure (AUC) 2- and 4-fold, respectively. After co-administration with ketoconazole, the corresponding increase in eletriptan C_{max} and AUC was about 3- and 6-fold, respectively. Preliminary results from the ketoconazole-eletriptan study were submitted to the original NDA. Since there were safety concerns that may be related to higher eletriptan plasma concentrations, the approvable letter contained label revisions with a contraindication section for all concomitant use of eletriptan and CYP3A4 inhibitors.

Between the time of the approvable letter (10/27/99) and the current resubmission (6/1/00), discussions among the sponsor and FDA representatives took place. The sponsor suggested that weaker CYP3A4 inhibitors should be excluded from the list of contraindicated drugs, and the discussions related to what scientific evidence would be needed for the removal of certain CYP3A4 inhibitors from the list. It was agreed that it might be possible to remove some drugs from the list of contraindicated drugs, after evaluation of the results from a combination of *in vitro* inhibition studies, and an *in vivo* study in healthy volunteers. The latter study investigated the potential pharmacokinetic interaction between verapamil, a CYP3A4 inhibitor suggested to have intermediate inhibition potential, and eletriptan. The sponsor was concerned that the verapamil study results (observed increase in AUC and C_{max} of eletriptan) could in part be influenced by a pharmacologically mediated increase in hepatic blood flow by verapamil. Therefore, the sponsor initiated a 4th interaction study, with fluconazole, a more pure 'intermediate' CYP3A4 inhibitor, without other pharmacological effects that could influence the pharmacokinetics of eletriptan. The preliminary pharmacokinetic results of the study with verapamil were submitted 8/9/00, and the full, final report was submitted 10/13/00 together with an abbreviated report of the study with fluconazole.

The major safety concern is related to the coronary artery vasoconstricting effects of eletriptan at therapeutic doses. The pharmacologically elicited vasoconstriction appears to be related to C_{max} rather than exposure (AUC) of eletriptan.

The Clinical Pharmacology and Biopharmaceutics section of this Class I resubmission contains *in vitro* inhibition studies and two final study reports from studies in healthy volunteers where the interaction between eletriptan, and ketoconazole and verapamil, respectively, were investigated. The sponsor has also resubmitted data listings regarding eletriptan's interaction potential with oral contraceptives from the original NDA, and an abbreviated study report investigating the potential pharmacokinetic interaction between fluconazole and eletriptan. The sponsor has also performed a meta-analysis of the pharmacodynamic (blood pressure) /pharmacokinetic relationship of eletriptan.

TABLE OF CONTENTS

Pharmacokinetics of eletriptan

The relevant pharmacokinetics of eletriptan was described in the original review of NDA 21-016 dated August 9, 1999, by Dr. Rae Yuan, and is as follows;

- Fast and relatively complete absorption (80%) with moderate 1st pass extraction and an absolute bioavailability (F) of 50% (t_{max} 1-2 hr, F=34% in males, F=64% in females)
- Moderate plasma protein binding (approx. 85%) for both parent drug and active metabolite with a large volume of distribution after i.v. dosing (138 L; 125 L in males, 143 L in females)
- Metabolized by CYP3A4 to an equi-potent active metabolite, UK-135,800, which appears in the plasma at an exposure of <20% of the parent drug, and has a t½ of 13 h
- Minor metabolism by CYP1A and CYP2D6 (not considered as important routes of metabolism)
- Mostly metabolized with approximately 10% of renal excretion attributed to the parent drug elimination (CL_{iv}=36 L/h, Cl_R=3.9 L/h, estimated in male subjects)
- Secreted into nursing milk (0.02%)
- AUC and C_{max} are not dose proportional from 20-80mg
- A terminal half-life of about 4 hours
- No effect on eletriptan PK after oral doses was found for age, gender, menstrual cycle, moderate to severe renal impairment, and CYP2D6 polymorphic status
- Effects on eletriptan PK after oral dosing were found for race, the onset of the disease (reduction in C_{max} and AUC, t_{max} prolonged), food intake (C_{max} and AUC +20-30%), mild to moderate hepatic impairment (30% decrease in CL), propranolol co-administration (AUC +30%), and erythromycin co-administration administration (AUC +357%)

1. In vitro studies: Cytochrome P450 inhibition potential

(Submission 6/1/00)

Background

In the proposed label sent with the approvable letter, FDA suggested that eletriptan should not be given concomitantly with the drugs listed in Table 1, which are cytochrome P450 3A4 inhibitors. Data in the original NDA showed that the exposure (both C_{max} and AUC) of eletriptan increased substantially during concomitant administration with known CYP 3A4 inhibitors, erythromycin or ketoconazole. The sponsor has responded, and agreed to contraindicate certain CYP 3A4 inhibitors, also shown in Table 1.

TABLE 1. FDA's proposal of contraindicated CYP 3A4 inhibitors. The drugs marked in **bold***, indicate the drugs the sponsor agrees to keep in the section for contraindications.

CONTRAINDICATIONS		
Antifungals/bacterials:	*Protease inhibitors:*	*Others:*
itraconazole*	**nelfinavir***	
ketoconazole*	**ritonavir***	
	Antidepressants/Antipsychotics:	
Macrolide antibiotics:	**nefazodone***	
clarithromycin*		
troleandomycin*		

†replaces ——, which was inadvertently added to FDA's contraindicated CYP 3A4 inhibitors;
††not in original list

Sponsor's *in vitro* data regarding CYP 3A4 inhibitors

In the approvable letter, FDA indicated that the list of contraindicated CYP 3A4 inhibitors might be excessive, depending on the effect of weaker inhibitors on the pharmacokinetics of eletriptan. In subsequent teleconferences with the sponsor, it was agreed that the sponsor would investigate the inhibition potential of CYP3A4 inhibitors on eletriptan's metabolism *in vitro,* and to perform an additional *in vivo* interaction study. The sponsor also undertook a thorough literature research, and ranked known CYP 3A4 inhibitors in three groups according to their inhibition potential, based on the *in vitro* Ki values for the different drugs. The three categories, A, B and C, would approximate potent, intermediate, and weak inhibition potential of different drugs.

Additional *in vitro* studies were also performed to investigate known CYP3A4 inhibitor's effect on the metabolism of eletriptan. For summaries regarding the two studies, please refer to Appendix 1. The results of the literature research and the *in vitro* inhibition studies are shown in Table 2.

TABLE 2. Published Ki values for a series of CYP 3A4 inhibitors ranked in order of most potent to least potent. The column to the far left denotes the result of the *in vitro* inhibition studies with eletriptan as a substrate.

Literature Ki Values Against CYP3A4 (mcM)							
Inhibitors	Substrates					Ki values for calculations	IC_{50} and (estimated Ki) values (mcM) determined from *in vitro* studies with eletriptan (DM32 and DM33)
	Midazolam	Cyclosporin	Testosterone	Alprazolam	Terfenadine		
Category A (Ki≤1mcM)							
Ritonavir	0.05[F]		0.11[I], 0.019[J]			0.05	
Ketoconazole	0.11[A], 0 18[B], 0.1[C], 0.015[O]	0 7[G], 0.3[H]	0.1[I]	0 046[L]	3[M] & 10[M]	0.1	1.8 (0.9)
Indinavir	0 2[F]		0.68[I], 0.17[J]			0.2	
Amprenavir			~0 5[O]			~0.5	
Troleandomycin**						1[N]	
Category B (Ki>1-50mcM)							
Nefazodone				1 51[L]		1 5	
Saquinavir	1.5[F]		4[I], 2.99[J]			1.5	
Itraconazole	2.3[M]				4[M] & 11[M]	2.3	3.6 (1.8)
Nelfinavir			4.8[I]			4 8	
Clarithromycin					4[M] & 10[M]	7	
Fluvoxamine				10.2[K] & 8 2[K]		9	>300
Verapamil	9.6[B]	23.5[G]				10	>300
Fluconazole	10.7[O]	63[H]			6[M] & 11[M]	11	>300
Paroxetine				39 4[K] & 36.7[K]		38	>300
Progesterone		45[G]				45	~300
Category C (KI>50mcM)							
Diltiazem	54[B]	51-75[G]				54	IA
Sertraline	64.4[E]			23.8[K] & 159[K]		65	>300
Fluoxetine	65.7[E]			83.3[K] & 47 2[K]		66	>300
Erythromycin*	194[A], 148[C]	75[G]			6[M] & 13[M]	170	
OC's : Ethinylestradiol		172[G]				172	IA
Metronidazole		223[H]				223	>300
Cimetidine	268[A]					268	>300

Note the superscript letters donate the references associated with these values and these are provided in the reference section of the attachment.
Note published Ki values could not be located for the following drugs: clotrimazole, abacavir (no clinical interaction data located), zileuton, isoniazid, ciprofloxacin and grapefruit juice.
*Erythromycin's mechanism of inhibition is not reflected by its relatively large Ki value with resultant clinical data indicating that this agent is a potent inhibitor of CYP3A4 activity (2). **The Ki of troleandomycin was estimated from the IC50 taken from a plot of testosterone metabolism to 6beta-hydroxy-testosterone. Also metabolic activation is required for inhibitory activity (N). IA = Not determined as drug interfered with assay

It should be noted that the above classification of weak inhibitors into the three categories, according to the drugs' Ki values, is arbitrary. A scientific consensus regarding an *in vitro* classification is not in place at this time. The sponsor has chosen a conservative approach in the choice of Ki value for the inhibitor where multiple substrate specific Ki's have been determined.

The sponsor agreed to keep the contraindications for all CYP3A4 inhibitors that have an *in vitro* Ki value < 5 μM. The sponsor also agreed to contraindicate the concomitant use of erythromycin

and clarithromycin, due to the *in vivo* results (erythromycin), which can be explained by the mechanism-based inhibition by the drugs that is not observed in the *in vitro* systems.

However, one major concern regarding the use of *in vitro* data of CYP 3A4 inhibitors is that any *in vivo* effects on first pass processes are not predictable, i.e. inhibition of CYP 3A4 in the intestinal lumen, or inhibition of P-glycoprotein (PGP). PGP mediates transcellular transport of drugs, especially efflux of drugs back to the intestinal tract.

2. *In vivo* studies: Eletriptan co-administered with CYP 3A4 inhibitors

(Submissions 6/1/00, 10/13/00)

Erythromycin, Ketoconazole, Verapamil, and Fluconazole

Background

The major safety concern regarding this submission is related to the coronary artery vasoconstricting effects of eletriptan at therapeutic doses. For further details, please refer to the medical review. The pharmacologically elicited vasoconstriction appears to be related to C_{max} rather than exposure (AUC) of eletriptan.

The sponsor has performed four studies in healthy volunteers to investigate the interaction potential of CYP 3A4 inhibitors (erythromycin, ketoconazole, verapamil, fluconazole) on the pharmacokinetics of eletriptan.

The final study report for erythromycin and the abbreviated study report for ketoconazole were submitted and reviewed in the original NDA. The current submission contains the final study reports for ketoconazole and verapamil, and an abbreviated study report for fluconazole. For details regarding the latter studies, please refer to Appendix 1.

As stated earlier, the choice of verapamil and fluconazole as CYP 3A4 inhibitors was due to their 'intermediate' inhibition potential, i.e. *in vitro* data showed that the inhibition potential of the two drugs would be marginal (IC_{50} > 300 μM). FDA recommended verapamil for the first study, since the drug is used off-label, for migraine prophylaxis. The sponsor was concerned that verapamil could in part influence the pharmacokinetics of eletriptan, by a pharmacologically mediated increase in hepatic blood flow, as well as by a CYP 3A4 inhibition. The sponsor initiated a 4th interaction study, with fluconazole, a more pure 'intermediate' CYP3A4 inhibitor, without other pharmacological effects that could influence the pharmacokinetics of eletriptan.

The demographics and dosing regimens used in the studies are described in Table 2. In all studies, frequent blood samples were collected up to 48 h (erythromycin 24 h) after eletriptan dosing and systolic and diastolic blood pressure and pulse were also followed after eletriptan dose-intake.

TABLE 2. Number of subjects, their ages (range), and dosing regimens in studies to investigate the interaction potential of CYP 3A4 inhibitors on eletriptan in healthy adult volunteers.

CYP3A4 Inhibitor	Number of subjects (Males/Females)	Age (years)	Dosing regimen (Design: randomized, 2-way cross-over)
Ketoconazole	18 (9/9)	19-44	Ketoconazole 400 mg or placebo q.d. for 4 days; 80 mg eletriptan on Day 3
Erythromycin	18 (12/6)	20-34	Erythromycin 500 mg or placebo b.i.d. for 7 days; 80 mg eletriptan on Day 7
Verapamil	17 (9/8)	19-40	Verapamil (sustained release tabl.) 120 mg or placebo b.i.d. on Days 1-2, 240 mg or placebo b.i.d. on Days 3-7; 80 mg eletriptan on Day 6
Fluconazole	18 (9/9)	19-35	Fluconazole 100 mg or placebo q.d. for 7 days (Day 1 loading dose of 200 mg q.d.); 80 mg eletriptan on Day 6

Pharmacokinetic Results

There was a substantial interaction between all investigated CYP 3A4 inhibitors and eletriptan, as shown in Figure 1.

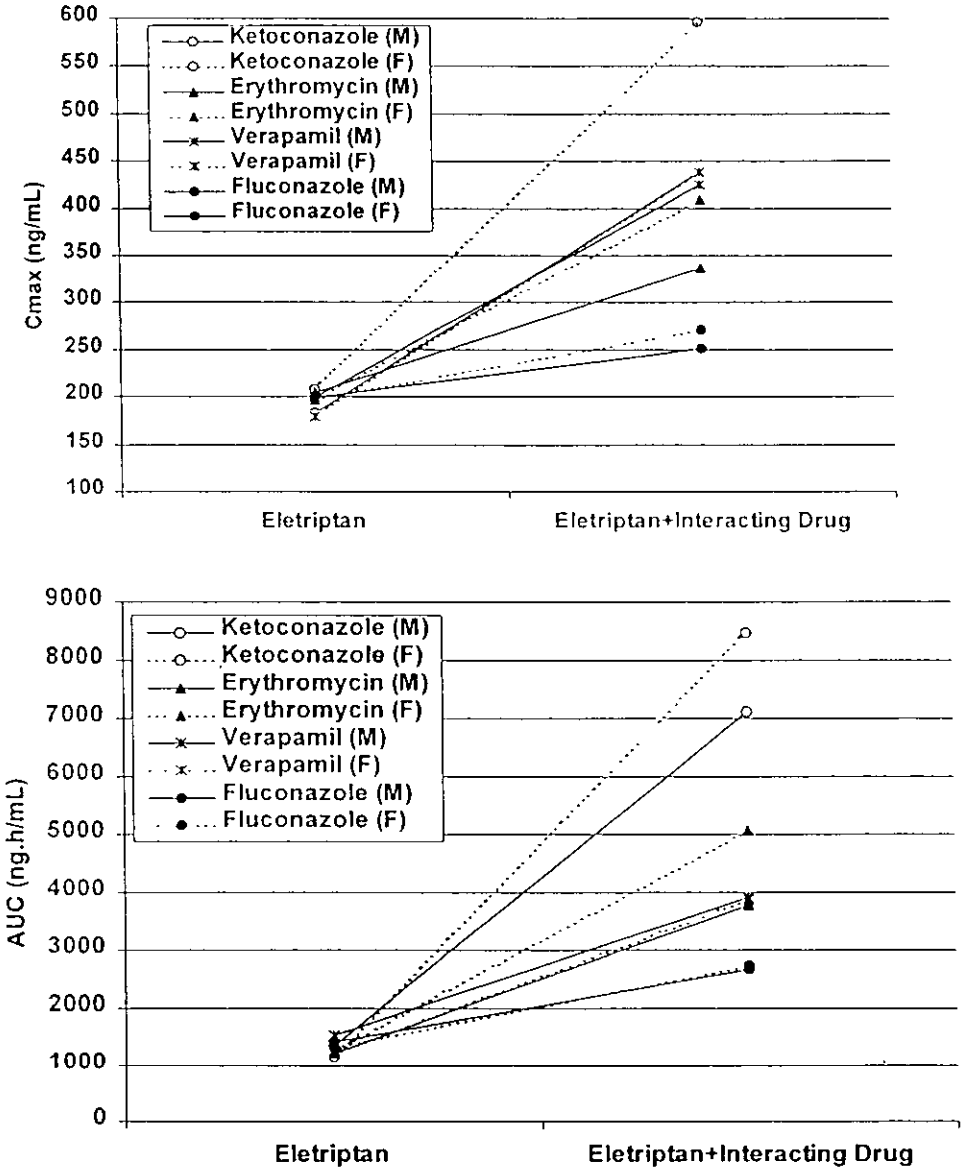


FIGURE 1. Arithmetic means of C_{max} (upper panel), and $AUC_{0\text{-infinity}}$ (lower panel) of eletriptan after a single dose of 80 mg during repeated doses of placebo and CYP 3A4 inhibitors in healthy adult male (solid lines) or female (dashed lines) volunteers.

Figure 1 is somewhat misleading, with an apparent gender difference, where females had larger increases in mean AUC and C_{max} values after co-administration of eletriptan - ketoconazole and eletriptan erythromycin compared to eletriptan alone. However, the individual increases in AUC and C_{max} did not show a similar trend, which shows that the mean increases after ketoconazole and erythromycin are influenced by a small number of female subjects (see Appendix 1 for individual graphs for the respective studies).

The arithmetic means for C_{max} and $AUC_{0\text{-infinity}}$ and point estimates (logarithmic) with confidence intervals of eletriptan after co-administration of placebo or the respective CYP 3A4 inhibitor are shown in Tables 3 and 4.

TABLE 3. C_{max} (arithmetic mean ± SD), of eletriptan after a single dose of 80 mg during repeated doses of a CYP 3A4 inhibitors or placebo in healthy adult volunteers. Ratios (% increase based on geometric means), and 95% or 90% confidence intervals between treatments are also shown.

CYP3A4 Inhibitor	C_{max} (ng/mL) Eletriptan + Placebo	C_{max} (ng/mL) Eletriptan + Inhibitor	Ln Ratio	95% or 90%* confidence interval
Ketoconazole	191±76	491±143	267%	229% - 310%
Erythromycin	200±95	372±97	198%	164% - 238%
Verapamil	190±42	430±116	224%	200%* – 252%*
Fluconazole	199±91	261±93	136%	117%* – 158%*

TABLE 4. $AUC_{0\text{-inf}}$ (arithmetic mean ± SD), of eletriptan after a single dose of 80 mg during repeated doses of CYP 3A4 inhibitors or placebo in healthy adult volunteers. Ratios (% increase based on geometric means), and 95% or 90% confidence intervals between treatments are shown.

CYP3A4 Inhibitor	$AUC_{0-\infty}$ (ng.h/mL) Eletriptan + Placebo	$AUC_{0-\infty}$ (ng.h/mL) Eletriptan + Inhibitor	Ln Ratio	95% or 90%* confidence interval
Ketoconazole	1288±557	7565±2964	591%	516% – 679%
Erythromycin	1230±421	4427±1458	357%	307% - 415%
Verapamil	1394±432	3893±1372	274%	247%* - 303%*
Fluconazole	1380±736	2692±1114	203%	187%* - 220%*

The increase (x-fold) of AUC and C_{max} for all volunteers, and also divided by gender, of the same data depicted in Tables 3-4, is also shown in Table 5. The terminal half-life of eletriptan was prolonged by co-administration of the inhibitors, where the order of prolongation was ketoconazole> erythromycin> fluconazole> verapamil.

TABLE 5. Increase of $AUC_{0-infinity}$ and C_{max} (arithmetic means ± SD of individual increases), of eletriptan after a single dose of 80 mg during repeated doses of placebo or CYP 3A4 inhibitors. Ratios (x-fold increase, range of minimal and maximal individual increases) and terminal t½ between treatments are shown.

CYP 3A4 Inhibitor	$AUC_{0-\infty}$ (ng.h/mL) Mean ± SD *(min-max)*	C_{max} (ng/mL) Mean ± SD *(min-max)*	t½ (h) (combination) Mean ± SD	t½ (h) (monotherapy) Mean ± SD
Ketoconazole All:	**6.2 ± 1.8**	**2.8 ± 0.8**	**8.7 ± 2.0**	**5.0 ± 1.1**
Males:	*5.5 ± 1.5*	*2.7 ± 0.8*	*9.2 ± 2.3*	*4.9 ± 1.0*
(n=9)				
Females:	***7.5 ± 1.6***	***3.0 ± 0.9***	***7.7 ± 0.9***	***5.1 ± 1.3***
(n=9)				
Erythromycin All:	**3.8 ± 1.3**	**2.1 ± 0.8**	7.05*	4.55*
Males:	*3.1 ± 0.7*	*1.8 ± 0.5*		
(n=12)				
Females:	***4.4 ± 1.5***	***2.5 ± 1.0***		
(n=6)				
Verapamil All:	**2.8 ± 0.7**	**2.3 ± 0.7**	5.0 ± 0.8	4.6 ± 0.8
Males:	*2.5 ± 0.4*	*2.2 ± 0.7*	*5.3 ± 0.9*	*5.0 ± 0.8*
(n=9)				
Females:	***2.8 ± 0.7***	***2.5 ± 0.7***	*4.6 ± 0.6*	*4.1 ± 0.7*
(n=8)				
Fluconazole All:	**2.1 ± 0.4**	**1.4 ± 0.5**	**6.6 ± 1.0**	**4.9 ± 1.1**
Males:	*2.1 ± 0.4*	*1.4 ± 0.5*	*7.0 ± 1.0*	*5.2 ± 1.1*
(n=9)				
Females:	***2.1 ± 0.4***	***1.4 ± 0.4***	*6.2 ± 1.0*	*4.5 ± 0.9*
(n=9)				

*Harmonic mean

Verapamil marginally increased hepatic blood flow (QH), by about 5%. There was a net increase in indocyanine green (ICG) clearance of 8%, but the variability was considerable (90% confidence intervals of ICG CL: -41 to 177 mL/min). The IC-green measurements were performed on the morning of Day 5, i.e., the day preceding the eletriptan dose intake (Day 6). Inspection of the data does not indicate a correlation between liver blood flow and eletriptan C_{max} and AUC, as shown in Figure 2.

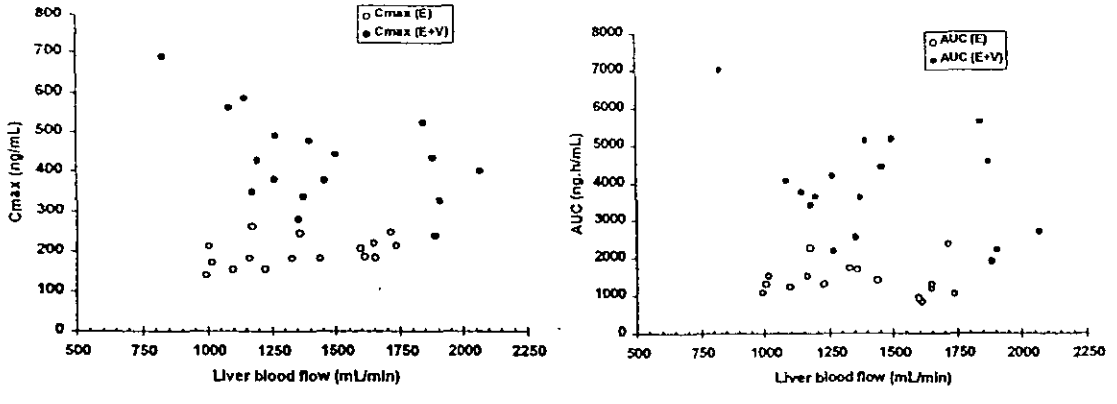


FIGURE 1. Influence of QH (Day 5) on C_{max} (left panel), and AUC (right panel) of eletriptan (80 mg Day 6) during b.i.d. dosing of placebo (unfilled circles) and verapamil (240 mg, filled circles).

This finding concurs with values reported in the literature, where only single doses of verapamil has been shown to exert an acute, augmenting effect on QH. This increase in QH has been reported to diminish during repeated administration of verapamil. Therefore, it is likely that the small alterations observed in QH do not make a major contribution to the observed interaction between the two drugs.

There was a somewhat higher incidence in adverse events (AEs) when eletriptan was co-administered with each of the CYP 3A4 inhibitors, compared to co-administration with placebo. Co-administration of eletriptan + ketoconazole gave the largest increases in AUC and C_{max}. This was also reflected in the adverse event profile, where more severe AEs on the combination of the two drugs were reported than with the other three CYP3A4 inhibitors. Eletriptan + ketoconazole co-administration resulted in severe AEs (six cases of asthenia, somnolence and vomiting in five subjects, 3F/2M), whereas only mild to moderate AEs were observed with eletriptan + placebo administration.

Oral Contraceptives

In the original submission, the sponsor made a population pharmacokinetic (PPK) analysis on data from Phase III studies, and did not find an influence of CYP 3A4 inhibitors, including oral contraceptives (OC), on the pharmacokinetics of eletriptan. In the original NDA-review concern was expressed that the drug analysis in saliva could be insensitive, or that the analysis may lack statistical power for certain subgroups due to limited number of subjects in those groups. The sponsor resubmitted data regarding efficacy, safety and pharmacokinetics from the original NDA.

Both progesterone and ethinylestradiol have been shown to inhibit CYP 3A4 *in vitro* (see Table 2, page 6 of this review). The sponsor could not determine an *in vitro* IC_{50} value for ethinylestradiol due to analytical interference, and an $IC_{50} \sim 300$ μM was determined for progesterone. In the four interaction studies with CYP 3A4 inhibitors, 10 women were taking OC's, and 13 women were using other means of contraception. A naïve pooling of the data for AUC and C_{max} eletriptan (+placebo) showed a very small interaction between use of oral contraceptives and eletriptan, as shown in Table 6.

TABLE 6. Pooled values $AUC_{0\text{-infinity}}$ and C_{max} (arithmetic means ± SD), of 80 mg eletriptan + placebo in female subjects from the four different studies with CYP 3A4 inhibitors.

Parameter	**Eletriptan + with OC's (n=10)**	**Eletriptan + without OC's (n=13)**	**Difference (%)**
$AUC_{0-\infty}$ (ng.h/mL)	1300 ± 409	1155 ± 361	13%
C_{max} (ng/mL)	203 ± 69	186 ± 76	9%

Comments

A cross-study comparison may be questionable, however a clear pharmacokinetic interaction between use of oral contraceptives and eletriptan was not observed, supporting the results from the previous PPK analysis.

3. Systolic and Diastolic Blood Pressure

In the initial dose escalation studies with eletriptan there were small dose related increases in blood pressure. The changes in diastolic blood pressure (DBP) were related to eletriptan concentration and maximum concentration (C_{max}) and maximum effect (E_{max}) occurred at about the same time. The first PK/PD analysis was presented in the original NDA. Subsequently, the sponsor has used additional modeling approaches to determine the PK/PD relationship between

DBP and eletriptan plasma concentrations. A more complete description of the meta-analysis can be found in Appendix 1 (Study #6).

Two of the modeling approaches were based on C_{max} with a third analysis using NONMEM to assess the overall concentration relationship. The PK/PD models using C_{max} resulted in predictions that were similar to those using NONMEM. Eletriptans PK/PD relationship was determined by use of data from 12 clinical pharmacology studies.

Five of the 12 studies included in the pooled analysis contained an estimate of the placebo BP response allowing an assessment of the variability of the placebo response for BP. The mean maximal increase in DBP across all studies was 6.9 mmHg (11.4% change from baseline), and the corresponding mean maximal increase in SBP was studies was 11.1 mmHg (9.6% change from baseline). There was a high within subject variability and a high variability between studies in the placebo response, for both SBP and DBP.

Two models (linear and E_{max}) were used in the PK/PD modeling. The models were fitted to the individual increases occurring at C_{max} or the full effect (DBP)- eletriptan plasma concentration profiles 0-12 h after eletriptan dose intake.

The initial linear model developed in the original NDA had a slope of 0.092 (%change per ng/ml). The slopes of the pooled analysis were 0.028 (%change per ng/ml) and 0.017 (mmHg change per ng/ml). The slopes of the NONMEM analyses where a linear model was fitted to the data were 0.0318 and 0.0276 (mmHg change per ng/ml) for the raw and placebo adjusted DBP data respectively. The models derived from the pooled data predict a smaller effect of eletriptan on blood pressure than originally predicted.

The E_{max} model [$E = E_{max}*(1/(1+EC_{50}/C))+E0$] from the pooled analysis of DBP *vs.* E_{max} gave a maximum effect (E_{max}) on DBP of 12.5 mmHg, with an eletriptan plasma concentration of 130 ng/mL producing 50% of E_{max} (EC_{50}). The base-line effect on DBP (E0) was determined to 0.0185 mmHg. A NONMEM analysis of the placebo adjusted DBP using the same model gave similar parameter estimates (placebo adjusted DBP: E_{max} of 11 mmHg and EC50 of 136 ng/mL; unadjusted DBP: E_{max} of 19.7 mmHg and EC50 of 391 ng/mL). The DBP - eletriptan plasma concentration profiles 0-12 h after eletriptan dose intake are shown in Figure 4.

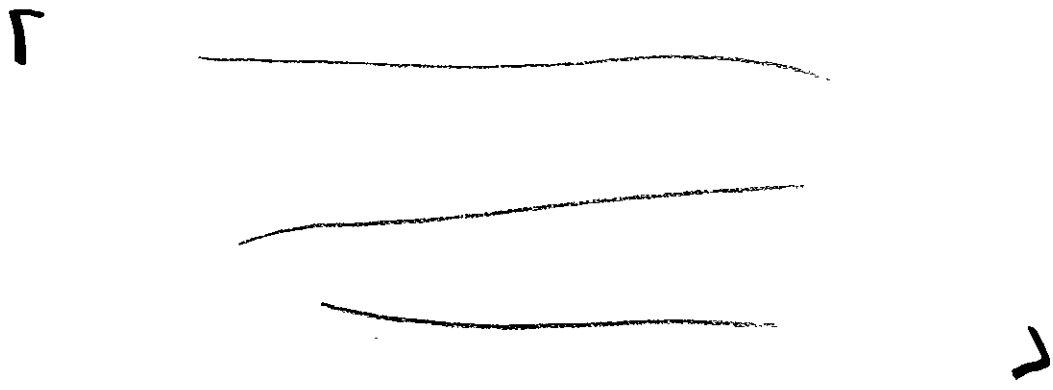


FIGURE 4. Actual and predicted BP (Raw: upper panel and placebo subtracted: lower panel) vs. eletriptan plasma concentrations from the NONMEM analysis.

Comments

There is a relationship between eletriptan plasma concentrations and DBP that can be described by an E_{max} model predicting a maximum effect on mean DBP. This model reasonably predicted the changes in peak DBP that were observed in the CYP3A4 drug interaction studies. The

sponsor did not submit a full description of the analysis, but the estimates seem reasonable. Eletriptan elicits moderate effects on DBP (and SBP) also at much higher drug plasma concentrations than expected at therapeutic doses (40 mg: C_{max} 90-100 ng/mL), as observed in the drug-drug interaction studies.

4. Overall comments

The sponsor has not shown a clear correlation between *in vitro* and *in vivo* effects of concomitant administration of eletriptan and CYP3A4 inhibitors. The sponsor's own *in vitro* evaluation did not discern the effects of the CYP3A4 inhibitors with intermediate interaction potential on the metabolism of eletriptan. Both verapamil and fluconazole co-administration *in vivo* showed increases in C_{max} and AUC of eletriptan, but the interaction potentials were not detected in the *in vitro* system. The sponsor refers to the lower *in vitro* Ki values of fluconazole reported in the literature (See Table 2, page 6 of review) as a better guide for predictions of the fluconazole interaction. Since literature data regarding Ki values are inherently difficult to use in *in vivo* extrapolations, due to differences between laboratory methods and experimental conditions, it is a problematical approach to potentially reduce the list of contraindicated drugs suggested by the FDA, and it is not recommended. The sponsor has only used literature Ki values to compare the *in vivo* observations of ketoconazole and fluconazole on eletriptan pharmacokinetics, and has not proposed to use literature Ki values for other observations.

The larger than anticipated interaction between verapamil and eletriptan that was observed *in vivo* was not explained by an additional effect on liver blood flow (QH). Although the determinations of QH was performed one day prior to eletriptan dosing, is seems unlikely that the lack of correlation between QH and eletriptan C_{max} and AUC would change dramatically between Days 5 and 6. Reports in the literature also indicate that repeated doses of verapamil do not increase QH by the same magnitude as after acute doses (Meridith PA *et al,* 1985, Lay C-S *et al,* 1988, Rocci ML *et al.* 1989). The sponsor also submitted a recent publication (Bennett MA *et al,* 2000). In this publication, it is shown that verapamil, among other calcium channel blockers, may act in part as a quasi-irreversible CYP3A4 inhibitor. This further limits the use of an *in vitro-in vivo* correlation to predict the pharmacokinetic interactions when eletriptan is co-administered with CYP3A4 inhibitors, since refined *in vivo* methods evolves continuously, and previously generated *in vitro* data may not be accurate. The interaction between verapamil and eletriptan did not increase the t½ of eletriptan, indicating that the clearance of eletriptan may be less influenced by verapamil compared to the other studied CYP3A4 inhibitors. The increase in AUC of eletriptan may occur during the first pass, i.e. the bioavailability of eletriptan may be increased during verapamil co-administration. One possible explanation to the observed *in vivo* interaction with verapamil and eletriptan may be an inhibition of P-glycoprotein of verapamil, which has been shown to also inhibit PGP. Using the indication of PGP inhibition by inspecting t_{max}, there was a slight decrease after co-administration of the drugs (t_{max} monotherapy: 2.6 h, t_{max} combination: 2.2 h). However, t_{max} was only reduced in nine subjects. A PGP inhibition of drug efflux across the intestinal lumen by verapamil, may be part of the observed interaction. A similar decrease in t_{max} was not observed when eletriptan was given in combination with the other CYP3A4 inhibitors.

The major safety concern, pharmacologically elicited vasoconstriction in coronary arteries, was observed after eletriptan intravenous administration, at therapeutic concentrations comparable to a 40 mg oral dose. The vasoconstriction appears to be related to C_{max} rather than exposure (AUC) of eletriptan. Concomitant administration of ketoconazole, erythromycin and verapamil increased the C_{max} of eletriptan 2 or 3-fold. Fluconazole was the only drug that only moderately increased C_{max} of eletriptan (+36%).

In conclusion, the studied CYP3A4 inhibitors substantially increase C_{max} and AUC of eletriptan. Verapamil and fluconazole should also be included in the label text of contraindicated drugs used in combination with eletriptan, until more safety data regarding the eletriptan's effects on coronary artery constriction is available.

Draft Labeling

[redacted]

RECOMMENDATION

From a pharmacokinetic point of view, this NDA amendment for use of eletriptan in treatment acute migraine attacks with or without aura in adults is acceptable to the Office of Clinical Pharmacology and Biopharmaceutics.

Please forward the labeling changes to the Medical Division.

Maria Sunzel, Ph.D., /S/ 11/20/00

RD/FT initialed by Ray Baweja, Ph.D., /S/ 11/20/00.

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

c.c.: NDA 21-016, HFD-120 (Katz, Feeney, Oliva), HFD-860 (Mehta, Baweja, Sunzel), HFD-340 (Viswanathan), Central Document Room (Biopharm files) and FOI files (HFD-19)

APPENDIX 1

Study #1. An open randomized, placebo controlled, two-period crossover study to investigate the effects of ketoconazole on the pharmacokinetics, safety and toleration of a single dose of eletriptan (80 mg) [Protocol A160-1045]

(Submission 6/1/00)

Objective

The primary aim of the study was to investigate the effects of ketoconazole on the pharmacokinetics of a single dose of eletriptan.

Study Design and Demographics

This was an open, randomized, placebo controlled, 2-period, crossover study in 18 healthy, adult volunteers (12M/6F, actual age range 19-44 years). The subjects received 400 mg (2x200 mg) ketoconazole or unmatched placebo once daily for 4 days. On the morning of the 3rd day, 80 mg (2x40 mg) eletriptan was co-administered.

Blood samples for plasma analysis of eletriptan were collected post-dose on Day 3, at 0, 0.5, 1, 1.5, 2, 3, 4, 6, 8, 10, 12, 18, 24, 36 and 48 h, of each study period. Supine systolic (SBP) and diastolic (DBP) blood pressure and pulse rate was taken in duplicate pre-dose, 1, 1.5, 2, 3, 4, 6, 8, 10, 12 and 24 h post dose on Day 3, the day of eletriptan dose intake. A semi-automated sphygmomanometer was used. Safety assessments (ECG, physical examination, laboratory safety monitoring) were performed at screening and follow-up visits. Adverse events and laboratory tests (Day 3) were monitored during the investigational periods.

Bioanalytical Methods

Plasma concentrations of eletriptan were determined by the use of a validated — procedure with UV detection. The method was validated over the concentration ranges of —— (LOQ) ——— For the calibration standards (standard curves) in plasma, the standard deviation was 7.7% or less, and the accuracy (relative error) was within the range of —

Pharmacokinetic and Pharmacodynamic Analysis

Pharmacokinetic parameters (C_{max}, t_{max}, AUC_{0-t}, $AUC_{0-\infty}$, and t½) for eletriptan were estimated by non-compartmental methods. The area under the effect – time curves during 12 h post eletriptan dose ($AUEC_{0-12h}$) for SBP and DBP were calculated by non-compartmental methods. The maximum change from base line was also determined.

Results

Pharmacokinetics

The mean plasma concentration-time curves of eletriptan during co-administration of placebo or ketoconazole are shown in Figure 1.1.

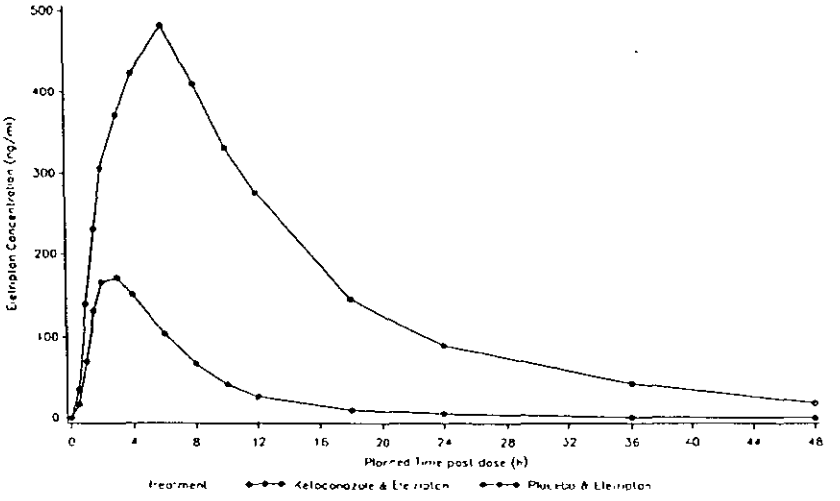


FIGURE 1.1 Mean plasma concentration-time curves of a single dose of 80 mg eletriptan Day 3, after co-administration of ketoconazole (400 mg QD; upper curve) or placebo (lower curve) in healthy adult subjects (n=18).

The pharmacokinetic parameters after a single 80 mg dose of eletriptan on Day 3 co-administered with ketoconazole (400 mg QD, 4 days) or placebo (QD, 4 days) are shown in Table 1.1.

TABLE 1.1 Pharmacokinetics of eletriptan (80 mg single dose, Day 3) during concomitant dosing of ketoconazole (400 mg) or placebo QD for 4 days (n=18). Upper panel: Geometric means and 95% confidence intervals Lower panel: Arithmetic means (SD) and coefficients of variation.

Parameter	Adjusted Means*		Ratio[1] or Difference[2] between Means	95% CI
	Ketoconazole & Eletriptan	Placebo & Eletriptan		
AUC (ng.h/ml)	7029	1190	591% [1]	516 to 676%
AUC_t (ng.h/ml)	6823	1183	Not analysed	Not analysed
C_{max} (ng/ml)	473.8	177.7	267% [1]	229 to 310%
T_{max} (h)	5.39	2.81	2.583 [2]	1.706 to 3.460
K_{el} (/h)	0.084	0.146	-0.062 [2]	-0.074 to -0.051
$t_{1/2}$ (h)	8.29	4.75	Not analysed	Not analysed

*Means are geometric for AUC, AUC_t and C_{max}, arithmetic for T_{max} and k_{el} and harmonic for $t_{1/2}$. Those for AUC_t and $t_{1/2}$ are unadjusted.

Parameter	N=18					
	Ketoconazole & Eletriptan			Placebo & Eletriptan		
	Mean	S.D.	CV(%)	Mean	S.D.	CV(%)
AUC (ng.h/ml)	7564.6	2963.56	39.2	1287.7	556.60	43.2
AUC_t (ng.h/ml)	7305.7	2767.13	37.9	1280.7	556.10	43.4
C_{max} (ng/ml)	490.8	143.11	29.2	190.7	76.10	39.9

Arithmetic means, standard deviations and coefficients of variation are between subject values.

As shown in Table 1.1, eletriptan AUC increased 5.9-fold and C_{max} increased 2.7-fold, during concomitant administration of ketoconazole. The increases in AUC and C_{max} were similar between males and females, as shown in Figure 1.2. However, a female subject reached the highest eletriptan C_{max} observed in the study, 904 ng/mL on the combination, compared to 245

ng/mL on monotherapy (3.7-fold increase). The same female subject (Subject 15, Caucasian, age 29, height 152.5 cm, weight 51.3 kg, non-drinker, taking oral contraceptives) also had the highest AUC, 13280 ng.h/ml, on the combination, compared to 1730 ng.h/mL on monotherapy (7.7-fold increase).

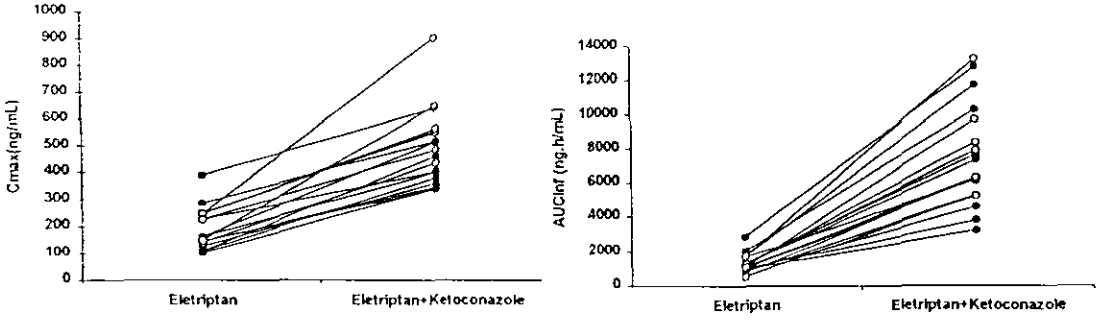


FIGURE 1.2 Individual eletriptan C_{max} (left panel) and AUC after an 80 mg single dose on Day 3, after co-administration of ketoconazole (400 mg) or placebo healthy adult male (n=12; filled circles) and female (n=6; unfilled circles) subjects.

In the Subject Data Listings of the study, pharmacokinetic data for the active metabolite UK-135,800 is given for two subjects (Subjects 3 and 15). This data is not presented in the main body of the report, or in the analytical report. The pharmacokinetics of UK-135,800 was determined for Subject 15 (female, age 29), who had the highest increases in eletriptan concentrations between the two treatments, and Subject 3 (male, age 20), who had the least increase in AUC (3.4 fold) and one of the lower increases in C_{max} (2.4-fold) between the two treatments. The pharmacokinetic parameters of UK-135,800 are shown in Table 1.2.

TABLE 1.2 The pharmacokinetics of UK-135,800 after a single dose of 80 mg eletriptan given together with repeated doses of placebo (E) or 400 mg ketoconazole (E+K)

Parameter	Subject 3 (male)	Subject 15 (female)
AUC, ng.h/mL (E)	183.2	362.7
AUC ng.h/mL (E+K)	241.3	690.9
Increase (x-fold)	1.3	1.9
C_{max}, ng/mL (E)	18.7	39.7
C_{max}, ng/mL (E+K)	12.7	22.1
Increase (x-fold)	0.7	0.6
T_{max}, h (E)	2	3
T_{max}, h (E+K)	6	18
t½ (E)	5.9	6.5
t½ (E+K)	11.1	11.0

The AUC of UK-135,800 were about 20% of the AUC of eletriptan given together with repeated doses of placebo, and about 5% when given together with ketoconazole.

Pharmacodynamics

The effect on mean DBP after eletriptan + placebo and eletriptan + ketoconazole are shown in Figure 1.3.

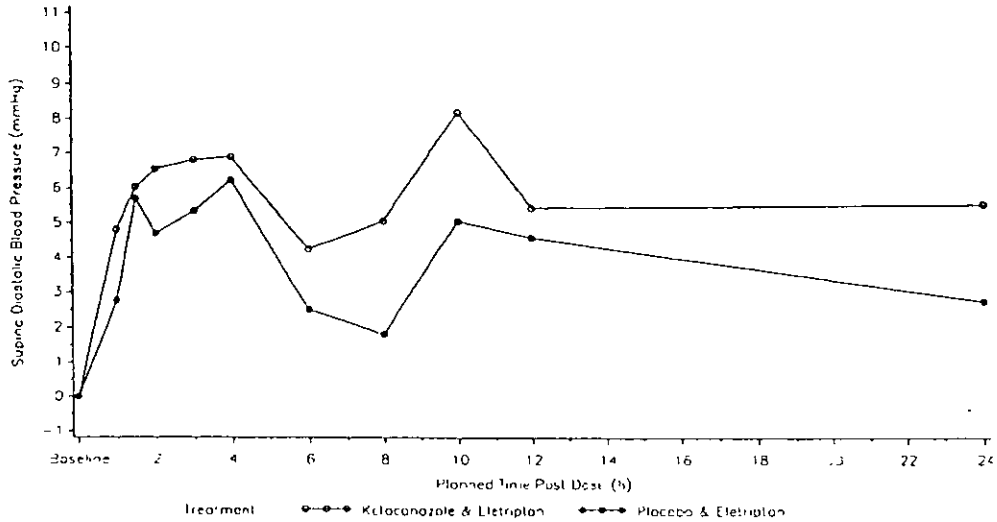


FIGURE 1.3 Mean change from baseline in supine DBP (mmHg) over time after a single dose of 80 mg eletriptan Day 3, co-administrered with ketoconazole (400 mg QD; upper curve) or placebo (lower curve) in healthy adult subjects (n=18). Baseline (average of 2 measurements) was determined just prior to eletriptan dose intake.

Both the mean SBP and mean DBP showed treatment related increases, as shown in Table 1.3.

TABLE 1.3. The area under the effect – time curves during 12 h ($AUEC_{0\text{-}12h}$) and maximum increases with 95% confidence intervals for SBP and DBP after a single dose of eletriptan (80 mg single dose, Day 3) during concomitant dosing of ketoconazole (400 mg) or placebo QD for 4 days (n=18).

Parameter	Adjusted Arithmetic Means		Difference between means	95% CI
	Ketoconazole & Eletriptan	Placebo & Eletriptan		
Change in AUEC Systolic blood pressure (mmHg.h)	51.23	37.55	13.68	0.29 to 27.06
Change in AUEC Diastolic blood pressure (mmHg.h)	70.60	44.92	25.69	8.24 to 43.13
Maximum increase from baseline in systolic blood pressure (mmHg)	13.39	13.08	0.31	-2.33 to 2.95
Maximum increase from baseline in diastolic blood pressure (mmHg)	12 62	9 74	2.88	0.68 to 5.09

Co-administration of ketoconazole produced statistically significant treatment-related increases in AUEC from pre-eletriptan baseline for both systolic (p=0.0458) and diastolic (p=0.0068) blood pressure. The actual mean differences observed were 13.68mmHg.h and 25.69mmHg.h, respectively. The differences between means for maximum increase from baseline were 0.31 mmHg for systolic blood pressure (p=0.8063) and 2.88 mmHg for diastolic blood pressure (p=0.0138).

Adverse events

There were more treatment related adverse events in the ketoconazole + eletriptan group (n=15) than the placebo + eletriptan group (n=13) and more in both of these groups compared to ketoconazole (n=4) and placebo (n=6) alone. All adverse events that were classified as severe occurred during ketoconazole + eletriptan treatment (six cases of asthenia, somnolence and vomiting in five subjects, 3F/2M). All of these events cleared and required no action.

Comments:

There was a large interaction after co-administration of eletriptan and the potent cytochrome P450 3A4 inhibitor, ketoconazole. The point estimate of the AUC increase was 6.2-fold (arithmetic mean), however the largest individual increase was 9.8-fold (subject 13, female). The point estimate of the C_{max} increase was 2.8-fold (arithmetic mean), the corresponding largest individual increase in C_{max} was 4.4-fold (subject 14, female). Ketoconazole has been reported to also inhibit P-glycoprotein (PGP), which mediates transcellular transport of drugs, especially efflux of drugs back to the intestinal tract. It is not possible to estimate the influence of a potential PGP inhibition, however the increase in half-life of eletriptan indicates CYP3A4 inhibition. Also, one indication of PGP inhibition would be a decrease in t_{max}, but this was not observed in the study (t_{max} monotherapy: 2.8 h, t_{max} combination: 5.4 h).

The sparse data regarding the active metabolite, UK-135,800, indicate that the elimination of the metabolite is mediated via CYP3A4, since the t½ was increased to 11 h during eletriptan + ketoconazole treatment, and about 6 h after eletriptan alone. In the original NDA review, the t½ of UK-135,800 was reported to be about 12 h, a half-life that is twice as long compared to the approximately 6 h reported for the two subjects in this study. After co-administration of the two drugs, the increases in AUC were 30% and 90%, for subject 3 and 15, respectively. This increase in AUC of UK-135,800 were modest compared to the increases in AUC of eletriptan. Therefore, it seems likely that the interaction is of minor importance regarding UK-135,800, as the potential contribution of additional pharmacological effects from the metabolite diminishes during co-administration of eletriptan and a CYP3A4 inhibitor, since the relative exposure (AUC) to UK-135,800 diminishes during combination therapy.

In conclusion, co-administration of ketoconazole and eletriptan increases the C_{max} 3-fold and AUC 6-fold. It is recommended that the co-administration of eletriptan and potent CYP3A4 inhibitors be contraindicated in the label, due to the large increase in C_{max} and exposure of eletriptan.

Study #2. An open randomized, placebo controlled, two-period crossover study to investigate the effects of sustained release verapamil on the pharmacokinetics, safety and toleration of a single dose of eletriptan (80 mg) [Protocol A160-1058]

(Submission 10/13/00)

Objective

The primary aim of the study was to investigate the effects of verapamil on the pharmacokinetics of a single dose of eletriptan.

Study Design and Demographics

This was an open, randomized, placebo controlled, 2-period, crossover study in 18 healthy, adult volunteers (enrolled: 9M/9F, actual age range 19-40 years). One subject (female, subj. 18) withdrew informed consent (not related to study drug) after the first period (eletriptan + verapamil dosing). The subjects received verapamil (sustained release tablets) 120 mg or placebo b.i.d. Days 1-2. On days 3-7 the subjects received 240 mg or placebo b.i.d. (480 mg verapamil/day). On the morning of the 6th day, 80 mg (2x40 mg) eletriptan was co-administered. Indocyanine (IC)-green was administered intravenously (bolus of 0.5 mg/kg) in the morning of day 5 (verapamil or placebo treatment), and samples were collected pre-dose and up to 15 min post-dose for determination of IC-green clearance.

Blood samples for plasma analysis of eletriptan were collected post-dose on Day 6, at 0, 0.5, 1, 1.5, 2, 3, 4, 6, 8, 10, 12, 18, 24, 36 and 48 h, of each study period. Supine systolic (SBP) and diastolic (DBP) blood pressure and pulse rate was taken in duplicate pre-dose, 1, 1.5, 2, 3, 4, 6, 8, 10, 12 and 24 h post dose on Day 6, the day of eletriptan dose intake. A sphygmomanometer was used. Safety assessments (ECG, physical examination, laboratory safety monitoring) were performed at screening and follow-up visits. Adverse events and laboratory tests (Day 6) were monitored during the investigational periods.

Bioanalytical Methods

Plasma concentrations of eletriptan were determined by the use of a validate — procedure with UV detection. The method was validated over the concentration ranges of — (LOQ) — For the calibration standards (standard curves) in plasma, the standard deviation was 14.1% or less, and the accuracy (relative error) was within the range of —

IC-green was analyzed by a spectrophotometrical method. Standard curves were prepared from spiked serum samples. No analytical report for the IC-green analysis was submitted.

Pharmacokinetic and Pharmacodynamic Analysis

Pharmacokinetic parameters (C_{max}, t_{max}, AUC_{0-t}, $AUC_{0-\infty}$, and $t_{½}$) for eletriptan were estimated by non-compartmental methods. The same parameters and also CL_{tot} was calculated for IC-green. The area under the effect – time curves during 12 h post eletriptan dose ($AUEC_{0-12h}$) for SBP and DBP were calculated by non-compartmental methods. The maximum change from baseline was also determined.

Results

Pharmacokinetics

The mean plasma concentration-time curves of eletriptan during co-administration of placebo or verapamil are shown in Figure 2.1.

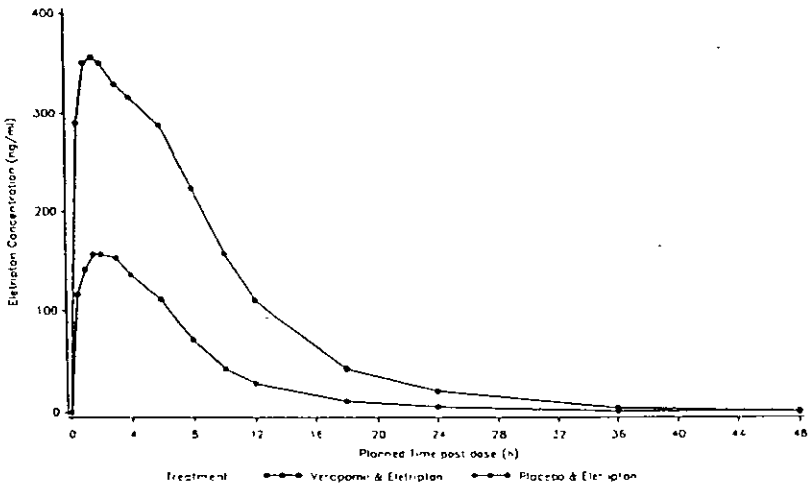


FIGURE 2.1 Mean plasma concentration-time curves of a single dose of 80 mg eletriptan Day 6, after co-administration of verapamil (240 mg b.i.d , Days 3-7; upper curve) or placebo (lower curve) in healthy adult subjects (n=17).

The pharmacokinetic parameters after a single 80 mg dose of eletriptan on Day 6 co-administered with verapamil (240 mg b.i.d., Days 3-7) or placebo (QD, 7 days) are shown in Table 2.1.

TABLE 2.1. Pharmacokinetics of eletriptan (80 mg single dose, Day 6) during concomitant dosing of verapamil (240 mg b.i.d., Days 3-7) or placebo QD for 7 days (n=17). Upper panel: Geometric means and 90% confidence intervals Lower panel: Arithmetic means (SD) and % CV

Parameter	Eletriptan + verapamil (N=17)	Eletriptan + placebo (N=17)	Mean ratio/difference	90% CI
AUC (ng.h/ml)	3666[a]	1340[a]	ratio 2.74	2.47, 3.03
AUC_t (ng.h/ml)	3647[a]	1329[b]	n/a	n/a
C_{max} (ng/ml)	415[a]	185[a]	ratio 2.24	2.00, 2.52
T_{max} (h)	2.2[c]	2.5[c]	difference –0.302	-1.272, 0.667
k_e (/h)	0.1419[c]	0.1550[c]	difference –0.0131	-0.0220, -0.0042
$t_{1/2}$ (h)	4.9[d]	4.5[d]	n/a	n/a

Source: Tables 5.1.2 to 5.1.6 and 5.2; [a]adjusted geometric mean, [b]unadjusted geometric mean, [c]adjusted arithmetic mean, [d]unadjusted harmonic mean, n/a= not analysed.

Parameter	Eletriptan + Verapamil*			Eletriptan + Placebo		
	mean	SD	CV%	mean	SD	CV%
AUC (ng.h/mL)	3893	1372	35	1394	432	31
AUC_t (ng.h/mL)	3882	1366	35	1385	428	31
C_{max} (ng/mL)	430	116	27	190	42	22

*Without subject 18, female that withdrew consent before the 2nd period (AUC_{0-inf} 3555 ng.h/mL; C_{max} 304 ng/mL; t_{max} 4 h; t½ 6 h)

As shown in Table 2.1, eletriptan AUC increased 2.7-fold and C_{max} increased 2.2-fold, during concomitant administration of verapamil. The increases in AUC and C_{max} were similar between males and females, as shown in Figure 2.2. However, a female subject reached the highest eletriptan C_{max} observed in the study, 689 ng/mL on the combination, compared to 180 ng/mL on

monotherapy (3.8-fold increase). The same female subject (Subject 15, Asian, age 19, height 160 cm, weight 54.1 kg, non-drinker, taking norfloxacin during the eletriptan + verapamil period) also had the highest AUC, 7017 ng.h/ml, on the combination, compared to 1516 ng.h/mL on monotherapy (4.6-fold increase).

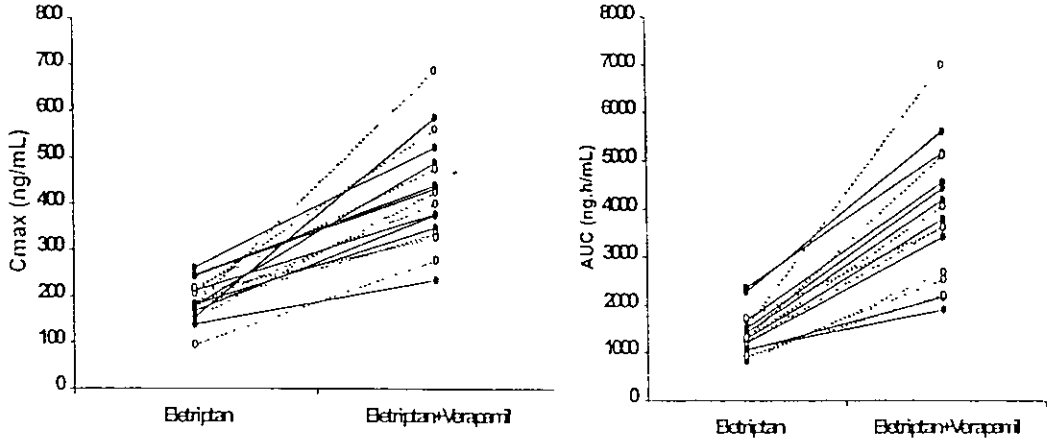


FIGURE 2.2. Individual eletriptan C_{max} (left panel) and AUC after an 80 mg single dose on Day 6, after co-administration of verapamil (240 mg b.i.d.) or placebo healthy adult male (n=9; filled circles, solid lines) and female (n=8; unfilled circles, dashed lines) subjects.

Liver blood-flow

The pharmacokinetics of IC-green to determine effects on liver blood-flow (QH) was determined on the morning of Day 5 of verapamil or placebo dose-intake, the day prior to eletriptan dose intake. The results are shown in Table 2.2.

TABLE 2.2 The pharmacokinetics of IC-green on Day 5 after repeated doses of 240 mg verapamil b.i.d. (480 mg/day Days 3-7; 240 mg/day Days 1-2) or placebo

IC-green: Source: Tables 5.3.2, 5.3.6, 5.3.8 and 5.4; [a]adjusted geometric mean, [b]unadjusted geometric mean [c]adjusted arithmetic mean, [d]unadjusted arithmetic mean, [e]unadjusted harmonic mean, n/a= not analysed.

Parameter	Verapamil+ IC-green	Placebo+ IC-green	Mean ratio/difference	90% CI
AUC (µg.min/ml)	41.6[a]	44.5[a]	ratio 0.94	0.818, 1.069
AUC_I (µg.min/ml)	39.3[b]	42.4[b]	n/a	n/a
C_{max} (µg/ml)	8.4[a]	6.8[a]	ratio 1.233	0.990, 1.535
T_{max} (min)	1.84[c]	2.24[c]	difference -0.397	-1.081, 0.287
k_{el} (/min)	0.2534[c]	0.2384[c]	difference 0.0150	-0.0150, 0.0451
$t_{1/2}$ (min)	2.79[d]	2.89[d]	n/a	n/a
CL (ml/min)	874[c]	806[c]	difference 68.2	-41.0, 177
Hepatic blood flow (ml/min)	1427[e]	1360[e]	n/a	n/a

A marginal increase in QH of approximately 5% was observed. QH was calculated from CL_{ICG} (8%) but the confidence intervals were wide, as shown for $CL_{IC\text{-}green}$ (Table 2.2).

Pharmacodynamics

Verapamil alone produced a statistically significant decrease on the mean SBP, mean DBP and pulse rate. The effects on SBP, DBP and pulse rate over 24 h after the eletriptan dose intake, are shown in Figure 2.3.

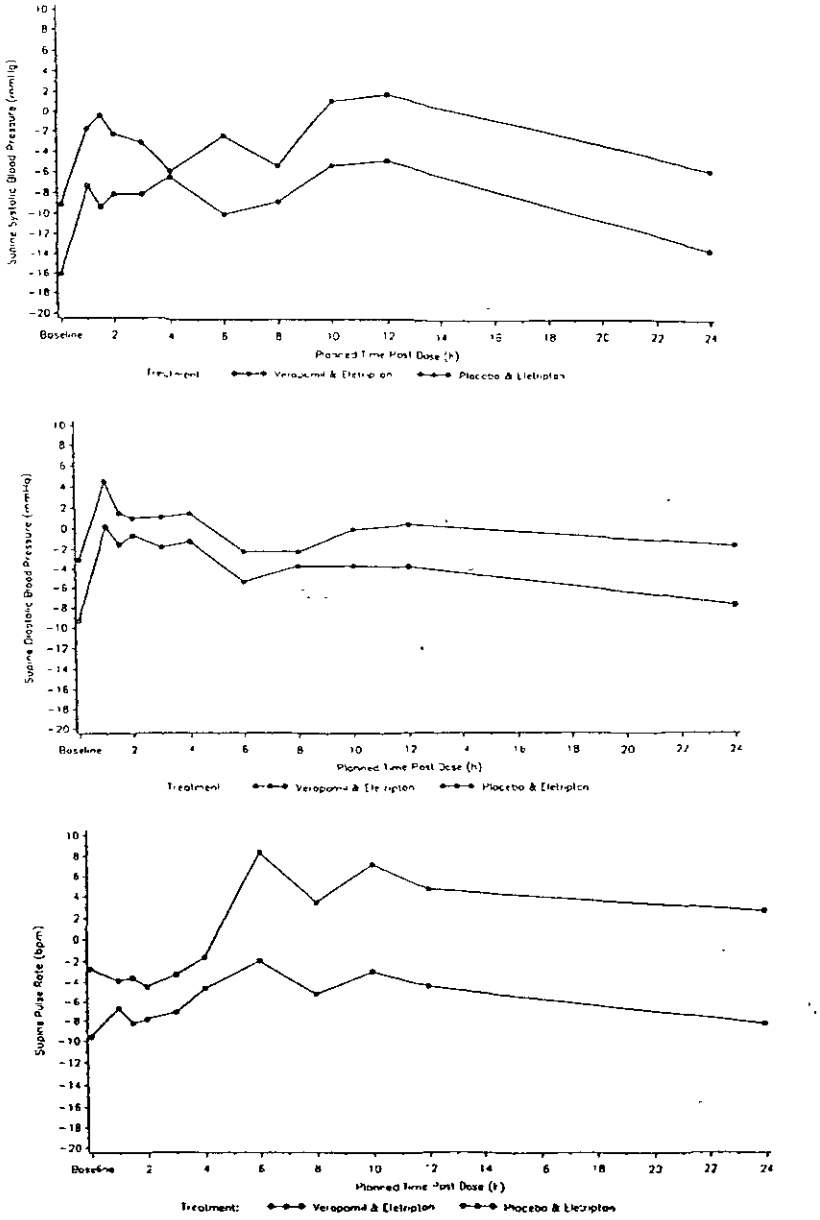


FIGURE 2.3 Mean blood pressure and pulse (difference from baseline) *vs.* time after a single dose of eletriptan + placebo (upper curve in each panel) or eletriptan + verapamil (lower curve in each panel). Upper panel: SBP *vs.* time; Middle panel: DBP *vs.* time; Lower panel: Pulse rate *vs.* time

The maximum increases in SBP and DBP and the AUEC's for these effect parameters are shown in Table 2.3.

TABLE 2.3 The maximum increases and area under the effect – time curves during 12 h ($AUEC_{0-12h}$) and 95% confidence intervals for SBP and DBP after a single dose of eletriptan (80 mg single dose, Day 6) during concomitant dosing of verapamil (240 mg) or placebo b.i.d. for 7 days (n=17).

Parameter	Eletriptan + verapamil (N=17)*	Eletriptan + placebo (N=17)*	Mean difference	95% CI	p value
Max. increase in SBP (mmHg)	-1.54	7.88	-9.42	-13.22, -5.61	0.0001
Max. increase in DBP (mmHg)	2.27	8.01	-5.74	-8.12, -3.37	0.0001
SBP $AUEC_{0-12}$ (mmHg.h)	-115.2	-18.12	-97.11	-137.68, -56.55	0.0002
DBP $AUEC_{0-12}$ (mmHg.h)	-46.22	2.31	-48.54	-67.92, -29.15	<0.0001
Pulse rate $AUEC_{0-12}$ (bpm.h)	-25.99	-16.95	-9.04	-41.72, 23.64	0.5623

Source: Table 5.10; *adjusted arithmetic mean changes.

The effect analysis showed that the mean increase in AUEC for DBP after eletriptan + placebo was statistically significantly lower than after eletriptan + verapamil. The mean change from Day 1 baseline SBP to Day 6 for eletriptan + verapamil did not increase above the mean change from Day 1 baseline SBP to Day 6 for eletriptan + placebo up to 24 hours after the eletriptan dose. This may indicate that the vasodilator effects of verapamil are greater than the vasoconstrictor effect caused by the eletriptan dose.

There was no direct relationships between the effect parameters (SBP, DBP, pulse rate) and eletriptan plasma concentrations, at C_{max} or over the entire 24-h plasma sampling period.

Adverse events

The incidence and percentage of subjects that experienced at least one adverse event that was judged as treatment related are shown in Table 2.4.

TABLE 2.4 Adverse events during the respective periods of verapamil (120 mg b.i.d. Days 1-2; 240 mg b.i.d. Days 3-7), placebo (b.i.d., Days 1-7) and concomitant dose intake of a single dose of eletriptan (80 mg, Day 6)

No. of subjects evaluable [subject days of drug exposure]	Verapamil N=18 [90]	Eletriptan + verapamil N=18 [36*]	Placebo N=17 [85]	Eletriptan + placebo N=17 [34*]
Subjects with ≥1 adverse event	10 (56%)	17 (94%)	1 (6%)	15 (88%)
Asthenia	3 (17%)	10 (56%)	0 (0%)	5 (29%)
Headache	5 (28%)	9 (50%)	1 (6%)	5 (29%)
Dysphagia	0 (0%)	4 (22%)	0 (0%)	4 (24%)
Hypertonia	0 (0%)	1 (6%)	0 (0%)	2 (12%)
Paraesthesia	0 (0%)	2 (11%)	0 (0%)	2 (12%)
Hiccough	0 (0%)	2 (11%)	0 (0%)	0 (0%)

Source: Tables 6.2.1 and 6.2.3; *Adverse events starting on Day 7 were assigned to the interaction groups.

The number of severe adverse events was similar across the treatments. One subject (female, age 38) experienced moderate chest pain after eletriptan + placebo dose intake. The event took place in the morning, with a duration of 45 min (no information of time of dose intake available; C_{max} 153 mg/mL, t_{max} 3 h, AUC 1236 ng.h/mL).

Comments:
There was a large interaction after co-administration of eletriptan and the intermediate CYP3A4 inhibitor, verapamil. The *in vivo* results are not in accordance with the findings in the *in vitro* study, where verapamil showed no interaction potential (IC_{50} >300 µM). The point estimate of the AUC increase was 2.8-fold (arithmetic mean), however, the largest individual increase was 4.6-fold (subject 15, female). The point estimate of the C_{max} increase was 2.3-fold (arithmetic mean), and the corresponding largest individual increase in C_{max} was 3 8-fold (subject 15, female).

Subject 15, who had the largest increases of AUC and C_{max} during eletriptan + verapamil dosing, was also taking norfloxacin (protocol violation), which has been shown to inhibit CYP3A4 and CYP 1A2 *in vitro*. Norfloxacin has also been shown to increase cyclosporin A concentrations (a CYP 3A4 substrate) *in vivo*. However, another female subject (Subject 14, Caucasian, age 19, weight 79.7 kg, height 181 cm), also took norfloxacin, but during the period of eletriptan + placebo dosing. This subject also took oral contraceptives throughout the study. Her AUC and C_{max} were 1721 ng h/mL and 181 ng/mL, respectively. The C_{max} of Subject 14 was comparable to the mean for all subjects (190 ng/mL), and the AUC was approximately 20% higher than the mean for all subjects (1394 ng.h/mL) in the study. However, it is possible that, at least in part, some of the effect seen in Subject 15, who had the largest increases in eletriptan C_{max} and AUC, could be a combination of the effect on CYP3A4 by the concomitant intake of verapamil and norfloxacin. Nevertheless, if the data should be reanalyzed without Subject 15, the impact would not be great. The difference in AUC would change from a 2.8-fold increase to 2.7-fold increase (arithmetic mean), and C_{max} would change from 2 3-fold increase to 2.2-fold increase (arithmetic mean).

The sponsor was concerned that verapamil would increase liver blood flow, which could increase the bioavailability of eletriptan (F=50%), and therefore invalidate the use of verapamil as a 'clean' model drug for intermediate CYP 3A4 inhibition. However, verapamil only marginally increased hepatic blood flow (QH) with about 5%. There was a net increase in indocyanine green (ICG) clearance of 8% (90% confidence intervals of ICG CL: -41 to 177 mL/min). This finding concurs with values reported in the literature, where single doses of verapamil has an acute, augmenting effect on QH. This increase in QH has been reported to diminish during repeated administration of verapamil. Therefore, it is likely that the small alterations observed in QH do not make a major contribution to the observed interaction between the two drugs.

The half-life of eletriptan was only marginally increased, indicating that this is a interaction that occurs during the initial first pass. Verapamil has been reported to inhibit P-glycoprotein (PGP). Using the indication of PGP inhibition by inspecting t_{max}, there was a slight decrease after co-administration of the drugs (t_{max} monotherapy: 2.6 h, t_{max} combination: 2.2 h). However, t_{max} was only reduced in nine subjects. A PGP inhibition of drug efflux across the intestinal lumen by verapamil, may be part of the observed interaction.

The sponsor also submitted a recent publication (Bennett MA et al, Drug Metabol Disp, 2000, 28:125-130) with the study report. In this publication, it is shown that verapamil, among other calcium channel blockers, may act in part as a quasi-irreversible CYP3A4 inhibitor, depending on the experimental conditions (NADPH used in pre-incubations). Since this finding shows that the experimental conditions for the *in vitro* methods are crucial for any extrapolations to the *in vivo* situation, it further limits the use of an *in vitro-in vivo* correlation to predict the pharmacokinetic interactions when eletriptan is co-administered with CYP3A4 inhibitors.

In conclusion, co-administration of verapamil and eletriptan increases C_{max} 2-fold and AUC 3-fold. It is recommended that the co-administration of eletriptan and verapamil be contraindicated in the label, since verapamil is used (off-label) for migraine prevention and the combination is likely to occur in a portion of the patient population.

Study #3. Abbreviated Report: An open randomized, placebo controlled, two-period crossover study to investigate the effects of fluconazole on the pharmacokinetics, safety and toleration of a single dose of eletriptan (80 mg) [Protocol A160-1059]

(Submission 10/13/00)

Objective

The aim of the study was to investigate the effects of fluconazole on the pharmacokinetics of a single dose of eletriptan.

Study Design and Demographics

This was an open, randomized, placebo controlled, 2-period, crossover study in 18 healthy, adult volunteers (9M/9F, actual age range 19-35 years). The subjects received a loading dose of 200 mg (2x100 mg) fluconazole or unmatched placebo on Day 1, followed by once daily doses of 100 mg (2x50 mg) of fluconazole or placebo on Days 2-7. On the morning of the 6th day, 80 mg (2x40 mg) eletriptan was co-administered.

Blood samples for plasma analysis of eletriptan were collected post-dose on Day 6, at 0, 0.5, 1, 1.5, 2, 3, 4, 6, 8, 10, 12, 18, 24, 36 and 48 h, of each study period. Supine systolic (SBP) and diastolic (DBP) blood pressure and pulse rate was taken in duplicate pre-dose, 1, 1.5, 2, 3, 4, 6, 8, 10, 12 and 24 h post dose on Day 6, the day of eletriptan dose intake. A semi-automated sphygmomanometer was used. Safety assessments (ECG, physical examination, laboratory safety monitoring) were performed at screening and follow-up visits. Adverse events and laboratory tests (Day 6) were monitored during the investigational periods.

Bioanalytical Methods

Plasma concentrations of eletriptan were determined by the use of a validated — procedure with UV detection. The method was validated over the concentration ranges of — (LOQ)

— No study specific bioanalytical report has been submitted yet.

Pharmacokinetic and Pharmacodynamic Analysis

Pharmacokinetic parameters (C_{max}, t_{max}, AUC_{0-t}, $AUC_{0-\infty}$, and $t_{½}$) for eletriptan were estimated by non-compartmental methods. The area under the effect – time curves during 12 h post eletriptan dose ($AUEC_{0-12h}$) for SBP and DBP were calculated by non-compartmental methods. The maximum change from base line was also determined.

Results

Pharmacokinetics

The mean plasma concentration-time curves of eletriptan during co-administration of placebo or fluconazole are shown in Figure 3.1.

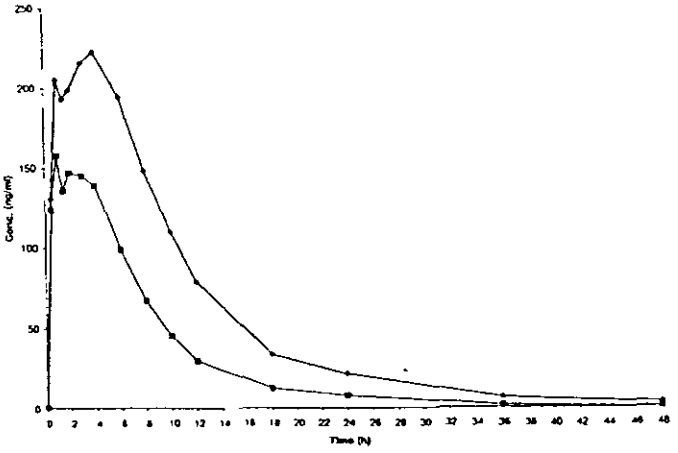


FIGURE 3.1. Mean plasma concentration-time curves of eletriptan (80 mg) Day 6, after co-administration of fluconazole (100 mg QD; upper curve) or placebo (lower curve) in healthy adult subjects (n=18).

The pharmacokinetic parameters after a single 80 mg dose of eletriptan on Day 6 co-administered with fluconazole (200 mg Day 1, 100 mg QD, Days 2-7 days) or placebo (QD, 7 days) are shown in Table 3.1.

TABLE 3.1 Pharmacokinetics of eletriptan (80 mg single dose, Day 6) during concomitant dosing of fluconazole (100 mg) or placebo QD for 7 days (n=18). Upper panel: Geometric means and 90% confidence intervals Lower panel: Arithmetic means (SD) and coefficients of variation.

Adjusted mean pharmacokinetic parameters

Parameter	Study A160-1059 (adjusted means)		
	Placebo	Fluconazole	Ratio' (90% CI's)
C_{max} (ng/ml)	180.3	244.8	136 (117-158)
AUC (ng.h/ml)	1225.8	2482.3	203 (187-220)
T_{max} (h)*	1.9	2.8	0.92 (0.20-1.63)
K_e (1/h)*	0.1481	0.1075	-0.0406 (-0.0470 to -0.0342)
$t^1/_2$ (h)*	4.7	6.4	n/d

Mean C_{max} and AUC are geometric. a = arithmetic mean, b = harmonic mean, 1= difference between the adjusted means (fluconazole - placebo) and corresponding 90% CI's for T_{max} and k_{el}

Parameter	Eletriptan + Fluconazole			Eletriptan + Placebo		
	mean	SD	CV%	mean	SD	CV%
AUC (ng.h/mL)	2692	1114	41	1380	736	53
AUC_t (ng.h/mL)	2666	1091	41	1371	412	53
C_{max} (ng/mL)	261	93	36	199	91	46

As shown in Table 3.1, eletriptan AUC increased 2-fold and C_{max} increased 1.4-fold, during concomitant administration of fluconazole. The increases in AUC and C_{max} were similar between males and females, as shown in Figure 3.2.

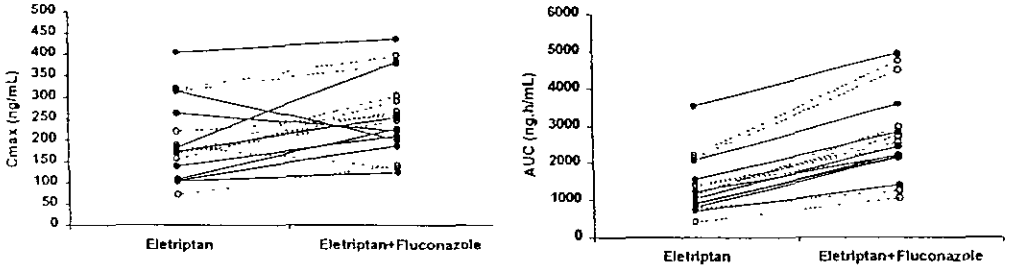


FIGURE 3.2. Individual eletriptan C_{max} (left panel) and AUC after an 80 mg single dose on Day 6, after co-administration of fluconazole (100 mg) or placebo in healthy adult male (n=9; filled circles, solid lines) and female (n=9; unfilled circles; dashed lines) subjects.

An increase in C_{max} was not observed in all subjects when fluconazole and eletriptan was co-administered, and the largest individual increase in C_{max} was 2.1-fold (Subject 12, male). The increase in AUC was unidirectional, and the largest individual increase in AUC was 2.6-fold (Subjects 9 and 18, a male and female subject, respectively).

Pharmacodynamics

There were no statistically significant increases in the mean SBP and mean DBP and AUECs, as shown in Table 3.3.

TABLE 3.3 The maximum increases and area under the effect – time curves during 12 h ($AUEC_{0-12h}$) and 95% confidence intervals for SBP and DBP after a single dose of eletriptan (80 mg single dose, Day 3) during concomitant dosing of fluconazole (100 mg) or placebo QD for 7 days (n=18).

Parameter	Adjusted means		Mean diff	95% CI	p-value
	Placebo+ eletriptan	Fluconazole+ eletriptan			
DBP Max (1-12) (mmHg)	11.6	11.7	0.1	-2.5 – 2.7	0.9343
DBP AUEC(0-12) (mmHg.h)	40.6	58.2	17 6	-3.8 – 39.0	0.1008
SBP Max (1-12) (mmHg)	9.1	9.4	0.3	-5.7 – 6.3	0.9181
SBP AUEC(0-12) (mmHg.h)	14.0	23 3	9.3	-36.5 – 55.0	0.6715
PR AUEC(0-12) (b/min.h)	-38.0	-49.1	-11.0	-41.2 – 19.1	0.4478

Adverse events

According to the provisional report, there were slightly more triptan-like adverse events during eletriptan + fluconazole dosing (n=11), compared to eletriptan + placebo co-administration (n=8). No subject reported chest pain.

Comments:

There was a moderate interaction after co-administration of eletriptan and fluconazole, compared with the other CYP3A4 inhibitors, that have been investigated. The point estimate of the AUC increase was 2.1-fold (arithmetic mean), and the increase in C_{max} was 1.4-fold (arithmetic mean). Fluconazole has not been reported to inhibit P-glycoprotein (PGP), and there was no trend observed in t_{max} after co-administration of fluconazole + eletriptan, which would have been an indication of PGP inhibition (t_{max} monotherapy: 1.9 h, t_{max} combination: 2.8 h). There was a moderate increase in half-life of eletriptan (t½ monotherapy: 4.7 h, t½ combination: 6.4 h) which is an indication of a CYP3A4 inhibition.

Study #4. DM32: Eletriptan *in vitro* interaction studies with CYP3A4 inhibitors and substrates

(Submission 6/1/00)

The potential effect of ketoconazole, itraconazole, metronidazole, sertraline, verapamil and cimetidine (CYP3A4 inhibitors and substrates) on eletriptan metabolism were investigated *in vitro*.

Methods:

Hepatic microsomes were prepared from a combination of eight human livers by means of differential centrifugation.

For each of the assays the final incubation volume was made up of 50 mM phosphate buffer (pH 7.4) and 5 mM $MgCl_2$. Reducing equivalents required for P450 metabolism were provided by NADPH, which was generated *in situ* (an isocitric acid/isocitric acid dehydrogenase system in conjunction with 5 mM NADP). The incubation mixture was pre-incubated at 37°C in the presence of substrate (at a concentration close to its Km) and inhibitor prior to addition of NADP.

Eletriptan (150 µM=57 ng/mL) was incubated with increasing concentrations of CYP3A4 inhibitor/substrate (ranging from 0.001 to 1000 µM), for 30 min at 1 mg/ml microsomal protein. All compounds (with the exception of itraconazole) were dissolved in methanol with a final concentration in the incubation not exceeding 1% methanol. Itraconazole was dissolved in methanol/0.1M HCl (8/1).

At the end of the incubation, the reaction was terminated by adding dichloromethane. Internal standard was added, and the samples were prepared (mix, centrifugation, evaporation and reconstitution) and analyzed by — method with UV detection.

Results:

The effects of the CYP3A4 inhibitors and substrates on the N-demethylation of eletriptan are shown in Table 4.1.

TABLE 4.1 Summary of *in vitro* reactions with eletriptan

CYP Inhibitor/Substrate	IC_{50} (µM)
Ketoconazole	1.8
Itraconazole	3.6
Metronidazole	>300
Sertraline	>300
Verapamil	>300
Cimetidine	>300

Metronidazole, sertraline, verapamil and cimetidine did not significantly inhibit eletriptan metabolism, as shown by the IC50 >300 µM. Ketoconazole and itraconazole were potent inhibitors of the N-demethylation of eletriptan, with IC50's of 1.8 and 3.6 µM, respectively.

Study #5. DM33: Eletriptan *in vitro* interaction studies with CYP3A4 inhibitors and substrates

(Submission 6/1/00)

The potential effect of fluconazole, fluoxetine, fluvoxamine, lovastatin, paroxetine and progesterone (CYP3A4 inhibitors and substrates) on eletriptan metabolism (N-demethylation) were investigated *in vitro*. Propranolol, a CYP2D6 substrate, was also investigated. Ketoconazole served as a positive control for inhibition.

Methods:

Hepatic microsomes were prepared from a combination of eight human livers by means of differential centrifugation.

For each of the assays the final incubation volume was made up of 50 mM phosphate buffer (pH 7.4) and 5 mM $MgCl_2$. Reducing equivalents required for P450 metabolism were provided by NADPH, which was generated *in situ* (an isocitric acid/isocitric acid dehydrogenase system in conjunction with 5 mM NADP). The incubation mixture was pre-incubated at 37°C in the presence of substrate (at a concentration close to its Km) and inhibitor prior to addition of NADP.

Eletriptan (150 µM =57 ng/mL) was incubated with increasing concentrations of CYP3A4 inhibitor/substrate (ranging from 0.003 to 1000 µM), for 30 min at 1 mg/ml microsomal protein. All compounds (with the exception of fluconazole) were dissolved in methanol with a final concentration in the incubation not exceeding 1% methanol. Fluconazole was dissolved in methanol/0.1M HCl (8/1).

At the end of the incubation, the reaction was terminated by adding dichloromethane. Internal standard was added, and the samples were prepared (mix, centrifugation, evaporation and reconstitution) and analyzed by [redacted] method with UV detection.

Results:

The effects of the CYP3A4 inhibitors and substrates on the N-demethylation of eletriptan are shown in Table 5.1.

TABLE 5.1 Summary of *in vitro* reactions with eletriptan

CYP Inhibitor/Substrate	IC_{50} (µM)
Fluconazole	>300
Fluoxetine	>300
Fluvoxamine	>300
Lovastatin	>300
Paroxetine	>300
Progesterone	~300
Propranolol	>300

Eletriptan metabolism was not significantly inhibited by any of the compounds investigated, all compounds yielded IC50 values of 300 µM (progesterone) or greater. The positive control,

ketoconazole (10 μM and 100 μM), inhibited eletriptan N-demethylation by 54% and 64%, respectively.

Study #6. Meta analysis of systolic and diastolic blood pressure

(Submission 6/1/00)

In the initial dose escalation studies with eletriptan there were small dose related increases in blood pressure. The changes in diastolic blood pressure (DBP) were related to eletriptan concentration since maximum concentration (C_{max}) and maximum effect (E_{max}) occurred at about the same time. The first PK/PD analysis was carried out for study 160-208 and this model was presented in the original NDA. Subsequently, the sponsor has used additional modeling approaches to determine the PK/PD relationship between DBP and eletriptan plasma concentrations.

Two of the modeling approaches were based on C_{max} with a third analysis using NONMEM to assess the overall concentration relationship. The PK/PD models using C_{max} resulted in predictions that were similar to those using NONMEM. Eletriptans PK/PD relationship was determined by use of data from 12 clinical pharmacology studies (160-001. 202, 208, 701,701a, 203. 204, 213, 214, 220, 222 and 226).

Placebo

Five of the 12 studies included in the pooled analysis contained an estimate of the placebo BP response allowing an assessment of the variability of the placebo response for BP. The mean maximal increase in DBP across all studies was 6.9 mmHg (11.4% change from baseline). The standard deviation (SD) for this mean response was 7.5 mmHg (12.8% change from baseline) indicating a high within subject variability in the placebo response. The placebo response was also highly variable between studies with the mean maximum percentage increase ranging from 4.7 to 17.6% for DBP.

The mean maximal increase in SBP on placebo across all studies was 11.1 mmHg (9.6% change from baseline). The SD for this mean response was 8.3 mmHg (7.4% change from baseline) indicating that there was also high within subject variability in the placebo response. The placebo response was also highly variable between studies with the mean maximum percentage increase ranging from 6.2 to 13.9% for systolic BP.

Eletriptan

The time course of the BP change appeared to follow the eletriptan plasma concentration-time profile and no significant hysteresis was evident, the pharmacodynamic parameters absolute change and maximum percentage change in blood pressure at t_{max} were selected for comparison to eletriptan C_{max}. Scatter plots from the 12 studies of the maximum increases in DBP and SBP (maximum absolute changes) against C_{max} are shown in Figure 6.1.

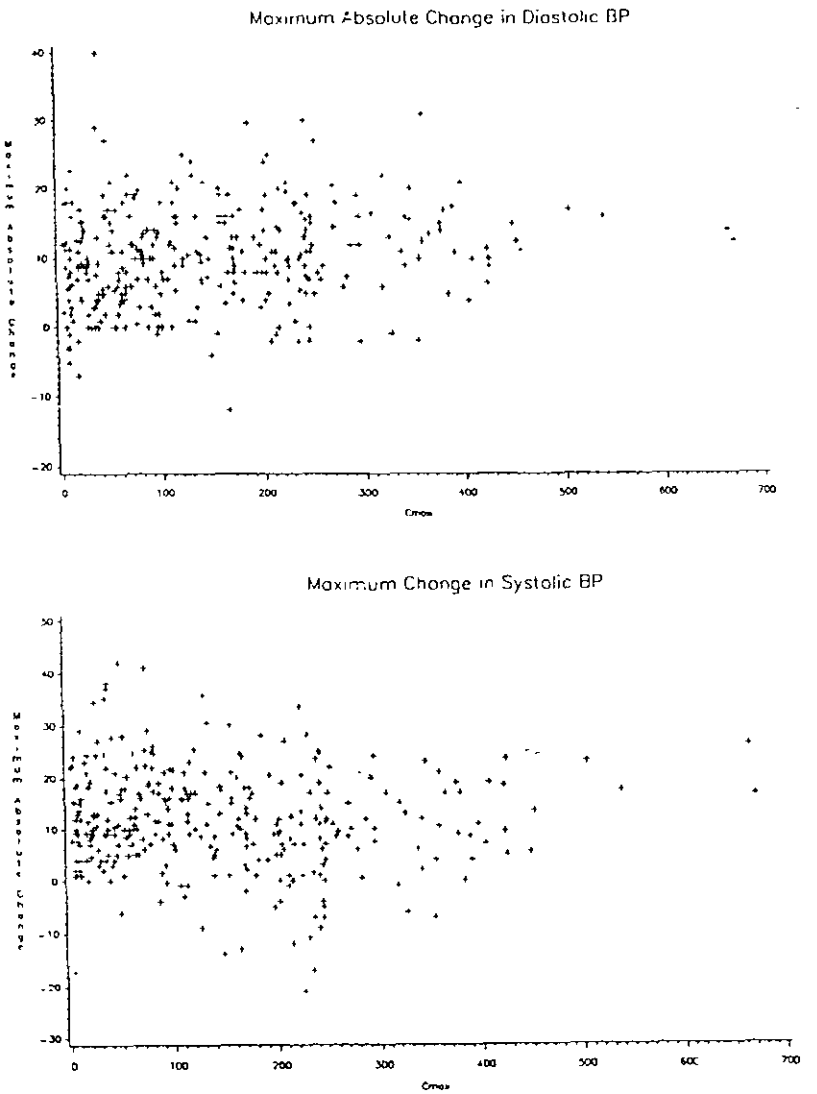


FIGURE 6.1 Maximum absolute change (mmHg) in DBP (upper panel) and SBP (lower panel) *vs.* C_{max} (ng/ml)

Two models (linear and E_{max}) were used in the PK/PD modeling. The models were fitted to the individual increases occurring at C_{max} or the full effect (DBP)- eletriptan plasma concentration profiles 0-12 h after eletriptan dose intake.

The initial linear model developed in the original NDA had a slope of 0.092 (%change per ng/ml). The slopes of the pooled analysis were 0.028 (%change per ng/ml) and 0.017 (mmHg change per ng/ml). The slopes of the NONMEM analyses where a linear model was fitted to the data were 0.0318 and 0.0276 (mmHg change per ng/ml) for the raw and placebo adjusted DBP data respectively. The models derived from the pooled data predict a smaller effect of eletriptan on blood pressure than originally predicted. The linear model resulting from the pooled analysis predicts that for an 80mg dose there would have to be at least a 4.5 fold increase in C_{max} before the average increase in DBP would reach 15 mmHg. The linear NONMEM model (for the raw data or placebo corrected data) predicts that concentrations would have to increase by 2.5-fold for a similar average increase to be observed.

The E_{max} model {$E = E_{max}*(1/(1+EC_{50}/C))+E0$} from the pooled analysis of DBP *vs.* E_{max} gave a maximum effect (E_{max}) on DBP of 12.5 mmHg, with an eletriptan plasma concentration of 130 ng/mL producing 50% of E_{max} (EC_{50}). The base-line effect on DBP (E0) was determined to 0.0185 mmHg. No information regarding the goodness of fit for the model was submitted. A NONMEM analysis of the placebo adjusted DBP using the same model gave similar parameter estimates (placebo adjusted DBP: E_{max} of 11 mmHg and EC50 of 136 ng/mL; unadjusted DBP: E_{max} of 19.7 mmHg and EC50 of 391 ng/mL). The DBP - eletriptan plasma concentration profiles 0-12 h after eletriptan dose intake are shown in Figure 6.2.

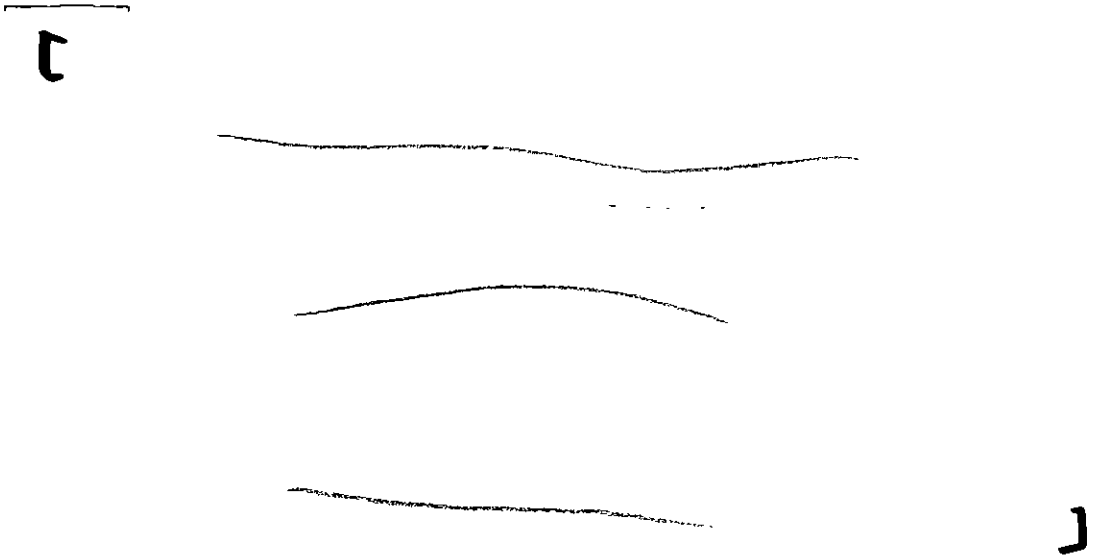


FIGURE 6.2. Actual and predicted BP (Raw: upper panel and placebo subtracted: lower panel) vs. eletriptan plasma concentrations from the NONMEM analysis.

The data from the drug-drug interaction studies (erythromycin and ketoconazole) were used for model validation. Eletriptan C_{max} increased to 358 ng/ml during combination therapy in the erythromycin study and to 473.8 ng/mL in the ketoconazole study. The observed and predicted changes in diastolic BP are presented in Table 6 1.

TABLE 6.1. The observed and predicted changes in DBP based on the pooled analysis using the linear model and the NONMEM E_{max} model (data not adjusted for placebo effects)

	Maximum change in diastolic BP at T_{max}		Maximum change in diastolic BP overall	
Interaction study	Pooled analysis linear model	Actual observed mean maximum	NONMEM analysis mean maximum increase (mmHg) predicted based on C_{max} (raw data)	Actual observed mean maximum increase (mmHg) with inhibitor
Difference between erythromycin and placebo (226)	3.10	4.00	3.21	5.90
Difference between ketoconazole and placebo (1045)	5.15	3.60	4.64	2.88

Note- Difference between inhibitor and placebo determined from mean blood pressure changes

16 page(s) of revised draft labeling has been redacted from this portion of the review.

COMPLETED AUG 0 9 19

AUG 9 1999

Office of Clinical Pharmacology and Biopharmaceutics Review

NDA 21-016
Relpax™ (Eletriptan)
(20, 40 and 80 mg — tablets)

Type of submission: NDA (NME)
Submission Date: Oct. 27, '98, Jan. 21, '99, April 8,'99.

Sponsor: Pfizer
INDICATION: Migraine
REVIEWER: Rae Yuan, Ph.D.
Pharmacometrics Node: Joga Gobburu, Ph.D.
Team Leader: Chandra Sahajwalla, Ph.D.

CONTENT

Erythromycin

(VI) Eletriptan Affecting Other Drugs' PK-

III. Biopharmaceutics
Bioequivalence Study
Dissolution

2. Suggested Labeling

3. Appendix of Individual Studies

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AUG 9 1999

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW

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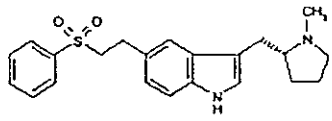
Team Leader: Chandra Sahajwalla, Ph.D.

SYNOPSIS

Introduction:

The mechanism of migraine is thought to be due to the intracranial vasodilation. Eletriptan (UK-116,044) is a selective agonist for the vascular 5HT1B, neuronal 5HT1D receptors, as well as for the 5-HT1F receptor related to the anti-migraine action. In animal models, Eletriptan causes constriction of intracranial vessels, being more selective for the carotid distribution than for the coronary arteries. In humans, the sponsor attempts to provide evidence showing that Eletriptan is an effective, rapid treatment of the pain and associated symptoms of acute migraine headache with or without aura. The proposed dosage strengths are 20, 40 and 80 mg, given as needed but with 2 hr separation between the two doses.



Thirty six (36) phase I and II studies have been conducted in approx. 550 healthy adult volunteers, 100 adult migraine patients, 24 pediatric migraine patients aged 7 to 16 years old, 16 elderly subjects aged 65 to 93 years old, and subjects with hepatic impairment, renal impairment or undergoing coronary angiography to evaluate the pharmacokinetic and dynamic characteristics of the drug. Eight (8) pre-clinical studies have been conducted to examine the plasma binding, metabolic fate and potential for drug-drug interaction of eletriptan in vitro. In addition, 2 Phase III studies investigated the population pharmacokinetics of eletriptan in male and female migraine patients. All the phase I studies were conducted using 80mg dose with the exception of that in dose finding studies.

Overall pharmacokinetics of eletriptan are summarized as follows:

- AUC and Cmax are not dose proportional from 20-80mg.
- Fast absorption (80%) with moderate 1st-pass extraction (Tmax ~1-2 hr, F=34% in male and 64% in female).
- Metabolized by CYP3A4 to an equi-potent active metabolite, UK-135,800, which appears in the plasma at an exposure of <20% of the parent drug.
- Mostly metabolized with approximately 10% of renal excretion attributed to the parent drug elimination (CL_{iv}=36 L/hr, Clr=3.9 L/hr, estimated in male).
- Moderate protein bound (~85%) for both parent drug and active metabolite with a large volume of distribution after i.v. (125 L in male, 143 L in female).
- Secreted into nursing milk (0.02%).
- No effect on eletriptan PK after oral dosing was found for age, gender, menstrual cycle, renal impairment, and CYP2D6 polymorphic status.
- Effects on eletriptan PK after oral dosing were found, however, for race, the onset of the disease, food intake, hepatic impairment, propranolol coadministration, and erythromycin coadministration.

Issues identified in this submission are:

1. The sponsor did not thoroughly search for the metabolic enzymes for eletriptan metabolism. For example, the only pathways that have been explored are CYPs, while others have not been investigated. The potential of eletriptan to inhibit metabolic pathways other than CYP has not been studied.
2. The plasma level of the metabolite has not been thoroughly examined. The identity of a metabolite present in the plasma with longer half-life than that of the parent drug has not been identified. The relative percentage of the total dose being converted to the active metabolite was not determined in the mass balance study, even though the relative ratio of the active metabolite vs. parent drug was assessed in a separate study.
3. The active metabolite level was not measured in any of the studies, except a IR-CR western study and a Japanese study.
4. In several studies, though not all, the plasma profiles show double peak with the second peak occurring 1-2 hr after the first peak. This phenomenon is especially striking in studies with female subjects (Study #003, 004 and 215) and multiple dosing studies (Study # 205 and #703). The sponsor did not provide the explanation for the second peak.
5. The sponsor has not systemically pursued the PK-PD relationships of eletriptan. No mechanistic approach on modeling was attempted other than plotting the mean value of PD observation versus the average plasma concentrations of eletriptan.
6. Population PK study (using NONMEM) examined the effects of covariates on eletriptan saliva PK. However, the study was not well designed, thus failed to detect several covariates found in the individual studies. In addition, the model explored by the sponsor (2-compartmental model) did not link plasma with saliva concentrations. Thus, the value of this population study was not clear.
7. Gender effect was inconsistent throughout the studies.
8. In some subjects, menstrual cycle showed decreasing effect on eletriptan exposure, but not in all subjects.
9. The role of Oral Contraceptive on eletriptan was not explored.
10. Eletriptan could be excreted in breast milk with the potential to stay much longer in nursing babies than adults.

11. Hepatic impairment patients (mild and moderate) showed only 30% decrease in clearance. Eletriptan in severely liver impaired patients have not be evaluated.

The above issues have been communicated to the sponsor in a telecon on 7/21/1999.

Detailed Information:

I. Preclinical-

Physical Chemical Property: Eletriptan has a molecular weight of 463.4 g/mol. It is readily soluble in water. It dissolves quickly and completely in all the tested media including that of 0.01M HCL to SIN (Q equals — at 15 min). Pka of the drug is 9.2.

Binding Property: In rats using radiolabeled drug given iv, it was detected that eletriptan is distributed quickly to various tissues especially in kidney, small intestine, bile and retina. The concentrations in rats' brain are 25% of the blood concentrations at 0.1 hr, the time when the drug distribution in other tissues exceeds that in blood. By 1 hr, concentrations generally diminished except that in bile and retina. The binding property in human is not known, except that in the blood. The study conducted in only one subject's blood demonstrated that the distribution of the drug from blood to plasma is close to 1 over a concentration range of —— , and plasma binding of the drug is constant over the range —— (The therapeutic concentration after 80mg dose is 200-300 ng/ml). The plasma binding of active metabolite over the concentration range of (—— remains below 84%. These data suggest that eletriptan is not likely to interfere with protein binding of other highly plasma protein bound drugs, and eletriptan may be eliminated by biliary excretion.

In Vitro Metabolism of Eletriptan: Three pre-clinical studies investigated the metabolic pathways of eletriptan by CYP superfamily. It was demonstrated that CYP1A1, 2D6 and 3A4 could metabolize eletriptan with the order of activity as 1A1>2D6>3A4. However, considering the actual amount of protein of these enzymes, it was concluded that CYP3A4 is the major metabolic enzyme for eletriptan. It was also shown that CYP3A4 is responsible for the formation of the active metabolite with Km of 144 uM and Vmax of 156 pmol/mg/min, but the sequential metabolism of this active metabolite was not investigated. In vitro, ketoconazole at 0.1 uM inhibits ~70% of eletriptan metabolism. Considering the pharmacokinetic feature of eletriptan (discussed later), these evidence indicated that strong drug-drug interactions between eletriptan and CYP3A4 modulators should be expected.

The Inhibitory Potential of Eletriptan on CYP enzymes: Eletriptan did not inhibit CYP1A2, CYP2C9, CYP2E1 or CYP3A4 activity at the concentrations of 0.01-100μM, but did exhibit an inhibitory effect on CYP2D6 activity with a approximate IC50 of 41μM. Considering the therapeutic concentration of eletriptan being 0.6 uM, the potential of eletriptan to inhibit CYP2D6 metabolism in vivo is minimum unless the uptake of eletriptan by hepatocyte is very high. The potential of eletriptan to inhibit other non-CYP metabolic pathways has not been studied.

The Induction Potential of Eletriptan on CYP enzymes: Eletriptan is able to induce CYP3A4 protein in four of six tested cultures of human hepatocytes at concentrations greater than 5μM, with the induction potential of 5 fold in protein, and 0.9 fold in activity. In comparison, the positive control, rifampicin at an equivalent dose produced greater than 10-fold induction of CYP3A4 protein and 7-fold induction of CYP3A4 activity. The induction seen for eletriptan is comparable to that observed with omeprazole. It was also shown that Eletriptan,

rifampicin and omeprazole were capable of inducing CYP2A6, however this isoform metabolizes very few clinically relevant compounds. Eletriptan did not affect protein levels of CYP1A2, CYP2C9, CYP2C19, CYP2D6 and CYP2E1. Considering the following reasons (1) the therapeutic concentration of eletriptan is 0.6 uM; (2) induction occurs usually after multiple dosing of an inducer, rather than multiple single dosing of an inducer such as the case with eletriptan; (3) unless the intra-cellular concentration of eletriptan can be accumulated to a great extent, the induction potential of eletriptan is mild to moderate, the induction potential of eletriptan on CYP3A4 is unlikely. However, the induction potential of CYP on other non-CYP metabolic enzyme systems has not been studied.

II. Phase I Clinical Pharmacology---

1. Basic ADME:

Single Dose Escalation/Proportionality: Six single dose escalation studies in North America/European population covering doses of 10-120 mg were conducted to look for the safe and efficacious dose in human. Due to the different formulations tested, route of administration and the subjects studied, two relevant studies were reviewed. It was shown that eletriptan was rapidly absorbed. Higher than expected Cmax and AUC were observed. However, in the study examining 20, 40 and 80mg dose proportionality, it was shown that an apparent dose proportionality between 40 and 80 mg was achieved, but not between 20 and the higher doses. A higher Kel at lower doses was observed, suggesting that a saturable high affinity/low capacity elimination pathway. The reviewer stratified the data by gender and showed that the nonlinearity was more pronounced in female than in male. A gender difference in Cmax and AUC existed at each dose level.

Multiple Dose: One pivotal multiple dose study in Caucasian males was conducted to examine the PK of eletriptan using a non-To-Be-Marketed 10 mg formulation in the following 3 cohorts: *Cohort I*-Multiple doses of 20mg or placebo over 5 days. Two doses on Days 1 and 2 separated by two hours, two doses on Days 3 and 4 separated by one hour and three doses on Day 5 each separated by four hours. *Cohort II*- Multiple doses of 30mg or placebo over five days, with the same regimen as for 20 mg. *Cohort III*: 20mg tid or placebo over seven days with a single dose on Day 7. The data in cohort I and II showed that Cmax doubles after the second dose given 2 hrs after the first one.

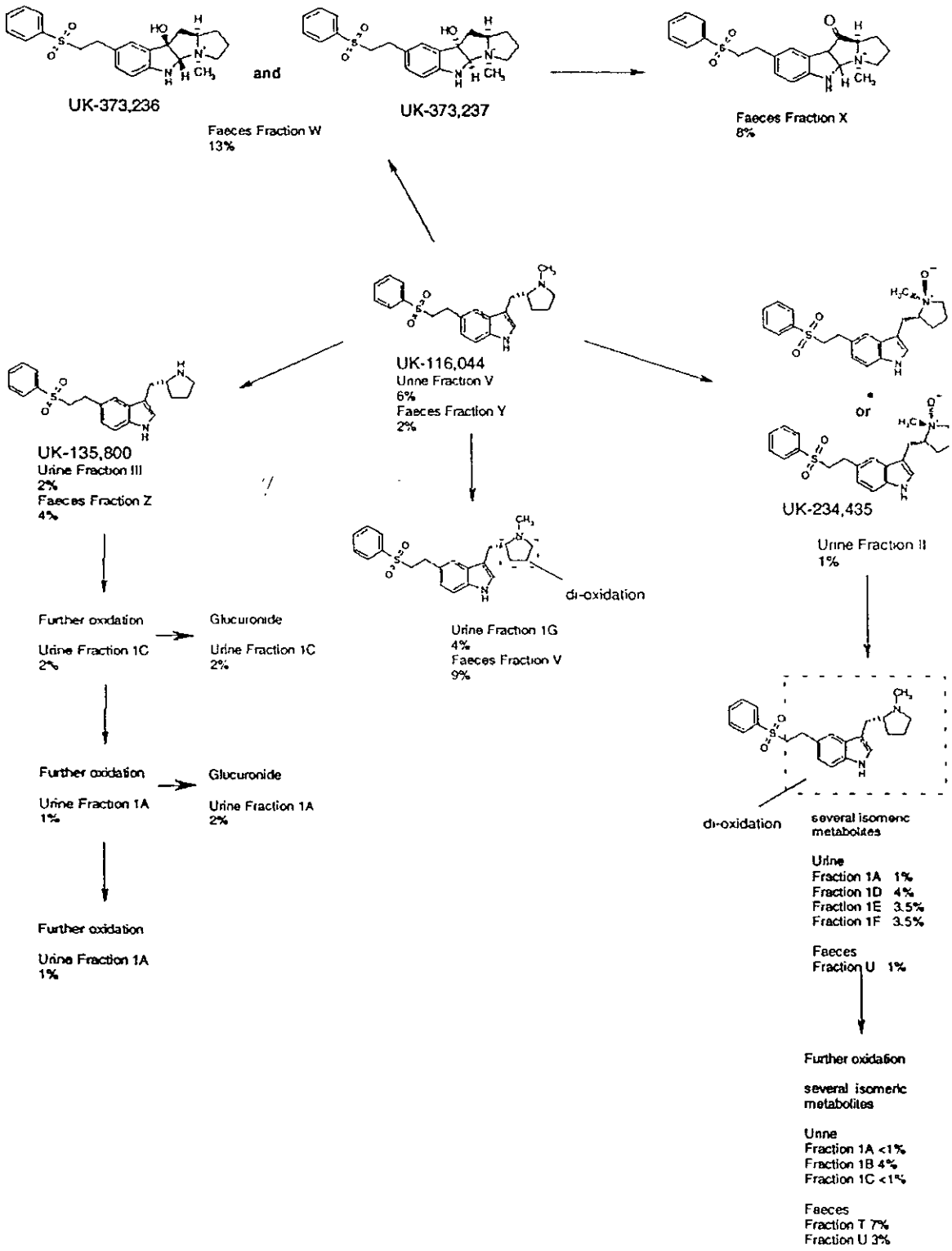
Absorption: Absolute bioavailability (F) of the drug was examined in a study with 6 mg iv and 80 mg oral administrations (n=6 male & 6 females), and showed that F was 35% in males and 65% in females. The reviewer re-analyzed the data and showed that the oral clearance of eletriptan in males is 1.7 times of the value in females. After oral administration, in male, 32% of the drug was extracted by liver and 34% by GI; whereas in female, 34% by liver and 2% by GI. After iv administration, however, systemic clearance in female is 14% higher than in male. Food, which was not the FDA-required high fat/high calorie food, was shown by the sponsor to increase AUC and Cmax by 17% and 12%, respectively. The reviewer found that there was one individual with exceedingly high AUC in both fed and fasted arms. Excluding this subject in both arms results in a 30% greater AUC in fed than in the fasted armed, and this percentage was later confirmed by another food study in Japanese population. This indicates the eletriptan PK is sensitive to changes in pH, motility, blood flow, lipopholicity environment or any other factors in GI system. In addition, the moderate extraction ratio of eletriptan makes it susceptible for drug-drug interactions with CYP3A4 modulators (via first-pass effect).

Distribution and Metabolism: A mass balance study in 3 males using both iv and oral administration (parallel design) was conducted to show that the absolute volume distribution of eletriptan is 1.77 L/hr, exceeding the body water volume, and the metabolic fate of the parent drug as on the following page. In plasma, parent drug accounts for 20% of the total dose, but AUC and half-life for the total radioactivity after i.v and p.o. were respectively much higher and longer than those for the parent drug. This suggests the existence of circulating metabolites with half-life longer than the parent drug. In the plasma samples collected 1 hr post-oral-dosing (Tmax=1 hr), 4 components were found to be eletriptan, pyrrolidine N-oxidated and N-demethylated metabolites of eletriptan and an unidentified fourth component, accounting for 30, 23, 7, and 35% of the total radioactivity, respectively. However, the total exposure to these metabolites, especially that of the active N-demethylated metabolite UK-135,800, was not assessed in this study. The sponsor estimated the absolute bioavailability to be 60% in this study and the systemic oral absorption ratio (calculated from radioactivity in urine after p.o. dosing over that after iv dosing) to be 0.81. But it should be noted that the study was a parallel design study with only 3 male subjects who are or close to be the elderly in each group, and the oral formulation is solution, and not to-be-marketed tablet. In urine, most of the radioactivity (55% $\pm$ 5% after i.v. and 45% $\pm$ 1.4% after p.o. administration) was recovered up to 24 hours post-dose. In feces, most of the radioactivity (30 $\pm$ 1.0% after i.v. and 45% $\pm$ 3.3.% after p.o. administration) was recovered 24 to 48 hours post-dose. Approximately 10% and 20% of the dose was excreted as unchanged drug after p.o. and i.v. dosing, respectively. The profile of metabolites in excreta was similar to that in plasma.

Active Metabolite: In a study originally designed to determine the bioavailability of medium and extended controlled release formulations of eletriptan relative to that of immediate release tablets, the sponsor investigated the relative plasma concentrations of eletriptan and the active metabolite UK-135,800 following the IR (20mg x4) formulation arm. The active metabolite with half-life of 12.6 hr exhibited 17% and 11% of the AUC and Cmax, respectively, of those for the parent drug. In the Japanese single dose study, the active metabolite measured after 120-mg dose of eletriptan was found to be 10% of the parent drug's AUC. The CYP2D6 genotype does not contribute much to the variation of kinetics of eletriptan.

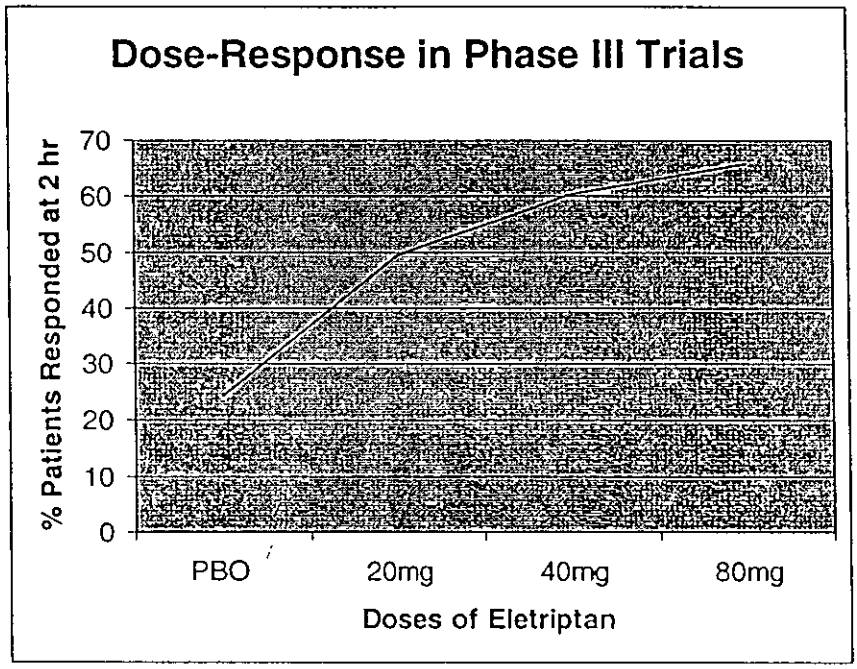
ELETRIPTAN PROTOCOL 207

SUMMARY OF THE PROPOSED METABOLIC PATHWAYS OF [^{14}C]UK-116,044 IN MAN FOLLOWING AN ORAL DOSE (30MG)



2. PK-PD relationship and Population PK-

(1). Efficacy vs. PK: The sponsor performed the dose-response information based on the data obtained from 7 pivotal clinical phase III studies, but did not perform a plasma concentration vs. response analysis for eletriptan. The dose-response relationship data, provided by Dr. Armondo Olivia, the medical reviewer, is as follows:



The facts that all the pivotal clinical trials were conducted in out-patient population and the disease onset interfere with the pharmacokinetics of the drug introduce the difficulty in carrying out a post-hoc PK-PD analysis based on healthy volunteers studies in Phase I and II.

(2). Safety vs. PK: the sponsor conducted No in-depth analysis on safety vs. concentrations of eletriptan. In one cross-over study (Study#208), the sponsor studied the systolic and diastolic blood pressure and mean pulse rate after 30, 60, 90 and 120mg doses in 12 healthy subjects. When the mean concentrations of eletriptan were plotted against the mean change of diastolic blood pressure from the baseline, a linear relationship was observed. No modeling was performed by the sponsor, but is being explored by the reviewers. However, it was clear that all three-safety parameters (systolic blood pressure, diastolic blood pressure and pulse rate) increases with increased eletriptan concentrations.

(3) Population PK: The sponsor provided a population PK analysis based on two phase III clinical trials. The PK analysis was conducted on drug concentrations in saliva, which was shown to be consistently 20-25% of the plasma concentrations. A total of 779 patients and 2,048 saliva samples were available in the study. The patients were instructed to take placebo, 40 or 80 mg eletriptan at onset of migraine attack, with the option of taking a 2nd dose to treat non-response or recurrence 2 hrs later. Saliva was collected at 2 hr after each dose during migraine attack. During the first post attack visit, 20-mg eletriptan was given to the patients and another saliva (off-peak) and plasma sample were collected. A mixed effect modeling was performed for population analysis. The analysis showed that saliva PK follows a 2-compartment model with 1st order input for eletriptan. Only migraine attack reduced the bioavailability by 34%, other

covariates, including age, gender, race, menstruation status, renal function, coadminstration of beta-blockers, tricyclic anti-depressants, estrogen therapy, oral contraceptives, SSRIs, inhibitors for CYP2D6 and inhibitors for CYP3A4, had no effect on eletriptan PK. The failure to detect some of the covariates, such as CYP3A4 inhibitors, could be due to lack of statistic power (small number of subjects under a specific category), insensitive changes in saliva concentration with respect to changes in plasma concentrations or the confounding factors of drug/disease interaction with saliva secretion. No attempt to analyze plasma data using population approach was made.

3. Intrinsic Factors Affecting Eletriptan PK-

(1). Gender: A study on 16 males (8 young and 8 elderly) and 16 females (8 young and 8 elderly) did not detect gender difference in eletriptan pharmacokinetics, but a difference in Ke between the young and the elderly was found. The overall mean value of AUC in female was only 10% higher than that in male. However, the sponsor acknowledges that "While there was only one statistically significant difference between the young and elderly subjects and none between the male and female subjects, it is not possible to rule out differences in the pharmacokinetics between these groups of subjects. This difficulty in interpreting results from the fact that the study, while powered to test for differences between genders and age groups, is insufficiently powered to deal with the interactions between these variables." A separate analysis conducted by this reviewer also failed to detect any gender difference in Ke with the matching age group, but a lower Ke in the elderly subjects was detected.

(2). Age: In a single dose study with 24 pediatric subjects (12 aged 6-12, and 12 aged 12-16) administered with 20-80 mg eletriptan, a trend of nonlinearity of dose vs. AUC or Cmax was observed. Unfortunately, children at different age groups were administered with different dose. Thus, the age effect on eletriptan PK was confounded with the nonlinearity observed in adults. When normalized by body weight, clearance appears to be slightly higher in the children (1.46 L/hr/kg for 6-12 yr.-old, 1.16 L/hr/kg for 12-16 yr-old) than in adults (0.94 L/hr/kg). Un-normalized (by body weight) volume of distribution increased with age by 50%, but not with body weight. Volume of distribution normalized body weight was only slightly larger in the older children (6.5 L/kg) than the younger ones (5.4 L/kg). A slightly higher exposure (10%) was also seen in elderly adults compared to young adults in another study (mixed with gender effect). Thus, a restriction on using dose 40 in the younger children and elderly adults should be considered.

(3). Menstrual Cycle: A single dose study on 13 female subjects was conducted following 4 treatment periods that was based on 28-day menstrual cycle. Although the mean exposure to eletriptan throughout the 4 cycles were not statistically different, half of the individuals showed decreased AUC in phase 4 as compared to that in phase 1. The arithmetic mean value of AUC in phase 4 is 87% of that in phase 1, while geometric means is 78%. Thus, menstrual cycle could affect the absorption or elimination of eletriptan, however, a large inter-individual variability should be expected.

(4). Nursing: A single dose study to determine the excretion of eletriptan in breast milk and the pharmacokinetics of eletriptan in plasma and breast milk was conducted in 8 women who were at least one month postpartum and able to produce a minimum of 300ml of breast milk over 24 hours. Breast milk eletriptan concentrations varied greatly, but the mean concentrations were around one-fourth of plasma eletriptan concentrations. The elimination half-life of eletriptan in breast milk (3.6 hr) was slightly shorter than in plasma (4.7 hr). The mean total amount of eletriptan excreted into breast milk over 24 hours was 12.9μg or 0.02% of the 80mg dose given. A total of seven adverse events were considered to be both treatment emergent and treatment

related were recorded for four subjects during treatment with eletriptan, including mild nausea, dizziness, mild rhinitis and chest pain within 1 hr after dosing. Even though the total amount of eletriptan excreted in milk is small, however, considering the small body weight (thus volume of distribution) of a nursing baby, the concentration of eletriptan in a nursing baby could be substantial. Secondly, the major metabolizing enzyme for eletriptan, CYP3A4, in the newborn is extremely low and its level usually rises to about 30% of the adult at 1 month of age. Lastly, the active metabolite with longer half-life than the parent drug was not monitored in this study but could be excreted in the breast milk as well. Thus, eletriptan could stay in the circulation of a nursing baby for a much longer time than in adult. Without knowing the effect of eletriptan on a nursing baby's physiological and developmental process, its use in nursing women should not be advised.

(5). Race: PK of Eletriptan was examined in 3 studies in Japan to describe dose linearity, multiple dose kinetics and food effect on eletriptan. In a single dose escalation study from 20 to 160 mg, the sponsor reported a lack of dose-proportionality of the geometric means over the dose range, with a doubling of dose producing an estimated 2.4 fold increase in AUC. The nonlinearity of eletriptan kinetics in Japanese population might arise from non-constant elimination rate. A cross study comparison with the Western males (study #215) indicated that the Japanese population had a reduced AUC by 33 % at 80-mg dose. Food study confirmed the analysis made by the reviewer in the western study, showing 30% increase in Cmax and AUC associated with food intake (common Japanese breakfast). The multiple dose study showed that AUC on Day 7 was 40% greater than that on Day 1, following either 40 mg tid or 80 mg bid administration, indicating a time-dependent saturable kinetics. Dose normalized AUC24 on Day 1 or 7 (data not shown) following 80 mg dose was ~50% higher than that following 40 mg dose. Correspondingly, Ke on Day 7 was lower than on Day 1. Renal clearance was lower by 20-30% on Day 7 compared to Day 1 for both 40 and 80 mg dose. Since the renal clearance is lower than the normal creatinine clearance, the lowered value could be due to the reduced extent of absorption. Since no multiple dose study of 40 and 80 mg has been conducted in the Western population, a direct cross-study comparison was not possible.

4. Disease Affecting Eletriptan PK-

(1). Migraine Attack: One study in 36 migraine patients was conducted with one dose being administered on a planned migraine-free phase, and another dose within 6 hours of onset of a migraine attack. Plasma samples were collected during each of the two study periods at baseline (immediately prior to dosing) and at specified times up to 8 hours post-dose. Compared to the migraine absent phase of the study, the AUCt and Cmax of eletriptan were significantly reduced by approximately 20-30% and the Tmax was significantly increased from 1.5 to 2.8 hours during the migraine present study period. Twenty five percent of subjects have their Cmax reduced by more than 50% with the occurrence of migraine. Two subjects have Cmax equal to 2 and 4 ng/ml in the presence of migraine when the corresponding value was 45 and 95 ng/ml, respectively, in the absence of migraine. In the study, the plasma sample was collected up to 8 hours, while the elimination half-life is 4-5 hr. Therefore, the estimated AUCt was partial AUC, may or may not reflect the bioavailability of the drug. These evidence suggested a decreased rate of absorption of eletriptan during a migraine attack. A further analysis conducted by this reviewer to stratify the data according to gender indicated that in both absence and presence of migraine attack, a 30% difference in the Cmax was observed between the two genders.

(2). Renal Impairment: A single dose study in healthy and renally impaired subjects including mild, moderate and severe degree of impairment was conducted with 80 mg dose. Other than a statistically significant increase of Tmax in the Severe group (5.6 hr vs. 2.6 hr), the sponsor

reported no significant change in all other pharmacokinetic parameters in renal patients. The statistically significant delay on Tmax observed in the severe group may be the result of renal impairment. Renal impairment is known to be able to affect the rate of absorption and the extent of absorption. Besides Tmax, the reviewer found a trend of decrease in Cmax with the increasing creatinine clearance. Renal excretion of the drug was not monitored in this study. Though not contributing to the assessment on the total plasma clearance change, the estimation of renal clearance can help us to understand the renal effect on non-renal clearance.

(3). Hepatic Impairment: A single 80mg dose study was conducted in 11 subjects with biopsy-confirmed hepatic cirrhosis (eight were Child-Pugh class A, 1 scored 5 and the rest 6; four were Child-Pugh class B, 3 scored 7 and 1 scored 9) and 11 subjects with normal hepatic function (Child-Pugh scores are not determined). Normal subjects were age- and weight-matched to the hepatically impaired subjects, on entry to the study. A 30% increase in AUC0-inf was reported by the sponsor in the liver impairment group, compared to the normal subjects. This increase in AUC was associated with the 25% decrease in CL/F and 15% increase in t1/2 in the liver patients. Two liver patients have above-average high unbound fraction of eletriptan, but the mean in this group is not significantly different from the normals. Eletriptan is predominantly eliminated through metabolism, therefore it was not surprising to see that patients with liver failure had increased exposure to the drug. The severely hepatically impaired patients have not been studied, and the active metabolite in the impaired patients have not been evaluated. Dose less than 80 mg in hepatic patients should be recommended, and eletriptan should not be used in severely liver impaired patients.

5. Drugs Affecting Eletriptan PK-

(1). Propranolol: A placebo controlled two way crossover study with 7 day dosing of 80 mg bid propranolol and single dose of 80mg eletriptan on day 7 were conducted in 6 males and 6 females. Statistically significant differences were observed between the treatment groups for AUC and kel. The AUC of propranolol treatment group was larger than that of placebo treatment group by 33%, and Kel was slightly (7%) lower. But Cmax and Tmax of the two groups were the same. The analysis (assessed by comparing day 7 pre-eletriptan-dosing data to day 1 data) showed that propranolol statistically significantly reduced DBP and pulse rate (PR) compared with placebo. The specific effect analysis (comparing pre- and post dosing of eletriptan on day 7 following either propanolol or placebo) showed that eletriptan, in the presence of propranolol, statistically significantly reduced the maximum increase in DBP compared with placebo. In addition, all the other pharmacodynamic parameters were reduced in the presence of propranolol, but not to the level of statistical significance. In contrast, compared to placebo, the overall effect analysis (assessed by comparing post-eletriptan dosing on day 7 to propanolol/placebo dosing on day 1) showed that all the pharmacodynamic parameters for eletriptan were statistically significantly reduced in the presence of propranolol.

(2). Erythromycin: A placebo controlled, two-way cross over study with 7 day dosing of erythromycin (500mg, twice daily) and single dose of eletriptan (80mg) on day 7. Eletriptan AUC increased approximately 4-fold, Cmax increased two-fold, and kel reduced by -0.054/h following co-administration with erythromycin. The plasma half life of eletriptan was increased from 4.55h in placebo treatment to 7.05h in erythromycin treatment. There was no evidence of a treatment related change in Tmax. The treatment difference in AUC means, compared to co-administration with placebo, held true in each gender. However, the difference was more pronounced in females than in males. Co-administration of erythromycin produced statistically significant treatment related increases in both AUEC and maximum increase from pre-eletriptan baseline for both systolic and diastolic blood pressure. The differences between means for

maximum increase from baseline were 5.5mmHg (systolic blood pressure) and 5.9mmHg (diastolic blood pressure), but the interpretation of this observation is limited by the variability associated with the method of BP measurement. More subjects reported adverse events whilst receiving eletriptan with erythromycin than other treatment. The highest incidences of treatment related adverse events were reported for the nervous system, but no subjects reported nervous system adverse events when receiving erythromycin or placebo alone. Due to the safety concerns at higher concentration of eletriptan, coadministrating this drug at 80 mg with CYP3A4 inhibitors should not be recommended.

6. Eletriptan Affecting Other Drugs' PK-

Other than the in vitro study discussed in the preclinical section, there is no clinical drug interaction study conducted to demonstrate the modulating potential of eletriptan on the pharmacokinetics of other drugs. In the Western food effect single dose study (Study #225), urine samples were collected in the three 24 hour periods, i.e., pre-first dose, post-first dose and post-second dose, to determine the 6-ß-hydroxycortisol/cortisol ratios as a marker for CYP3A4 activity. It was found that the ratio of post-dose was 142.5% of pre-dose values under the fasted conduction, but similar under the fed condition. Even though the increased ratio under the fasting condition was observed in 10 out of 18 subjects (Five of these 10 induced subjects had the ratio increased to >2 fold), the reviewer believes that it may not indicate the induction of CYP3A4. Because the study was single dose, which is unlikely to induce CYP3A4 and the increased ratio were not observed under the fed condition. This conclusion was confirmed by the 6-ß-hydroxycortisol/cortisol ratio measurement following a multiple dosing of eletriptan in Japanese population. After either 40 mg tid or 80mg bid dosing, the post-dose ratio on Day 7 is similar to the pre-dose ratio on Day 1. Thus, eletriptan does not induce CYP3A4.

III. Biopharmaceutics:

1. Bioequivalence Study:

Because of the dosage change during the phase I and II drug development process and manufacture site change after phase III studies, the sponsor conducted two BE studies to link the important phase I, II and III formulations, namely 20mg of 10%, 80mg of 20% drug load products manufactured at Sandwich, UK and 80 mg manufactured at Brooklyn, US. The to-be-marketed formulations (20, 40 and 80 mg tablets from Brooklyn site) are manufactured from the same blend.

One study was two way crossover study to compare the relative bioavailability of eletriptan from tablets with a 20% drug load with that from tablets with a 10% drug load following either 1x80mg (20% drug load), or 4x20mg (10% drug load) tablets in 24 healthy male subjects. Data indicated that the 10% and 20% drug load formulations were bioequivalent, because 90% confidence intervals of both AUC (89.7-101.6%) and Cmax (81.3-96.1%) were within the acceptable range of 80-125%. However, the point estimate comparison between the two products on Cmax and AUC is 88.4% and 95.5%, indicating a lower rate of absorption from the product with 20% drug loading. Consistently, the average Tmax of the 20% drug loading product is 0.66 hr more than the 10% product. One subject (#20) had 5.5 hr longer Tmax from the 20% product than the 10% product.

The other study was to compare the commercial tablet from the "biobatch" manufactured in Brooklyn (20% of full scale production batch) to that produced in Sandwich (10% and 20% drug load) used in the previous clinical trials upto the date of this study. The study was conducted

with the highest dose strength (80mg), to compare 4 x 20mg tablets (10% drug load; Sandwich manufacture) and 1 x 80mg tablet (20% drug load; Sandwich manufacture) to 1 x 80mg dose (20% drug load; Brooklyn "biobatch") in 36 subjects as 3-way crossover design. The 90% confidence intervals for the AUC and Cmax for the 10% vs. Biobatch comparison are 84-97% and 80-97%, respectively; and for 20% vs. Biobatch comparison are 90-104% and 85-103% respectively.

2. Dissolution:

The sponsor had conducted a dissolution testing in 0.01M HCL, 0.1M HCL, pH 6.5 buffer and SIN, and 0.1M HCL was chosen as the most appropriate medium. The sponsor first tested the USP Apparatus II (paddle) at paddle speeds at 50, 75 and 100 rpm and 100 rpm was chosen for the robust results. Later, USP Apparatus II (basket) was chosen to replace the paddle for consistency results obtained with this method from all the formulations tested. Based on the 6 units per dosage strength tested, the final dissolution methods and specifications were proposed:

Apparatus: Basket Apparatus (USP 1) at 100 rpm
Media: 900 mL Aqueous 0.1 M HCL
Specifications: Q=— at 15 min.

Recommendation:

The general pharmacokinetic characteristics and the biopharmaceutics of eletriptan have been studied by the sponsor, and are acceptable to OCPB. However, the sponsor has not well addressed the drug interaction potentials of eletriptan with other drugs that can inhibit the metabolism of eletriptan, with the exception of the study on eletriptan and erythromycin combination. Metabolism based drug interaction could be an important safety issue, given the magnitude of interaction seen for erythromycin-eletriptan interaction, large number of commonly prescribed drugs that can inhibit eletriptan metabolism, the therapeutic range of eletriptan (20-80 mg) and the adverse effect profile of drug. Thus, further investigations on drug interaction between eletriptan and its metabolism modulators are necessary to ensure the safe use of the drug.

Primary Reviewer: **Rae Yuan, Ph.D** /S/ — 8/5/99

Teamleader: **Chandra Sahajwalla, Ph.D** /S/ 8/5/99

Office of Clinical Pharmacology and Biopharmaceutics.

Cc: HFD-120, HFD-860 (Mehta) and CDR (Biopharm review).

18 page(s) of revised draft labeling has been redacted from this portion of the review.