

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

21-016

MEDICAL REVIEW

DIVISION OF NEUROPHARMACOLOGICAL DRUG PRODUCTS

CLINICAL REVIEW OF NDA

RESPONSE TO APPROVABLE LETTER

Brand Name: Relpax

Generic Name: Eletriptan hydrobromide

Sponsor: Pfizer

Indication: Migraine

NDA Number: 21-016

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1. Executive Summary

1.1 Recommendations

1.1.1 Recommendation on Approvability

The Agency issued an approvable letter for eletriptan on December 1, 2000. In this letter, the Agency requested that the Sponsor document that the increased exposures observed when eletriptan is given in conjunction with CYP3A4 inhibitors do not make the risk of such concomitant use unacceptable (CYP3A4 is the predominating enzyme metabolizing eletriptan). This Agency viewed this issue as critical because even if this concomitant use is contraindicated in labeling, the Agency cannot be confident that such use will not occur. The Agency asked the Sponsor to conduct a placebo-controlled study to assess the potential of eletriptan to constrict coronary arteries at eletriptan concentrations providing exposures comparable to those seen with CYP3A4 inhibition.

This submission is the Sponsor's complete response to the approvable letter. It contains final results from three additional clinical studies (two coronary angiography studies and one comparative efficacy study). The resubmission also contains updated safety data, including a summary of postmarketing experience in countries where eletriptan has been already approved.

Study A160-1072 is the study requested in the approvable letter. Its primary endpoint was the change in coronary artery diameter after administration of eletriptan intravenously, sumatriptan subcutaneously, or placebo. Study A160-1072 can not be regarded as positive for because it lacked assay sensitivity. The imbalance in adverse events of coronary vasoconstriction between patients randomized to eletriptan (33%) and patients randomized to sumatriptan (0%) or to placebo (0%) suggests, but do not prove conclusively, that eletriptan may lead to increased rates of cardiac ischemic events when given jointly with CYP3A4 inhibitors.

The second coronary angiography study, Study 160-309, does not provide any information on the safety of eletriptan when administered jointly with CYP3A4 inhibitors. This study gives only modest reassurance about the possible side effects of eletriptan in the cardiac population. Overall, the coronary angiography studies do not answer the request of the December 1, 2000 approvable letter.

I believe that an excess of risk of cardiovascular adverse events and deaths (compared to existing therapies) should not be tolerated in the treatment of migraine, which is a benign condition for which several other safe and effective drugs of the same class (triptan) are available. Even though the coronary angiography study do not provide the necessary evidence to rule out that excess of risk, the postmarketing experience in foreign countries provides reassurance about the cardiovascular safety of eletriptan up to a total daily dosage of 40mg, without establishing eletriptan safety at the exposure level seen when taken jointly with CYP3A4 inhibitors. Based on this evidence, I recommend to limit the total daily dose of eletriptan to 40mg.

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Eletriptan 20mg, 40mg and 80mg doses were shown effective in the treatment of migraine attack in the original NDA submission (Dr. Oliva's review dated 7/9/99). I recommend approval of eletriptan 20mg and 40mg tablets, with changes in the proposed labeling as described in the labeling review. I recommend non approval of the 80mg dose, because that dose exceeds the total recommended daily dose of 40mg, and because the 80mg dose has a higher incidence of adverse events, without demonstrated superior efficacy over the 40mg dose. Because of the high exposure achieved when eletriptan is given jointly with CYP3A4 inhibitors, and because of the uncertainty about the cardiovascular risk at that exposure level, I recommend the contraindication of eletriptan in patients taking potent CYP3A4 inhibitors.

1.2 Summary of Clinical Findings

1.2.1 Brief Overview of Clinical Program

Eletriptan is a selective 5HT_{1B/1D} agonist proposed for oral administration (tablet). The proposed indication is the acute treatment of migraine with or without aura in adults. The clinical program was described by Dr. Oliva in his review (dated 7/9/99) of the original NDA (submitted 10/27/98). The clinical program at the time of the original NDA consisted of 34 clinical pharmacology studies and 18 phase 2/3 studies. Of the 18 phase 2/3 studies, 2 were intravenous phase 2 studies and the remaining 16 were oral phase 2/3 trials. Three of the 16 oral phase 2/3 studies were long term extensions of other trials.

In the present submission, the Sponsor is providing the detailed results of 3 additional studies (2 coronary angiography studies in which 43 subjects received eletriptan, and a phase 3 comparative study with sumatriptan in which 825 patients received eletriptan, non integrated in the safety database), and safety data out of 5 additional studies in which 1590 subjects were assigned to eletriptan. Overall, a total of 9334 subjects treating 74225 attacks with eletriptan are described in the safety database (with at least 1386 subjects enrolled in more than one study). The Sponsor is also reporting on the postmarketing experience in foreign countries after the sale of eletriptan tablets.

1.2.2 Efficacy

From the data presented in the original NDA, Dr. Oliva (who conducted the original NDA review) concluded the following: (1) Eletriptan 20mg, 40mg, and 80mg are all effective

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treatment for acute migraine, based on the effects on the 2-hour headache response rates, and associated migraine symptoms. (2) The 5mg dose, although numerically superior to placebo in one study, was not shown to be statistically superior. Nonetheless, it is possible that doses lower than 20mg (e.g. 10mg or even 5mg) are effective, but this would require additional studies, with sufficient power, in order to establish this possibility. (3) Treatment with eletriptan was generally associated with decreased incidence of recurrence within 24 hours. (4) Treatment with a second dose of eletriptan for recurrence was generally effective. However, the use of a second dose to treat persistent pain was not shown to be effective.

A pooled efficacy analysis of the data for the first attack from the seven outpatient efficacy studies part of the original NDA shows a robust treatment effect size for the 20mg, 40mg and 80mg dosages. For the primary outcome (2-hour headache response rate), the response rate for placebo, the 20mg dose, the 40mg dose and the 80mg dose were respectively 24.4%, 49.5%, 60.2% and 65.8%. I did not re-evaluate eletriptan efficacy, since it was clearly established in the original NDA review. I refer the reader to Dr. Oliva's review (dated 7/9/99) for further details.

In the review (dated 11/1/00) of the first response to approvable letter (submitted 6/1/00), Dr. Oliva reviewed in greater detail the safety and efficacy of the 80mg eletriptan dose. Dr. Oliva observed that in the only study specifically designed to demonstrate a benefit of the 80mg over the 40mg dose, the primary outcome was negative, and concluded that other studies do not establish an efficacy benefit of the 80mg dose. I refer the reader to the review of the approvable letter (11/1/00) for further details on the 80mg dose review.

The only efficacy study part of the present submission was study A160-1048. This was a large multi-center trial showing incomplete evidence for the superiority of eletriptan 40mg over sumatriptan 100mg. In the original NDA review, Dr. Oliva noted that in the two studies that used sumatriptan and excluded sumatriptan non-responders, eletriptan 40mg appeared to beat sumatriptan 50mg and 100mg in one study but failed to beat sumatriptan 25mg and 50mg in the other study. Eletriptan 80mg beat sumatriptan 25mg and 50mg in one study and beat sumatriptan 50mg and 100mg in another study.

1.2.3 Safety

Eletriptan safety was reviewed by Dr. Oliva in the original NDA review (dated 7/9/99), and in the review of the first response to approvable letter (dated 11/1/00). I refer the reader to these reviews for full details. Overall, a total of 9334 subjects treating 74225 attacks with eletriptan are described in the safety database (with at least 1386 subjects enrolled in more than one study). The number of subject exposed and duration (including long term studies) was already adequate prior to this submission. The Sponsor is also reporting on the postmarketing experience in foreign countries after the sale of eletriptan tablets.

The main issue in this response to approvable letter was the cardiovascular safety of eletriptan when taken jointly with CYP3A4 inhibitors. Dr. Oliva commented in his 11/1/00 review on a small earlier coronarography study with eletriptan conducted by the Sponsor (Study 211). This study had several limitations. The main one was the low eletriptan exposure, lower than that

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achieved with the 80mg dose. Dr. Oliva concluded that the in vivo effect of eletriptan on coronary arteries relative to other triptans remained largely unknown, particularly at eletriptan exposures achieved when a 40mg or 80mg dose is given in association with verapamil or another more potent CYP3A4 inhibitor. He also concluded that despite the cerebroselectivity claims put forth in two expert reports provided by the Sponsor, the degree of maximum coronary vasoconstriction seen with the naratriptan and eletriptan doses studied in vivo are, at best, similar. These studies lacked a placebo arm, which limited the interpretation of the data. Dr. Oliva also reviewed prior coronarography studies with sumatriptan, that showed a greater degree of vasoconstriction than seen in Study 211, but that were performed in subjects with more severe underlying coronary artery disease (and with sumatriptan exposures higher than would be expected using the 6mg sumatriptan dose).

In light of these observations, which raised concerns regarding the risk of eletriptan to the myocardium, Dr. Oliva suggested to design and conduct another (placebo-controlled) coronary angiography study that uses higher exposures to eletriptan, and also includes a positive control. Dr. Oliva requested that the subjects studied should be those with suspected coronary artery disease who have been selected for diagnostic coronary angiography, but who are then found to have normal coronary arteries in the catheterization lab. This request was addressed in study 1072, a coronarography study in subjects with "normal" coronary arteries. This Study was developed in collaboration with the Agency. The Sponsor also conducted an additional self-initiated study (Study 309), in which subjects with single vessel disease were evaluated. In addition, the Sponsor provided a safety update, and a summary of post-marketing experience.

The two new coronarography studies have not provided convincing evidence supporting the cardiovascular safety of eletriptan when given with CYP3A4 inhibitors.

In study 1072, only eleven subjects reached the eletriptan concentration level expected when patients take a single 80mg tablet jointly with a potent CYP3A4 inhibitor (564 ng/ml). In addition, there was a relatively strong time trend in coronary artery diameters even in the placebo group (diameter reduction over time), and the study failed to show a drug effect for the active comparator (sumatriptan). Overall, the study can not be regarded as positive for the primary endpoint of change in coronary artery diameter because it lacked assay sensitivity. The lack of statistically significant difference in the primary endpoint among eletriptan, sumatriptan, and placebo is not informative.

Coronary vasoconstriction was reported only in the eletriptan group (33%), and the imbalance in vasoconstriction adverse events between eletriptan and both sumatriptan and placebo is striking and worrisome. In most cases of vasoconstriction, there was a severe discordance between quantitative coronary assessments by a blinded laboratory and investigator descriptions of the timeline of the vasoconstrictive events (in case report forms). Two of the vasoconstriction events are concerning: one event was accompanied by ECG changes, and another event in a subject with a myocardial bridge led to the only adverse dropout from the study. There was no clear association between eletriptan plasma levels and the adverse events of vasoconstriction. The vasoconstrictive adverse events occurring only in subjects randomized to eletriptan are a cause

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for concern. They suggest, but do not prove conclusively, that eletriptan may lead to increased rates of cardiac ischemic events.

Study 309 does not provide any new information on the safety of eletriptan when administered jointly with CYP3A4 inhibitors. Study 309 did not show any evidence of major coronary vasoconstriction with eletriptan at blood level equivalent to those seen after a 80mg dose, or with sumatriptan. This study gives a modest reassurance about the possible side effects of eletriptan in the cardiac population, but has several limitations, including the small population, the limited eletriptan exposure (compared to that achieved when eletriptan is taken jointly with CYP3A4 inhibitors), and the absence of central reading of angiograms.

The safety update does not add any new significant finding. Study 160-1048, a large multicenter, double-blind, placebo-controlled parallel group study showed a similar incidence of chest and cardiac symptoms in patients treated with eletriptan 40 mg and in patients treated with sumatriptan 100 mg.

Pharmacovigilance data show no cardiovascular serious adverse event (SAE) after the sale of _____ eletriptan tablets. There was one spontaneous SAE report described as an anaphylactic reaction to eletriptan. There was also a massive MI-leading to death reported (not part of this submission), in a patient who took one tablet of eletriptan 40mg and possibly up to two tablets of sumatriptan 50mg. Even though both triptans should not have been taken in the same 24-hour interval, their individual dosages remain well within the allowed maximum daily dosage. Overall, the post-marketing experience provides some reassurance about eletriptan cardiovascular safety. However, maximum recommended daily dosage varied between 40mg, 80mg or 160 mg across countries, with no breakdown provided by the Sponsor, so that this postmarketing experience provides information only supporting a maximum daily dosage of 40mg.

Since the risk associated with the drug-drug interaction with CYP3A4 inhibitors remains a concern, I recommend a contraindication of eletriptan with potent CYP3A4 inhibitors, including verapamil. There are several other triptans available in the United States for patients receiving CYP3A4 inhibitors.

1.2.4 Dosing

The 20mg, 40mg and 80mg doses were shown effective in the treatment of migraine attack. An additional benefit of the 80mg dose over the 40mg dose has not been established. In addition, there was a double incidence of chest pain with the 80mg dose as compared to the 40mg dose across single attack data. The pooled efficacy analysis (for the first attack) from the seven outpatient efficacy studies part of the original NDA suggested that the 20mg is effective. The 20mg dose was also associated with the lowest incidence of side effects. In the two studies where the 20mg was compared to the 40mg dose, the recurrence rate was numerically lower for the 20mg dose than for the 40mg dose.

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Since coronarography studies did not resolve the issue of the safety of the 40mg and of the 80mg dose when taken jointly with CYP3A4 inhibitors, and since postmarketing data did not offer useful information for total daily dosages over 40mg, I recommend a starting dose of 20mg, and a maximum daily dosage of 40mg. I recommend non-approval of the 80mg tablet, since it offers no clear benefit over the 40mg tablet, and since it was associated with more side effects, and has a greater potential to reach toxic levels when taken jointly with CYP3A4 inhibitors.

A second dose (40 or 80mg) was effective in the treatment of a headache recurrence. The efficacy of a second dose to treat persistent pain was not demonstrated. The 20mg dose was not examined for treatment of persistent or recurrent pain. If the migraine headache recurs within 24 hours of an initial response, I recommend that a second 20mg dose can be taken after 2 hours. A second dose has been shown to be effective in treating the recurrence for the 40mg dose, but it has not been specifically studied for the 20mg dose. There is however no safety concern in allowing that second dose. If a patient does not achieve a headache response to the first dose of eletriptan within 2 hours, a second dose should not be taken for the same attack as clinical trials that have examined that situation have not adequately established efficacy with the second dose.

In terms of dose escalation, the Sponsor only specifically examined the scenario where patients failed to respond to 40mg and received were randomized to received 80mg, 40mg or placebo at the second attack. The 80mg dose was numerically superior to the 40mg dose or placebo, but the difference failed to reach statistical significance.

Patients who do not obtain satisfactory efficacy after an appropriate trial of the starting dose (20 mg), may be effectively treated with 40 mg in subsequent migraine attacks (this situation has not been evaluated by the Sponsor).

The minimal effective dose was not established, and it is possible that doses lower than 20mg (e.g. 10mg or even 5mg) are effective.

1.2.5 Special Populations

Special populations were reviewed by Dr. Oliva in the original NDA review, and no new information was provided in the present submission. The following comments originate from Dr. Oliva's NDA review.

The response rates were generally consistent group by group between genders. There was neither a statistically significant treatment by gender interaction nor a statistically significant gender effect.

Among the adult population, there was a statistically significant treatment by age interaction, likely due to the high placebo response rate in the elderly.

There was no statistically significant race effect and no statistically significant treatment by race interaction among the four race groups analyzed (white, black, asian, other).

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Two small single dose PK studies looked at subjects with chronic stable cirrhosis and subjects with varying degrees of renal impairment. There was one case of severe hypertension in a subject with hepatic cirrhosis who received eletriptan 80mg.

A study enrolled adolescent migraineurs between the ages of 12-17. It compared 40mg to placebo in the treatment of an acute migraine. The response rates for 40mg at two hours were similar to that seen in the adult studies (57.2%); however the placebo response rates were very high (57.4%) and there appeared to be no benefit of the 40mg dose over placebo in this study population. The pediatric program can not be considered as complete. A full scale efficacy and safety study in pediatrics would be required if Pfizer wants pediatric labeling for eletriptan. The Division agreed to consider a Written Request for a Relpax Pediatric Study.

Since the migraine population is predominantly composed of females of reproductive age, it can be expected that the drug will be used in pregnant woman. There were 11 pregnancies in eletriptan treated women. Eight pregnancies have resulted in six normal births, and the remaining two were progressing normally at the time of the original NDA review. Three other pregnancies were not carried to term: two were miscarriages (one diagnosed with Turner's syndrome). The third pregnancy was aborted at the request of the patient. She later became pregnant again, with a normal pregnancy.

Eletriptan is excreted in human milk, but in extremely low quantities. The mean total amount of eletriptan excreted in breast milk over 24 hours was only 0.02% of an 80mg oral dose.

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2. *Clinical Review*

2.1 Introduction and Background

The Agency issued an approvable letter for eletriptan on 12/01/00. This submission represents the Sponsor's complete response to the approvable letter. It contains final results from three additional clinical studies (two coronary angiography studies and one comparative efficacy study with sumatriptan). The resubmission also contains updated safety data.

In the approvable letter, the Agency requested 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 (coronary angiography study part of the original NDA) and that are comparable to the exposure seen with CYP3A4 inhibition. Several active controls of available triptans were requested.

The Agency also requested that the Sponsor provides a safety update.

Study A1601072 (referred as Study 1072) is the study requested in the approvable letter. The subjects recruited into Study 1072 were subjects undergoing diagnostic coronary angiography for suspected cardiovascular disease, but who were found to have less than 20% arterial stenosis. Subjects were treated with a 40 minute intravenous (iv) infusion of eletriptan to very high plasma concentrations (24 subjects), a therapeutic dose of sumatriptan 6mg (18 subjects) subcutaneously (sc), or appropriate placebo (18 subjects).

In addition, the Sponsor conducted study 160-039 to investigate the potential effect of iv eletriptan on coronary artery diameter in subjects undergoing percutaneous transluminal coronary angioplasty for severe single vessel disease. Subjects were required to have angina pectoris and/or documented ischemia and, on the day of the procedure, to have >50% stenosis of the coronary arteries. Subjects were treated with a 15 minute iv infusion of 6mg eletriptan (19 subjects), sumatriptan 6mg sc (17 subjects), or appropriate placebo (10 subjects).

The Sponsor also submitted the complete results of study A160-1048, A Multicenter, Double-Blind, Randomized, Placebo-Controlled Parallel Group Comparative Study of the Efficacy and Safety of Oral Eletriptan (40mg) and Sumatriptan (100mg) Given for the Acute Treatment of Migraine. The Sponsor did not discuss that study in the summary, nor did he use it to support any labeling change.

2.1.1 Drug Established and Proposed Trade Name, Drug Class, Sponsor's Proposed Indication(s), Dose, Regimens, Age Groups

Eletriptan hydrochloride (Trade name Relpax) is a selective 5-hydroxytryptamine 1B/1D/1F agonist proposed for the treatment of acute migraine attack. Eletriptan belongs to the triptan drug class. The Sponsor proposes a starting dose of 40mg, to be adjusted on an individual

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basis up to a maximum daily dose of 160mg. The drug has been mostly evaluated in the adult population (age 18-65), and safety and effectiveness in pediatric subjects have not been established. In addition, only about 50 subjects over the age of 65 were exposed to the drug.

2.1.2 State of Armamentarium for Indication(s)

5-HT_{1B/1D} agonists (triptans) are at present amongst the most effective agents available for acute treatment of migraine attacks. Six triptans are currently approved in the United States: sumatriptan, eletriptan, zolmitriptan, almotriptan, naratriptan and frovatriptan. Each triptan has a different pharmacokinetic and clinical profile. As of prior to this submission, no triptan has been clearly established as superior to the others. Instead, practitioners usually choose the triptan based on personal preferences and patient response. Migraine specialists report that is not unusual in individual subjects to have a clinical response with one triptan and no response with another. Additional migraine attack therapy options include ergotamine derivatives, phenothiazines, non steroidal anti-inflammatory agents and opioids. Preventive medication therapy is indicated for subjects experiencing frequent and/or refractory attacks.

2.1.3 Important Milestones in Product Development

I summarized the administrative history from the NDA submissions, Dr. Oliva prior reviews of NDA 21-016, and various review documents filed in DFS. IND ~~_____~~ for oral eletriptan was submitted on 12/8/94. The end of phase 2 (EOP2) meeting was held on 5/20/96. The Division recommended that the eletriptan NDA contain 2 efficacy studies and one long term safety study. The Division considered the design and power of Study 314 sufficient to qualify this study as potentially pivotal. Study 314 and possibly Study 302 would provide sufficient data for the minimum effective eletriptan dose of 20mg. The 40 and 80mg doses were acceptable for use in the Phase 3 program. The Division anticipated that eletriptan would have the same cardiovascular safety labeling as sumatriptan. Long term treatment, in accordance with ICH guidelines, requires the treatment of 300 subjects for 6 months and 100 subjects (with the 80mg dose) for 1 year. The Division recommended that subjects treat a minimum of two headaches per month, although this could be negotiable.

The Division accepted the study design, statistical methodology and safety analysis proposed to support the claims for treatment of acute migraine, treatment of non-responders, and treatment of migraine recurrence. It was agreed that a step-down procedure for comparing treatment groups would be performed in the statistical evaluation of the primary efficacy endpoint (2 hour response rate) for studies involving several eletriptan dosage groups. It was also agreed that a prospectively defined meta-analysis would be acceptable in the evaluation of the ability of a second dose to treat non-responders and recurrence during each treated migraine attack across the clinical program (subsequently Pfizer decided to prospectively include Studies 102, 104, 305, 307 and 318 in the meta-analysis).

At Pfizer's request, a conference call was held with the FDA on 8/22/96 to discuss the FDA's 8/12/96 EOP2 follow-up correspondence. During this conference call, the Agency confirmed that Studies 314 and 102 (for which the protocol had recently been submitted) would provide

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adequate data on the 20mg eletriptan dose. The Division clarified that we did not consider migraine to be the same disease in pediatrics and adults and therefore, a full scale efficacy and safety study in pediatrics would be required if Pfizer wanted pediatric labeling for eletriptan.

At the FDA's request, a teleconference was held on 4/18/97 to discuss a treatment sequence alteration which the Division thought could potentially enhance the dosing and administration information generated from Study 103, a study designed to explore the efficacy, safety and toleration of the administration of an eletriptan 80mg dose in subjects who did not achieve a pain free response to 40mg eletriptan by 2 hours. The Division suggested that replacement of one of the two placebo arms in Dose 1 of Attack 1 with a 40mg eletriptan dose might serve to further enhance the quality of the information generated from this study by enabling Pfizer to best characterize a subject's response to a second dose. Pfizer informed the FDA that subject dosing had already been initiated in 3/97. This teleconference also served as an opportunity to address the FDA faxes of 3/24/97 and 4/1/97 concerning the eletriptan meta-analysis protocol and the eletriptan pediatric Protocol 160-105. The FDA further clarified the prognostic factors which should be included in the eletriptan meta-analysis and reconfirmed that six month safety data in 300 adolescent subjects was a suggestion and not a filing requirement for the 3Q98 eletriptan NDA.

On 1 21/98, the eletriptan pre-NDA meeting was held to discuss specific labeling, clinical, statistical and pharmacological issues essential in the preparation and submission of a cohesive eletriptan NDA. Consensus was reached with the Division on the presentation of efficacy and safety data; the adequacy of the eletriptan human hepatocyte induction study results in negating the need for a drug interaction study of eletriptan with oral contraceptives; the format of the clinical and statistical components of the eletriptan electronic submission, and format and content issues concerning the NDA and the NDA Safety Update. Discussions with the Division indicate that the eletriptan NDA filing would receive a Standard Review by the Agency.

The original NDA was received by the Agency on 10/27/98. The Agency issued an approvable letter for eletriptan on 10/27/99. FDA requested that the Sponsor document that the increased exposure that result when eletriptan is given in conjunction with CYP3A4 inhibitors does not make the risk of such concomitant use unacceptable. This was seen as critical by FDA, because even though this concomitant use was to be contraindicated in labeling, FDA could not be confident that such a use will not occur.

The Sponsor submitted a complete response in a 06/01/00 submission. It contained final results from four additional clinical studies (an interaction study with ketoconazole and three long-term safety studies). By mutual agreement, the Sponsor conducted a fifth study – a verapamil interaction study and the complete study report was submitted separately during the review period. It was also agreed in a teleconference on 4/26/00 that the Sponsor would conduct a drug-drug interaction study with verapamil, a moderate CYP3A4 inhibitor and a drug that is not uncommonly prescribed in this population.

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This submission led to a second approvable letter (12/1/2000). The Agency believed that the information submitted failed to establish that the risk of concomitant CYP3A4 inhibitors was acceptable, particularly since eletriptan did not appear to offer any additional therapeutic benefit over currently approved triptans. The Agency also noted that concomitant use of eletriptan with verapamil in migraine subjects results in substantial increases in eletriptan exposure, which is higher than the exposures evaluated in the coronary angiography study (Study 211). Study 211 suggested that even those plasma levels might be associated with clinically meaningful coronary vasoconstriction. The Agency remained concerned about the potential effects of eletriptan on the coronary arteries, particularly at exposures achieved during CYP3A4 inhibition, but also at exposures associated with 40mg and 80mg single dose without metabolic inhibition. The Agency requested the Sponsor to conduct a placebo-controlled study designed to assess the potential of eletriptan to constrict coronary arteries at eletriptan concentration that are higher than those achieved in Study 211 and that are comparable to exposures seen with CYP3 inhibition.

A meeting was held on 05/29/02 to discuss the results of the requested coronary angiography study, Study A1601072. The Agency inquired the Sponsor about the eight eletriptan subjects in Study 1072 with subjective observations of vasoconstriction. Dr. Goldstein, the principal investigator for Study 1072, explained that he was not aware of any significant vasoconstriction being reported during his attendance and was surprised to see them in the study database. He emphasized that there was no relationship between the quantitative coronary angiography and the subjective observations on these 8 subjects. He concluded that the disparity of these eight subjects compared to the others in the study emphasizes the limitations of subjectively assessing mild change in the coronary arteries in comparison to QCA. There was some discussion about the interpretation of data from study 1072. The Division agreed to consider if CYP3A4 inhibitors warrant a contraindication in the RELPAX label, or would simply be described somewhere in the label. The Division noted that an Advisory Committee Meeting to review the results of Study 1072 was not planned. The Division agreed to consider a Written Request for a RELPAX Pediatric Study. The Division also agreed on a format for the NDA supplement.

2.1.4 Other Relevant Information

Eletriptan has been approved for the migraine indication in 46 countries worldwide to date of the present submission. These include 17 countries in the European Union (EU), 7 Central American Countries, Australia, Israel, Singapore, Japan, South Africa, Switzerland, Hong Kong, Hungary, and Indonesia.

2.1.5 Important Issues with Pharmacologically Related Agents

Eletriptan is pharmacologically similar to sumatriptan. Because of the potential for 5-HT_{1D/1B} agonists to cause coronary vasospasm, they should not be used in subjects with coronary artery disease (CAD) or in subjects in whom unrecognized CAD is likely without a prior evaluation.

2.2 Clinically Relevant Findings From Chemistry, Animal Pharmacology and Toxicology, Microbiology, Biopharmaceutics, Statistics and/or Other Consultant Reviews

The chemistry, animal pharmacology, microbiology and biopharmaceutics sections originate from the original NDA review from Dr Oliva (7/9/99). The statistics section is a review of the 2 new coronary angiography study reports part of this submission.

2.2.1 Chemistry

Eletriptan is a white to pale colored powder which is readily soluble in water. The oral tablets contain 20, 40, or 80mg of eletriptan.

Generic Name: eletriptan hydrobromide

Trade Name: Relpax

Chemical Name: (R)-3-(1-methyl-2-pyrrolidinylmethyl)-5-[2-(phenylsulfonyl)ethyl]-1H-indole hydrobromide

Alternative Name: UK-116,044

Molecular Formula: C₂₂H₂₆N₂O₂S₂ HBr

Molecular Weight: 463.43

Eletriptan tablets stored for up to 12 months show good stability over the wide range of packaging alternatives and conditions evaluated.

2.2.2 Pharmacology

Eletriptan is a 5HT_{1B/1D} receptor agonist. It also has high affinity for 5HT_{1F} receptors. It is positive in both the carotid blood flow and the dural plasma protein extravasation animal migraine models.

2.2.3 Toxicology

In single dose toxicology studies, 1000 mg/kg was lethal in rats and mice. Clinical signs included convulsions, dyspnea, increased activity and tremors, salivation, mydriasis, tremors, and reduced body temperatures. There were no clinical signs nor mortality at 100 mg/kg in both species.

Repeated dose studies in rats and mice produced clinical signs similar to those seen in the single dose studies. Isolated deaths were seen above 200 mg/kg. From 25 mg/kg, increased liver weight with centrilobular hypertrophy was seen. Thyroid follicular hypertrophy was seen from 5 mg/kg upward.

Eletriptan did not cause mortality in dogs. Typical signs were hindlimb incoordination, hyperthermia, and barking. Transient corneal opacities were observed during the first days of studies lasting up to 1 month but not in the 6 and 12 month studies. Dose related increased systolic BP was seen. A minimal to mild myocardial fibrosis was diagnosed histologically in two dogs at 5 mg/kg after 1 month and in 1 dog at 7.5 mg/kg after 2 weeks, but was not observed in the 6- and 12-month studies.

Analysis of ECGs showed inversion of negative T-waves to a more normal positive morphology in a number of studies including the 6-month study, where control dogs were also affected. In the 12-month study only increase in the height of the T-wave was recorded. There was no prolongation of the QT-segment in the ECG. In the 6- and 12-month studies dosing was reduced to ½ during the first week and, thus the severity of clinical signs and heart rate/blood pressure changes was significantly diminished.

In the 6-month study, 1/8 dogs each at 2.5 and 5 mg/kg had chronic peptic stomach ulcers. This was felt to be the result of high local concentrations of eletriptan released from the experimental capsule formulation of dry powder. No mucosal changes were seen in the subsequent 12-month study when the tablet (clinical) formulation was used.

In reproduction studies, no effects on fertility and no teratogenic effects were observed despite evidence of maternal toxicity. Pre- and postnatal development of the offspring was not affected.

Eletriptan was subjected to a complete battery of mutagenicity tests in which no genotoxic or clastogenic potential was detected. Eletriptan was not carcinogenic in rats and mice.

2.2.4 Biopharmaceutics

A single oral dose of eletriptan is rapidly and well absorbed across the gastrointestinal tract (approximately 81%). The mean Tmax is independent of dose and occurs approximately 1.5h (1.3-2.1h). The absolute oral bioavailability of eletriptan across both males and females is approximately 50%. The pharmacokinetics of eletriptan is approximately linear between 20-80mg. Mean T1/2 is approximately 4h (range: 3.6 - 3.8h) over the 20 to 80mg clinical dose range.

The plasma protein binding of eletriptan is moderate (83 to 88%) and unaffected by hepatic impairment or renal impairment. Multiple dose regimens of oral eletriptan result in steady state levels of eletriptan within 2 to 4 days. In healthy male subjects, accumulation of both Cmax and AUC8 following multiple dose eletriptan (20mg every 8 hours for 7 days) is as predicted based on the dosing interval and single dose pharmacokinetics. Mean Tmax, Kel and T1/2 are similar to values obtained in single oral dose studies.

The rate and extent of absorption of eletriptan is decreased during a migraine attack. During a migraine attack, the AUC8 and Cmax were reduced by approximately 30% and the mean Tmax was increased from 1.5 to 2.8h.

There are no clinically important differences in the pharmacokinetics of eletriptan between the elderly (65 to 93 years old) and the young adult. The only finding was a statistically significant difference in Kel, resulting in an increased eletriptan T1/2 of 5.7h in the elderly compared to 4.4h in the young adult. Blood pressure increases associated with eletriptan may be greater in the elderly.

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A meta-analysis of AUC, C_{max} and T_{max} across six oral studies and a Population Pharmacokinetic analysis indicates that there are no significant gender differences in the pharmacokinetics of oral eletriptan.

First-pass metabolism of eletriptan is apparent in the difference between an oral absorption ratio and observed oral bioavailability. For both oral and intravenous administration of [¹⁴C]-eletriptan, the plasma AUC is higher and the T_{1/2} is longer for total radioactivity compared to eletriptan, indicating the presence of circulating metabolites. Four major circulating radioactive components were identified in plasma after oral dosing; eletriptan (30% of total radioactivity), the pyrrolidine N-oxide UK-234,435 (23%), the N-desmethyl metabolite UK-135,800 (7%), and what appears to be a mixture of hydroxylated metabolites accounting for 35% of the radioactivity.

The N-desmethyl metabolite UK-135,800 has activity similar to eletriptan in vitro, but its exposure is only at maximum 17% of the eletriptan exposure, with its levels not exceeding parent drug levels. After single intravenous and oral doses of [¹⁴C]-eletriptan, 44 to 55% of the total radioactivity was excreted in the urine, mainly up to 24 hours post-dose, and 30 to 45% was excreted in the feces, mainly 24 to 48 hours post-dose. The mean total recovery of radioactivity in urine and feces was 85% to 89% over the 9 days post-dosing. Metabolite profiles in the excreta were qualitatively similar following both routes of administration.

Eletriptan metabolism was investigated in vitro using human liver microsomes, primary human hepatocyte cultures, and cell lines expressing specific cytochrome P450 isozymes. CYP3A4 is the predominate enzyme metabolizing eletriptan; CYP2D6 is a minor pathway. Eletriptan metabolism is reduced slightly by quinidine, a selective inhibitor of CYP2D6. Eletriptan does not inhibit CYP1A2, CYP2C9, CYP2E1 or CYP3A4 at concentrations up to 100 μM (38 μg/ml), but does inhibit CYP2D6 activity with an approximate IC₅₀ of 41 μM. Eletriptan concentrations up to 100 μM do not induce CYP1A2, CYP2C9, CYP2C19, CYP2D6 or CYP2E1. Eletriptan moderately induces CYP3A4 in primary human hepatocytes at concentrations greater than 5 μM, but induction of CYP3A4 in vivo is unlikely since C_{max} following oral eletriptan 80mg is approximately 0.5 μM (191ng/ml), and chronic use is not indicated.

Eletriptan is not a substrate for monoamine oxidase. Eletriptan is primarily eliminated via hepatic cytochrome P450 metabolism, with CYP3A4 as the primary metabolic path. Single oral doses of eletriptan 80mg and multiple doses up to 160mg a day for 7 days appear to have little to no influence on the metabolic activity of CYP3A4 in vivo.

Exposure to eletriptan is increased (34% for AUC) in subjects with mild or moderate hepatic impairment but this does not result in a greater blood pressure response. Eletriptan has not been investigated in subjects with severe hepatic impairment.

The renal elimination of eletriptan is low, with an average 9.3% of an intravenous dose eliminated unchanged in urine during the first 24 hours post-dose. Mean CLR of eletriptan ranges from 64 to 80ml/min (3.8 to 4.8L/h) over the clinical dose range. Multiple daily doses

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of eletriptan up to 160mg a day for 7 days have no significant effect on eletriptan CLR. The pharmacokinetics of eletriptan are similar between normal subjects and subjects with mild, moderate or severe renal disease. Increases in blood pressure associated with eletriptan treatment are greater in renally impaired subjects compared to normal subjects.

Eletriptan is excreted into human breast milk. The mean total amount of eletriptan excreted into breast milk over 24 hours was only 0.02% of an 80mg oral dose. Exposure to orally administered eletriptan, as measured by AUC and C_{max}, is increased in the presence of food by approximately 20 to 30%. Food has no significant effect on T_{max} or T_{1/2} for eletriptan. Although food increases eletriptan exposure, this finding is not considered clinically relevant as it is unlikely that migraine subjects would be consuming food immediately prior to treatment.

Cafergot has an additive effect on increasing blood pressure when given one or two hours following eletriptan. The transient increases in blood pressure seen with both drugs are predictable.

Propranolol, a weak inhibitor of cytochrome P-450 metabolism used in the prophylactic treatment of migraine, appears to inhibit eletriptan metabolism. A statistically significant increase in eletriptan AUC (by 33%) and decrease in kel (by 7%) is observed in the presence of propranolol. While exposure to eletriptan increased, propranolol attenuated the pharmacodynamic effects of eletriptan, producing a smaller effect on SBP, DBP and PR changes than observed with placebo. Thus, the coadministration of eletriptan with propranolol does not appear to have a clinically relevant effect.

Erythromycin, a potent CYP3A4 inhibitor, has a clinically relevant effect on the pharmacokinetics and pharmacodynamics of eletriptan consistent with inhibition of eletriptan metabolism. Systemic exposure to eletriptan 80mg was significantly increased when coadministered with erythromycin (2-fold increase in C_{max} and 4-fold increase in AUC), and kel was significantly reduced resulting in a 2.5h increase in T_{max}. The transient elevations in blood pressure associated with eletriptan are more pronounced in the presence of erythromycin than in the presence of placebo.

In subjects undergoing diagnostic coronary arteriography, an intravenous infusion of eletriptan (50µg/kg) was generally associated with a slight decrease in coronary artery diameter from baseline (no greater than a mean change of -3.0% of baseline), which was not considered to be clinically important. However, one subject experienced a 65% reduction in coronary artery diameter.

Eletriptan is associated with small, transient, dose-related increases in blood pressure (primarily DBP), consistent with its mechanism of action and with other 5-HT_{1B/1D} agonists. The mean maximum increases in blood pressure are typically in the range of 5 to 15mmHg after single oral doses of eletriptan up to 160mg. The changes in blood pressure are not associated with any ECG changes or specific adverse events and are not altered by multiple daily dosing. There are no differences between males and females in the blood

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pressure effects of eletriptan. A linear PK/PD relationship has been demonstrated between eletriptan plasma concentrations and blood pressure changes. This model predicts that the average peak plasma levels will have to be increased by at least 25% following a single oral dose of 80mg before potentially clinically relevant blood pressure increases (>10% increase from baseline in DBP) are observed in healthy subjects.

Ophthalmologic slit-lamp corneal examinations indicate no clear evidence of a relationship between eletriptan treatment and the appearance of transient, minor corneal abnormalities. Additionally, there is no evidence of eletriptan affecting thyroid activity or cognitive function following multiple dose oral eletriptan (20 or 30mg) for up to 7 days

2.2.4.1 Pharmacodynamics

This NDA amendment contained two studies evaluating the pharmacodynamic effect of eletriptan on coronary arteries in human subjects. They are reviewed in section 2.6.3.5.1.

2.2.5 Statistics

I refer the reader to the separate statistics review document.

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2.3 Description of Clinical Data and Sources

2.3.1 Overall Data

This submission contains 3 clinical studies:

- Study A1601072 (requested in the approvable letter), in subjects undergoing diagnostic coronary angiography for suspected cardiovascular disease, but who were found to have less than 20% arterial stenosis. Subjects were treated with a 40 minute intravenous (iv) infusion of eletriptan to very high plasma concentrations, sumatriptan 6mg subcutaneously (sc), or placebo .
- Study 160-039 (Sponsor-initiated), to investigate the potential effect of iv eletriptan on coronary artery diameter in subjects undergoing percutaneous transluminal coronary angioplasty for severe single vessel disease (>50% stenosis of the coronary arteries). Subjects were treated with a 15 minute iv infusion of 6mg eletriptan, sumatriptan 6mg sc, or placebo.
- Study A160-1048, a comparative efficacy and safety study of eletriptan 40mg and sumatriptan 100mg for the acute treatment of migraine.

The submission also contains:

- Epidemiology studies and a review of the literature conducted by the Sponsor in an attempt to support the absence of an increased risk of acute myocardial infarction (MI), non-MI ischemic heart disease, unstable angina, ventricular arrhythmia, stroke, all-cause mortality or cardiovascular mortality in migraineurs using triptans.
- Updated safety data in 9334 subjects exposed to eletriptan in Phase 2/3 studies. COMMENT: subjects participating in both short-term and long-term studies were counted twice.

2.3.2 Tables Listing the Clinical Trials

The original NDA review of Dr. Oliva lists the original clinical development program which consisted of 34 clinical pharmacology studies and 18 phase 2/3 studies. In addition, the final data from the three long-term studies (1544 subjects received eletriptan) were part of the response to approvable letter of June 1, 2000. Phase 2/3 studies initiated since original filing and completed by the cutoff date of October 31, 2001 include study 160-1001, 160-1002, 160-1006, 160-1007, and 160-1027. In this submission, the Sponsor is providing detailed data on three studies (Table 1).

Table 1: Studies part of this submission

Study	Description	Total number of subjects
1072	Coronary angiography study in subjects with <20% artery stenosis, comparing eletriptan high dose, sumatriptan and placebo	60
309	Coronary angiography study in subjects with >50% stenosis of a single vessel, comparing eletriptan, sumatriptan and placebo	46
1048	Comparative efficacy and safety study of eletriptan 40mg and sumatriptan 100mg for the acute treatment of migraine	2421

2.3.3 Postmarketing Experience

At the time of this submission, Relpax was approved in 46 countries, including 17 countries in the European Union (EU) through the Mutual Recognition Procedure. In addition, Relpax is approved in 7 Central American countries, Australia, Israel, Singapore, Japan, South Africa, Switzerland, Hong Kong, Hungary, Indonesia, and other countries unlisted by the Sponsor. Post-marketing safety data cover the sale of over _____ eletriptan tablets.

2.3.4 Literature Review

The Sponsor reviewed two epidemiologic studies conducted using the General Practice Research Database (GPRD) in the United Kingdom and the United HealthCare Research Database in the United States to better understand the risk of cardiovascular and cerebrovascular morbidities and mortality of migraine subjects associated with triptan use. Data from both studies suggest that the use of triptans is not associated with increase risk of acute myocardial infarction (MI), non-MI ischemic heart disease (IHD) or unstable angina, ventricular arrhythmia, stroke/transient ischemic attack (TIA), all-cause mortality or cardiovascular mortality. In the GPRD study, triptans were less likely to be prescribed to those with cardiovascular risk factors, such as a history of hypertension, diabetes, heart disease and obesity. After adjusting for cardiovascular risk factors, a statistically significant increased risk of stroke and non-MI IHD was observed in all migraine subjects and non-users of triptans, but not in triptan users per se. In the United Healthcare study, migraine subjects had an increased risk for stroke, TIA, and unstable angina. However, the elevated risk does not appear to be associated with triptan use.

2.4 Clinical Review Methods

2.4.1 Overview of Materials Consulted in Review

The NDA was submitted entirely in electronic format and placed in the EDR (\\Cdsub1\21016). The main submission was contained in:

\\Cdsub1\21016\N_000\2002-06-27.

Additional submissions included:

- \\Cdsub1\21016\N_000\2002-07-15 (update on Study 309)
- \\Cdsub1\21016\N_000\2002-09-27 (4 months safety update).

In addition, I requested additional information from the Sponsor, which is located at:

- \\Cdsub1\21016\N_000\2002-10-29
- \\Cdsub1\21016\N_000\2002-10-30

I used these electronic files for my review. I used the NDA summary, individual study reports, patient profiles, case report forms, and datasets from clinical studies.

2.4.2 Overview of Methods Used to Evaluate Data Quality and Integrity

I performed my own statistical analyses of some of the datasets provided by the Sponsor for study 1072, study 309, and study 1048 (see 2.6.3.5.1.3, 2.6.3.5.3.4 and 2.5.3.1.2). I also requested the source documents for subjects who had a vasoconstriction adverse event in study 1072. There was no DSI inspection on the study sites.

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2.4.3 Was Trials Conducted in Accordance with Accepted Ethical Standards?

Trials were conducted in accordance with accepted ethical standards.

2.4.4 Evaluation of Financial Disclosure

2.5 Integrated Review of Efficacy

2.5.1 Brief Statement of Conclusions

I did not conduct a new integrated review of efficacy, which was evaluated by Dr. Oliva in the original NDA review. Comment 1-4 below originate from Dr. Oliva's prior review. I reviewed Study 1048 as a standalone study and integrated my conclusions to Dr. Oliva's prior conclusions on the comparative efficacy of eletriptan and sumatriptan (comment 5).

1. Eletriptan 20mg, 40mg, and 80mg are all effective treatment for acute migraine, based on the effects on the 2-hour headache response rates, and associated migraine symptoms.
2. There is evidence to suggest that the 40mg dose is better than 20mg, and that the 80mg dose is better than the 40mg dose.
3. Recurrence: treatment with eletriptan was generally associated with a decreased incidence of recurrence within 24 hours.
4. Second dose: treatment with a second dose of eletriptan for recurrence was generally effective. However, the use of a second dose to treat persistent pain was not shown to be effective.
5. Eletriptan 40mg appeared superior to sumatriptan 100mg in two studies (study 318 and 1048) but failed to beat sumatriptan 25mg and 50mg in study 104. Eletriptan 80mg beat sumatriptan 25mg and 50mg in study 104 and beat sumatriptan 50mg and 100mg in study 318. Eletriptan 80mg had a higher incidences of adverse events compared to sumatriptan 100mg, but eletriptan 40mg had a similar incidence of adverse events compared to sumatriptan 100mg.

2.5.2 General Approach to Review of the Efficacy of the Drug

Dr. Oliva established efficacy in the original NDA review. The only efficacy study reviewed here was study 1048. This study was not critical to prove efficacy, but was relevant because superiority over existing treatments is important in the evaluation of the risk/benefit of eletriptan.

2.5.3 Detailed Review of Trials by Indication

2.5.3.1 Study 1048

2.5.3.1.1 Study 1048 protocol and results

This study was a large (n=2421) double blind, parallel group, placebo-controlled, multicenter study comparing a single oral dose of eletriptan (40 mg; E40) vs. sumatriptan (100 mg; S100) for the acute treatment of a migraine attack. Subjects were randomized to one of three treatment groups in a 2:2:1 ratio (for E40, S100, and placebo, respectively) A second dose was allowed to treat migraine recurrence. The primary endpoint was headache response at 2 hours for the ITT sample (randomized subjects who had taken study medication, and had a baseline and a post-baseline evaluation). Headache response was defined as reduction in the severity rating from a moderate or severe headache at baseline, to a mild headache or being pain-free post-dose. The primary comparison was between the eletriptan 40 mg and sumatriptan 100 mg treatment groups. Of 2421 randomized subjects, 2113 were treated. Baseline characteristics were similar across groups, with a mostly caucasian (95%), female (81.9-83.3%), middle-aged population. Baseline frequency of headache attacks was 8.14-8.29 attacks per 3 months. There was a slightly higher incidence of subjects with depressive disorder in the eletriptan group (7.7%) than in the other groups (respectively 4% and 4.4% for sumatriptan and placebo). Table 2 shows that eletriptan was nominally superior to sumatriptan on the primary endpoint and on all critical secondary endpoints.

Table 2: Efficacy results of study 1048

EFFICACY VARIABLE	STUDY TREATMENT			P-Values for Pairwise Comparisons		
	E40 (N=835)	S100 (N=849)	P(N=429)	E40v S100	E40vP	S100vP
Headache response at 1h	34% (264/779)	27% (213/792)	11% (45/404)	0.0026	<0.0001	<0.0001
Headache response at 2h	67% (525/782)	59% (468/799)	26% (107/406)	0.0005	<0.0001	<0.0001
Headache response at 4 h	83% (623/748)	78% (592/756)	41% (152/370)	0.0202	<0.0001	<0.0001
Pain-free response at 2h	36% (284/782)	27% (213/799)	5% (21/406)	<0.0001	<0.0001	<0.0001
No nausea at 2h	74% (573/777)	67% (532/797)	57% (230/405)	0.0015	<0.0001	0.0010
No vomiting at 2h	96% (745/775)	96% (763/792)	94% (376/401)	0.6798	0.0982	0.0425
No photophobia at 2h	71% (553/779)	63% (500/796)	44% (179/406)	0.0017	<0.0001	<0.0001
No phonophobia at 2h	74% (571/774)	67% (535/797)	50% (202/405)	0.0068	<0.0001	<0.0001
Recurrence rate	31% (170/552)	37% (183/496)	47% (59/126)	0.0372	0.0007	0.0419
Rescue medication	20% (165/822)	27% (223/831)	53% (221/419)	0.0012	<0.0001	<0.0001
Treatment acceptability	64% (489/768)	56% (443/785)	23% (91/394)	0.0036	<0.0001	<0.0001

The proportions of subjects who took a second dose was similar for E40 (28%) compared to S100 (29%), and both were significantly lower than the number of subjects treated with placebo who took a second dose (33%). From 2 hours through 24 hours post-dose, treatment with E40 was associated with a significantly higher pain-free response than S100. The validity of the efficacy advantage of E40 compared to S100 does not appear to be attributable to atypically low response rates for S100 in this study. One major limitation of this study is that it did not exclude subjects known to be non-responders to sumatriptan. It is also unclear how many of these subjects received triptans prior to the study.

Eletriptan safety profile was similar to that of sumatriptan (see 2.6.3.2).

2.5.3.1.2 Reviewer's analysis

I created a subset table from the efficacy.xpt dataset. I splitted the table based on the variable CALC_TPD (timepoint). I obtained 2113 rows, which corresponds to the number of subjects who where treated. I selected subjects who had a baseline headache of intensity 2 or greater, which reduced sample size to n=2076. For these 2076 remaining subjects (823 eletriptan, 833 sumatriptan, 420 placebo), I used a LOCF approach. If no post-baseline data was available, I carried forward the baseline value up to the 2 hour timepoint. Headache response at 2 hour was observed respectively in 65.9%, 58.3% and 26.2% for subjects randomized to eletriptan, sumatriptan and placebo. Headache response was nominally superior in eletriptan subjects versus sumatriptan subjects ($p < 0.005$). Unfortunately, no dataset included data on nausea, photophobia and phonophobia (except if reported as an adverse event), so that my analysis was limited to headache response. A potential issue in that study is that it was so large that trivial differences between treatment may reach statistical significance. This was however not the case, since eletriptan provided pain response in an additional 7.6% subjects compared to sumatriptan, which is a relative increase of 23.6%. I am unable to make definite conclusions about this trial because sumatriptan non-responders were allowed to participate (and there may have been a recruitment bias towards subjects with unsatisfactory response to migraine treatment), and because the dataset was incomplete.

2.5.4 Efficacy Conclusions

From the data presented in the original NDA and in the first response to approvable letter, Dr. Oliva who conducted the original reviews concluded the following:

1. Eletriptan 20mg, 40mg, and 80mg are all effective treatment for acute migraine, based on the effects on the 2-hour headache response rates, and associated migraine symptoms.
2. The 5mg dose, although numerically superior to placebo in study 302, was not shown to be statistically superior. Nonetheless, it is possible that doses lower than 20mg (e.g. 10mg or even 5mg) are effective, but this would require additional studies, with sufficient power, in order to establish this possibility.
3. There is evidence to suggest that the 40mg dose is better than 20mg. In the only study specifically designed to demonstrate a benefit of the 80mg over the 40mg dose, the primary outcome was negative. Other studies are suggestive of a benefit (i.e., hypothesis generating) but do not establish a benefit.
4. Recurrence: treatment with eletriptan was generally associated with decreased incidence of recurrence within 24 hours.
5. Second dose: treatment with a second dose of eletriptan for recurrence was generally effective. However, the use of a second dose to treat persistent pain was not shown to be effective.
6. Adolescents: the efficacy of eletriptan to treat migraine in adolescents was not established in the single outpatient adolescent study (study 105). This was possibly due to a high placebo response rate (~57%).
7. Migraine Aura: Eletriptan was not effective in preventing the onset of a moderate or severe headache when given during the aura phase, and neither enhanced nor delayed the resolution of aura or onset of headache pain.

The only efficacy study part of this submission was Study 1048. This was a large multi-center trial supporting the superiority of eletriptan 40 mg versus sumatriptan 100 mg. In the original NDA, Dr. Oliva noted that in the two studies that used sumatriptan and excluded sumatriptan non-responders (104 and 318), eletriptan 40mg appeared to beat sumatriptan 50mg and 100mg in Study 318 but failed to beat sumatriptan 25mg and 50mg in Study 104. Unfortunately, Study 1048 did not exclude sumatriptan non responders, so that a recruitment bias can not be ruled out. Study 1048 was also much more powered to detect a difference between sumatriptan and eletriptan than study 104. Sample size of Study 104 (n=818) was much smaller than that of Study 1048 (n=2421), and Study 104 had five arms, versus only three for Study 1048. Eletriptan 80mg beat sumatriptan 25mg and 50mg in Study 104 and beat sumatriptan 50mg and 100mg in Study 318. Eletriptan 80mg also has a higher incidence of adverse events compared to sumatriptan 100mg.

2.6 Integrated Review of Safety

2.6.1 Brief Statement of Conclusions

The two new coronarography studies conducted by the Sponsor (Study 1072 and Study 309) have not provided convincing evidence supporting the cardiovascular safety of eletriptan when given with CYP3A4 inhibitors for the following reasons:

1. Study 1072 can not be regarded as positive for the primary endpoint of change in coronary artery diameter because it lacked assay sensitivity.
2. The imbalance in vasoconstriction adverse events between eletriptan and both sumatriptan and placebo in Study 1072 is striking and worrisome. These adverse events suggest, but do not prove conclusively, that eletriptan may lead to increased rates of cardiac ischemic events.
3. Study 309 does not provide any new information on the safety of eletriptan when administered concomitantly with CYP3A4 inhibitors. This study gives only modest reassurance about the possible side effects of eletriptan in the cardiac populations.

There was no clear association between the eletriptan plasma level and the adverse events of vasoconstriction in study 1072. This does not support the safety of a reduced dose of eletriptan in case of concomitant used of CYP3A4 inhibitors. The safety update does not add any new significant finding to eletriptan safety profile. Study 160-1048, a comparative study with sumatriptan, showed a similar incidence of chest and cardiac symptoms in patient treated with eletriptan 40 mg (3.1%) and sumatriptan 100 mg (2.8%). This study does not provide any information in support of cardiovascular safety of eletriptan at higher dosages.

The safety update does not add any new significant finding. Study 160-1048, a large a multicenter, double-blind, placebo-controlled parallel group study showed a similar incidence of chest and cardiac symptoms in patients treated with eletriptan 40 mg and in patients treated with sumatriptan 100 mg.

Pharmacovigilance data show no cardiovascular serious adverse event (SAE) after the sale of ~~_____~~ eletriptan tablets. There was one spontaneous SAE report described as an anaphylactic reaction to eletriptan. There was also a massive MI leading to death reported (not part of this submission), in a patient who took one tablet of eletriptan 40mg and possibly up to two tablets of sumatriptan 50mg. Even though both triptans should not have been taken in the same 24-hour interval, their individual dosages remain well within the allowed maximum daily dosage. Overall, the post-marketing experience provides some reassurance about eletriptan cardiovascular safety. However, maximum recommended daily dosage varied between 40mg, 80mg or 160 mg across countries, with no breakdown provided by the Sponsor, so that this postmarketing experience provides information only supporting a maximum daily dosage of 40mg.

2.6.2 Description of Patient Exposure

The phase 2/3 database presented at the time of the NDA submission contained data from 5033 subjects who received eletriptan and 1054 who received placebo. In addition, the final data from the three long-term studies contain 1544 subjects who received eletriptan were part of the response to approvable letter of June 1, 2000. Of these, 1024 completed 12 months of treatment (483 on 40mg and 541 on 80mg). Phase 2/3 studies initiated since original filing and part of the Sponsor safety database for this submission include study 160-1001, 160-1002, 160-1006, 160-1007, and 160-1027. These studies add 1590 subjects assigned to eletriptan to the database (998 eletriptan 40mg and 592 eletriptan 80mg). The safety database also contains data on 1376 subjects assigned to placebo, and 2249 subjects assigned to a comparator.

In addition, the Sponsor provided safety information from study 160-1048, which compared the efficacy and safety of oral eletriptan (40 mg) and sumatriptan (100 mg), completed after the 31 October 2001 cutoff date for the safety update. In study 1048, 835 subjects were treated with eletriptan 40mg, 849 subjects with sumatriptan 100 mg and 429 subjects with placebo. Twelve studies were categorized as “ongoing” on 31 October 2001, and were not included in the safety database (160-1005, 160-1010, 160-1015, 160-1016, 160-1017, 160-1019, 160-1020, 160-134, 160-1042, 160-157 and 160-1068). Table 3 shows the number of subjects and the number of attacks assigned to eletriptan by initial dose.

Table 3: Number* of Subjects Assigned to Eletriptan by Initial Dose (adapted from Sponsor table 1.1.1, safety update)

	5 mg	20 mg	30 mg	40 mg	60 mg	80 mg	Total
Subjects	141	734	178	4834	142	3305	9334
Attacks	351	4018	497	33171	3457	32731	74225

*Subjects from extension studies are counted twice, once in the initial study and once in the extension study

This submission also contains data on 2 coronarography studies in which 43 subjects received eletriptan, 35 subjects received sumatriptan and 28 subjects received placebo.

2.6.3 Methods and Specific Findings of Safety Review

My review is divided in 5 parts: safety update (post-original NDA), Study 1048, post-marketing data, 4 month safety update, and coronarography studies.

2.6.3.1 Safety update

This safety update contains data from all Phase 1, 2 and 3 studies that have occurred from November 1, 1998 (cutoff date for the 4 month safety update of the original NDA), through October 31, 2001.

2.6.3.1.1 Deaths

In the original NDA, Dr. Oliva identified 2 deaths within 30 days of end of treatment in eletriptan-treated subjects. none being attributed to eletriptan. There was one additional death in eletriptan-treated subjects in the safety update database. This patient's SAE is described below, and is not related to eletriptan in my opinion.

Subject 1013-1303

This 29-year-old white male received eletriptan 40mg tablets for multiple migraine attacks, the last one occurring on March 3, 2000. On March 18, 2000, the subject experienced accidental death by hanging. In the opinion of the investigator, this event was not due to the study drug. Review by the study Sponsor concluded the event was not related to eletriptan.

2.6.3.1.2 Serious adverse events

In the original NDA review, Dr. Oliva identified 92 serious adverse event (SAE) cases. A total of 59 SAEs were entered into the database from November 1, 1998 to the cut-off date of October 31, 2001. They are listed in table 1.8.1.2, page 489 of the safety update. I reviewed that listing, and I identified one case (A040373 1603093250010) of myocardial infarction on the day of administration of eletriptan 6mg (as part of Coronarography Study 309), non attributed to the study drug by the investigator. This patient is described in 2.6.3.5.3.2.

For the subjects who received eletriptan, 33 SAEs were reported in the safety update, of which 5 were considered related to study drug. Events that were reported two times or more include acute/severe/worsening migraine (three cases), exacerbated/persistent headache (two cases), ovarian cysts (three cases), appendicitis (two cases), hernia (two cases), and various cancers (three cases). The remaining events involved other illnesses or injuries (18 cases). The five eletriptan treated subjects that had SAEs considered related to the study treatment by the investigator were worsening/severe headache (3 cases), transient ischemic attack (1 case) and paresthesia of the tongue, neck, and arm (1 case). They are described below.

Subject 5095-1077

This 45-year-old white female subject received eletriptan prn, for multiple attacks. On November 27, 1998 the subject experienced a transient ischemic attack two hours after dosing. Symptoms were intermittent clumsiness and weakness of the left hand that lasted 1.5 to 2 hours, for which the subject did not seek treatment. Total daily dose closest to onset of event was 80mg. Subsequent doses of study drug were taken on November 30, 1998 and December 08, 1998 with no adverse reactions reported. On December 17, 1998, two hours after dosing, she

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experienced intermittent clumsiness and weakness of both hands for a duration of 1.5 to 2 hours, for which the subject did not seek treatment. During both attacks the subject experienced loss of motor function in the left hand, each lasting only 2 to 3 seconds, occurring 5 to 6 times over a 2-hour period. Magnetic resonance imaging of the brain and carotid ultrasound were normal. The event was considered resolved on December 17, 1998. The subject took one more dose of eletriptan on December 29, 1998 without any adverse events reported. In the opinion of the investigator, this event was due to eletriptan. The Sponsor concluded that the role of eletriptan could not be ruled out as a contributing factor in the event.

Subject 0026-301

This 20-year-old white female subject received eletriptan 40mg, on June 16, 2001. On the same day, the subject experienced worsening migraine headache, resulting in the subject's presentation to the emergency department where she was treated and released on the same day. On the next day, her migraine worsened again, resulting in the subject's return to the hospital where she was treated and discharged on the same day. The event was considered resolved on June 17, 2001. In the opinion of the investigator, this event was due to eletriptan. The Sponsor concluded the event was unlikely to be related to eletriptan, but could not be ruled out.

Subject 0322-746

This 39-year-old white female received eletriptan 40mg on November 5, 2000. Eletriptan 40mg and placebo were administered orally, prn, 5 hours later on November 6, 2000, for a total dose of 80mg. On November 7, 2000 the subject experienced persistent severe headache. On November 22, 2000 the subject reported the symptoms as ongoing and severe, resulting in hospitalization and treatment. The subject was discharged on November 24, 2000 with a diagnosis of tension headache. The event was considered resolved on December 24, 2000. In the opinion of the investigator, the event was probably not caused by study medication, but the investigator stated it was impossible to exclude eletriptan as the cause of the event. The Sponsor concluded that although it is unlikely the event was caused by eletriptan, the possibility cannot be completely ruled out.

Subject 0021-98

This 39-year-old white female subject received a single eletriptan 40mg dose on both May 1, 2001 and May 5, 2001. On May 1, 2001 the subject took a single dose of 40mg at 12:00 PM, and at 1:30 PM experienced tongue paresthesia and right lateral neck paresthesia. These events abated around 3:30 PM with no treatment or intervention. On May 5, 2001, at 7:15 AM, the subject independently took a 40mg dose of eletriptan to treat another headache and experienced tongue paresthesia, right lateral neck paresthesia and right arm paresthesia. These events abated around 10:00 AM with no treatment or intervention. In the opinion of the investigator, both events were due to eletriptan. Review by the study Sponsor concluded the events were related to eletriptan.

Subject 6050-0932

This 33-year-old Asian female received a dose of eletriptan 80mg on June 17, 1999 at 3:30 PM and the headache improved at 7:30 PM. At 9:30 PM the headache worsened and the subject presented to the hospital and was admitted. Computerized tomography scan revealed no abnormality. The event was considered resolved on June 23, 1999. In the opinion of the investigator, this event was due to eletriptan. The Sponsor concluded the event was not related to eletriptan, but due to the disease under study.

The Sponsor added the following case to the narrative list, although this was not attributed to eletriptan by the Sponsor.

Subject 0066-66

This 39-year-old white female subject received eletriptan 40mg on September 14, 2000 followed by a second dose five hours later. The next morning, the subject experienced paroxysmal atrial fibrillation. This event led to inpatient hospitalization. The subject went to her general practitioner at around 9:15 AM where she was treated with I.M. maxolon and diagnosed with atrial fibrillation. The subject was then sent to the ED via ambulance. The event was considered resolved on September 17, 2000. The subject had a past history of atrial fibrillation on December 17, 1999. In the opinion of the investigator, this event was due to other illness (hypokalaemia,

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vomiting/migraine/atrial fibrillation predisposition). The Sponsor concluded there is unlikely to be any relationship between eletriptan and this event, although it cannot be entirely excluded.

Comment: the only worrisome SAE was the report of a possible TIA. This report is however isolated, and symptoms may be related to the migraine attack as well.

2.6.3.1.3 Dropouts

In his NDA review, Dr. Oliva noted that of the 6,419 subject who received eletriptan in phase 2/3 studies, 1,299 (20.2%) discontinued the study prematurely. The proportion of discontinuations for each treatment groups were comparable among eletriptan, physician optimized therapy (POT) and placebo.

In the updated database, overall numbers of discontinuations remained similar for all three major treatment groups, i.e., eletriptan 1813/8529 (21.3%), placebo 252/1377 (18.3%) and active comparators 593/2275 (26.1%). The breakdown of the reasons for discontinuations, listed in Table 4 remains similar to that of the original NDA.

Table 4: Reasons for Discontinuations from All Phase 2/3 Studies (adapted from table 1.3.3. safety update)

Number of Subjects (%)	Eletriptan (N = 8529)	Placebo (N = 1377)	Active Comparator (N = 2275)
Total	1813 (21.3)	252 (18.3)	593 (26.1)
Related to Study Drug	458 (5.4)	58 (4.2)	84 (3.7)
Adverse Event	186 (2.2)	11 (0.8)	16 (0.7)
Insufficient Clinical Response	259 (3.0)	45 (3.3)	68 (3.0)
Laboratory Test Abnormality	13 (0.2)	2 (0.1)	0 (0.0)
Special Safety Test Finding	0 (0.0)	0 (0.0)	0 (0.0)
Death	0 (0.0)	0 (0.0)	0 (0.0)
Not Related to Study Drug	1355 (15.9)	194 (14.1)	509 (22.4)
Adverse Event	77 (0.9)	6 (0.4)	16 (0.7)
Laboratory Test Abnormality	18 (0.2)	2 (0.1)	1 (0.0)
Special Test Finding	1 (0.0)	0 (0.0)	0 (0.0)
Death	2 (0.0)	0 (0.0)	1 (0.0)
Lost to Follow-up	128 (1.5)	21 (1.5)	44 (1.9)
Protocol Violation	169 (2.0)	19 (1.4)	67 (2.9)
Failed Randomization Criteria	16 (0.2)	0 (0.0)	5 (0.2)
Withdrawn Consent	232 (2.7)	22 (1.6)	73 (3.2)
Other	712 (8.3)	124 (9.0)	302 (13.3)

In short term, placebo-controlled studies, overall numbers of discontinuations were similar for eletriptan (15.2%), placebo (18.3%) and active comparators (21.4%).

2.6.3.1.3.1 Adverse dropouts

The Sponsor compared all discontinuations up to April 30, 1998 (NDA cut-off date), to all discontinuations up to October 31, 2001 (safety update cut-off date). Table 5 shows that the

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rate of adverse dropouts in the safety update is slightly higher than in the original NDA. I suspect that this is related to the inclusion of long term safety data, with subjects exposed to eletriptan for a longer duration.

Table 5: Overview of Study Discontinuations – All Phase 2/3 Studies at Original NDA Filing Versus Safety Update –Eletriptan Only

	NDA Filing (N = 6419)	Safety Update (31 October 2001) (N = 8529)
Number (percent) of subjects		
Adverse Event	165 (2.6)	263 (3.1)
Insufficient Clinical Response	153 (2.4)	259 (3.0)
Laboratory Test Abnormality	20 (0.3)	31 (0.4)
Special Safety Test Finding	1 (0.0)	1 (0.0)
Death	1 (0.0)	2 (0.0)
Other	959 (14.9)	1257 (14.7)
Total	1299 (20.2)	1813 (21.3)

In the original NDA, Dr. Oliva noted that there were 17 ADOs due to chest pain for eletriptan (0.3%) but no cases for either placebo or sumatriptan (0%). Table 6 shows that that number increased to 30 (0.4%) in the safety update. Again, I suspect that this is probably related to the increased exposure in long term studies.

Table 6: All Causality Safety Related Discontinuations From Study At Original NDA Filing Versus Safety Update –General Categories That Differed By More Than 0.2% With Preferred Terms That Differed By At Least 0.1% (adapted from table 1.3.5, safety update)

	Eletriptan at NDA Filing (N = 6419)	Eletriptan at Safety Update (N = 8529)	Placebo (N=1377)	Active comparator (N=2275)
Number (percent) of subjects discontinued due to:				
Adverse Events	142 (2.2)	240 (2.8)	15 (1.1)	26 (1.1)
Objective Test Findings	12 (0.2)	24 (0.3)	3 (0.2)	0 (0)
Body As A Whole	54 (0.8)	98 (1.1)	3 (0.2)	12 (0.5)
Asthenia	17 (0.3)	31 (0.4)	0 (0)	1 (0)
Pain	5 (0.1)	13 (0.2)	0 (0)	2 (0.1)
Back Pain	3 (0.0)	6 (0.1)	0 (0)	2 (0.1)
Chest Pain	17 (0.3)	30 (0.4)	0 (0)	0 (0)
Nervous	67 (1.0)	107 (1.3)	4 (0.3)	11 (0.5)
Tremor	3 (0.0)	7 (0.1)	0 (0)	2 (0.1)
Vertigo	3 (0.0)	5 (0.1)	0 (0)	0 (0)
Somnolence	14 (0.2)	23 (0.3)	0 (0)	1 (0)
Speech Disorder	2 (0.0)	8 (0.1)	0 (0)	0 (0)
Thinking Abnormal	4 (0.1)	4 (0.0)	0 (0)	0 (0)
Hypesthesia	3 (0.0)	8 (0.1)	0 (0)	0 (0)

Table 7 supports that a large part of the increase in chest pain adverse dropout came from uncontrolled studies. Nevertheless, the contrast remains with the absence of adverse dropouts

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for active comparator treated subjects. The overall rate of adverse dropouts in placebo-controlled phase 2/3 studies was 1.8% in eletriptan-treated subjects, versus 1.0% in active comparator-treated subjects, and 1.1% in placebo-treated subjects.

Table 7: Comparison of adverse dropout in all phase 2/3 studies and in placebo-controlled safety studies in the safety update (adapted from table 1.3.5 and 1.3.7, safety update)

	Eletriptan in all phase 2/3 studies (N = 8529)	Eletriptan in placebo-controlled phase 2/3 studies (N=6252)	Placebo in placebo-controlled phase 2/3 studies (N=1377)	Active comparator in placebo-controlled phase 2/3 studies (N=1648)
Number (percent) of subjects discontinued due to:				
Adverse Events	240 (2.8)	105 (1.7)	15 (1.1)	16 (1.0)
Objective Test Findings	24 (0.3)	6 (0.1)	3 (0.2)	0 (0.0)
Body As A Whole	98 (1.1)	43 (0.7)	3 (0.2)	8 (0.5)
Asthenia	31 (0.4)	16 (0.3)	3 (0.2)	8 (0.5)
Pain	13 (0.2)	5 (0.1)	0 (0.0)	2 (0.1)
Back Pain	6 (0.1)	3 (0.0)	0 (0.0)	2 (0.1)
Chest Pain	30 (0.4)	16 (0.3)	0 (0.0)	0 (0.0)
Nervous	107 (1.3)	50 (0.8)	4 (0.3)	8 (0.5)
Tremor	7 (0.1)	4 (0.1)	0 (0.0)	2 (0.1)
Vertigo	5 (0.1)	4 (0.1)	0 (0.0)	0 (0.0)
Somnolence	23 (0.3)	9 (0.1)	0 (0.0)	1 (0.1)
Speech Disorder	8 (0.1)	2 (0.0)	0 (0.0)	0 (0.0)
Thinking Abnormal	4 (0.0)	2 (0.0)	0 (0.0)	0 (0.0)
Hypesthesia	8 (0.1)	5 (0.1)	0 (0.0)	0 (0.0)

2.6.3.1.4 Adverse events

Table 8 shows that the incidence of all causality, treatment emergent adverse events (AEs) for eletriptan treated subjects in all phase 2/3 studies at the time of the original filing was similar to that of all phase 2/3 studies in the safety update (up to October 31, 2001).

Table 8 (adapted from table 1.4.20, safety update): Treatment Emergent Adverse Events by Body System and Preferred Term (All Causalities) Occurring in 5% of Subjects or Greater or with 0.5% or Greater Difference in Incidence between Time of Original Filing (30 April 1998) and All Phase 2/3 Studies Combined (31 October 2001)

Body System COSTART Preferred Term	Eletriptan NDA Filing 30 April 1998					Eletriptan Database 31 October 2001				
	N	%	Severity (%)			N	%	Severity (%)		
			Mild	Moderate	Severe			Mild	Moderate	Severe
Subjects with AEs	3409	53.1	18.8	22.7	11.6	4614	54.1	18.8	23.8	11.5
Body as a Whole	1654	25.8	12.9	12.8	4.8	2264	26.5	14.0	13.7	5.0

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Body System COSTART Preferred Term	Eletriptan NDA Filing 30 April 1998					Eletriptan Database 31 October 2001				
	N	%	Severity (%)			N	%	Severity (%)		
Asthenia	1586	11.1	4.3	4.7	2.1	3090	11.6	4.3	5.0	2.3
Headache	497	5.5	2.4	2.1	1.0	829	5.7	2.3	2.3	1.1
Chest Pain	498	4.0	2.3	1.4	0.3	824	4.5	2.6	1.6	0.4
Cardiovascular	455	7.1	3.9	2.9	0.8	628	7.4	3.9	3.2	0.9
Migraine	107	0.8	0.1	0.4	0.3	156	1.3	0.2	0.6	0.4
Digestive	1428	22.2	11.3	10.1	4.1	2063	24.2	12.9	11.4	4.0
Nausea	1174	10.5	3.6	4.6	2.2	2086	12.2	4.6	5.3	2.2
Vomiting	318	4.1	0.7	2.1	1.3	594	5.4	1.3	2.7	1.3
Musculoskeletal	348	5.4	2.9	2.5	0.7	500	5.9	3.2	3.0	0.7
Nervous	1664	25.9	15.0	11.6	3.7	2182	25.6	15.1	12.0	3.6
Dizziness	868	8.3	4.7	2.9	0.8	1543	8.5	4.7	3.0	0.8
Somnolence	1325	8.4	2.8	4.1	1.5	2136	8.2	2.8	3.9	1.5
Respiratory	601	9.4	5.0	4.4	0.7	817	9.6	5.1	5.0	0.8

The most frequent adverse events remain nausea, asthenia, dizziness and somnolence.

2.6.3.1.4.1 Adverse Events with Concomitant CYP3A4 Inhibitor Use

Dr. Oliva examined the issue of AEs with concomitant CYP3A4 inhibitor use in his review of the response to original NDA approvable letter (6/1/00). Dr. Oliva noted difficulties in interpreting comparative data off and on CYP3A4 inhibitors for various reasons, including that most CYP3A4 inhibitors used were oral contraceptives, for which the effect on eletriptan pharmacokinetics is unknown (page 12-15, Dr. Oliva 11/1/00 review of the response to approvable letter). The effect of CYP3A4 inhibitors on eletriptan safety profile remained inconclusive.

In the safety update, the Sponsor provided a summary table of all causality, treatment emergent AEs by body system and where eletriptan alone versus eletriptan plus general CYP3A4 inhibitor differed by 0.3% or more. CYP3A4 inhibitors reviewed were the same as those from Dr. Oliva's review. Attacks where eletriptan was taken concomitantly with a CYP3A4 inhibitor were identified. Attacks, in the same subjects, treated with eletriptan without concomitant CYP3A4 inhibitors were identified for comparison.

The incidence of chest pain was nearly doubled (1.3% versus 0.7%) when eletriptan was taken with a CYP3A4 inhibitor. Overall incidence of side effects was slightly higher (22.5% versus 20.4%). Dosage of sumatriptan was possibly different across attacks, so that these data are difficult to interpret.

Table 9: Treatment emergent adverse events by body system and where eletriptan alone versus eletriptan plus general CYP3A4 inhibitor differed by 0.3% or more

Summary of All Causality, Treatment Emergent Adverse Events by Body System and Preferred Term, All Phase 2/3 Studies, Where Eletriptan Alone versus Eletriptan plus General CYP3A4 Inhibitor Differed by 0.3% or More				
Number of Attacks Treated	Eletriptan Controlled 4783		Eletriptan 7715	
	N	%	N	%
Attacks with Adverse Events	1076	22.5	1571	20.4
Body As A Whole	304	6.2	614	8.0
Appl. Inj. Inoculn/Insecta Site pain	3	0.1	32	0.4
Asthma	159	3.3	183	2.4
Chest Pain	62	1.3	55	0.7
Pain	34	0.7	78	1.0
Cardiovascular	37	1.6	47	0.6
Vasodilatation	40	0.8	13	0.2
Digestive	317	6.6	405	5.3
Diarrhea	33	0.7	24	0.3
Dysphagia	115	2.4	94	1.2
Dry Mouth	36	0.8	93	1.2
Nausea	92	1.9	118	1.5
Musculoskeletal	78	1.6	135	1.9
Arthralgia	11	0.2	47	0.6
Myalgia	24	0.5	11	0.1
Nervous	361	7.5	641	8.3
Dizziness	44	1.8	100	1.3
Hypersensitivity	12	0.3	72	0.9
Hypertonia	55	1.1	127	1.6
Hypoesthesia	11	0.2	52	0.7
Paralysis	2	0.0	41	0.5
Parosmia	44	0.9	48	0.6
Somnolence	123	2.6	177	2.3
Vertigo	13	0.3	48	0.6
Respiratory	173	3.6	182	2.4
Pharyngitis	64	1.3	72	0.9
Respiratory Tract Infection	38	0.8	27	0.4
Skin and Appendages	34	1.1	60	0.8
Pruritus	12	0.3	1	0.0
Urogenital	79	1.7	104	1.4

Data Source: Table 1.4.21

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2.6.3.1.5 Clinical laboratory tests abnormalities

In this safety update, the overall incidence of clinically significant laboratory test abnormalities for eletriptan treated subjects (irrespective of baseline abnormalities) in all Phase 2/3 studies was 36.92%. The incidence of laboratory test abnormalities was similar to placebo (32.18%) and active comparator (35.23%) treated subjects. The range of abnormalities observed was similar for all study treatments. In active comparator placebo controlled phase 2/3 studies, the incidence of test abnormalities was similar for eletriptan (32.77%), placebo (32.18%), and active comparator subjects (31.89%). There were no clinically significant changes in laboratory test variables within treatment groups and no clinically important differences in the median change from baseline for any variable when comparing eletriptan, active comparator and placebo.

In his original NDA review, Dr. Oliva noted that 11 subjects were discontinued due to clinically significant liver function abnormalities. In his analysis, Dr. Oliva concluded that none of the cases provided conclusive proof of eletriptan-induced elevated liver function

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tests, although some cases were suggestive. In his review of long term studies (11/1/00 review, page 31-33), Dr. Oliva observed a relatively higher incidence of LFT abnormalities in eletriptan treated subjects, but noted several confounders including increased testing in the eletriptan group, but also long time interval since the last dose of eletriptan (many days). Table 10 shows a similar incidence of liver test abnormalities between eletriptan, placebo and active comparator subjects in the safety update database.

Table 10: Incidence of Clinically Significant Liver Function Abnormalities in all phase 2/3 studies (adapted from table 1.5.1, safety update)

Lab Test	Eletriptan		Placebo		Active Comparator	
	Number tested	Abnormal (%)	Number tested	Abnormal (%)	Number tested	Abnormal (%)
Total Bilirubin increase	6738	48 (0.7)	512	7 (1.4)	1555	9 (0.6)
SGOT increase	6739	21 (0.3)	512	2 (0.4)	1554	3 (0.2)
SGPT increase	6577	30 (0.5)	512	1 (0.2)	1554	5 (0.3)

Also, the frequency of discontinuation due to laboratory test abnormalities (all causalities) was similar in eletriptan and placebo treated subjects in the safety update database, respectively 0.4% for eletriptan (31/8529), and 0.3 % (4/1377) for placebo. No discontinuations due to laboratory test abnormalities were reported in the active comparator group.

Among eletriptan treated subjects, five subjects discontinued due to abnormal liver function tests (two considered treatment related), five discontinued due to increased SGOT (3 treatment related) and six discontinued due to increased SGPT (4 treatment related). The incidence of discontinuations due to abnormal liver function tests was lower for both the placebo (1/1377 SGPT increase and 1/1377 liver test abnormality) and active comparator groups (0/2275) than for the eletriptan treated group. There was no evidence of persistent changes in laboratory test variables within treatment groups and no clinically important differences in the median change from baseline for any variable when comparing eletriptan, active comparator and placebo. These updated data do not modify Dr Oliva's conclusions on the significance of these liver abnormalities.

2.6.3.1.6 Vital signs

In his original NDA review, Dr. Oliva analyzed blood pressure changes in pooled data from phase 3 efficacy studies and found no evidence for a dose response change in systolic blood pressure, diastolic blood pressure or pulse. Dr. Oliva also noted small, transient increases in blood pressure in clinical pharmacology studies, consistent with eletriptan mechanism of action.

In the safety update, the Sponsor identified no discontinuations due to vital signs findings related to study drug. All causality data show that 7 eletriptan treated subjects (0.1%) discontinued due to hypertension, compared to 3 placebo treated subjects (0.2%) and 1 active comparator treated subject (0.1%). The overall incidence of clinically significant changes in systolic and diastolic blood pressure and pulse rate was low (<1%), with similar percentages

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reported for eletriptan, placebo, and active comparator treated subjects. There were no meaningful differences in the median change from baseline to last observation for blood pressure or pulse rate in any of the treatment groups for all Phase 2/3 studies.

2.6.3.1.7 ECG data

Table 11 shows that five eletriptan treated subjects experienced a QTc \geq 500 msec.

Table 11: Incidence of QTc Abnormalities and Change from Baseline for All Phase 2/3 Studies

Number (%) of subjects	Eletriptan (N = 6006)	Placebo (N = 514)	Active Comparators (N = 1316)
QTc \geq 500 msec at least once	5 (0.08)	0 (0)	0 (0)
QTc \geq 500 msec more than once	0 (0)	0 (0)	0 (0)
Increase from baseline			
< 30 msec	5289 (88.06)	438 (85.21)	1149 (87.31)
30 – 60 msec	643 (10.71)	68 (13.23)	151 (11.47)
> 60 msec	74 (1.23)	8 (1.56)	16 (1.22)

These cases were already discussed in the original NDA review. Two of them were measurement errors. As in the original NDA, there were no meaningful changes between baseline and LOCF medians for any of the ECG variables in any treatment group. Since, ECGs were collected at various time intervals after dosing with study drug in phase 2/3 studies, data from this population must be interpreted with caution.

2.6.3.2 Study 160-1048

Study 160-1048 compared the efficacy and safety of oral eletriptan (40 mg), sumatriptan (100 mg), and placebo in the acute treatment of one migraine attack. This study was not integrated in the combined database of the safety update, since it was completed after the cut-off date. This was a multicenter, double-blind, placebo-controlled parallel group study of 2421 subjects. 2109 subjects completed the study (832 eletriptan, 848 sumatriptan, 429 placebo). The number of subjects reporting at least one treatment-emergent, all-causality AE (Table 12) was similar for the two active study treatments (eletriptan 31%; sumatriptan 37%) and placebo (34%). The incidence of treatment-related AEs was higher for eletriptan (16%) and sumatriptan (21%) treated subjects than for subjects treated with placebo (9%). In general, both study treatments were well tolerated, with only nausea having an incidence >2% higher in eletriptan treated subjects than in placebo treated subjects (eletriptan, 5%; sumatriptan, 4%; placebo, 3%). The most commonly reported (>2%) all-causality, treatment-emergent AEs were nausea, vomiting, photophobia, asthenia, chest pain, and paresthesias. The incidence and pattern of AEs was consistent with previous eletriptan studies. One subject treated with eletriptan had a serious adverse event, gastro-esophageal reflux, which was not considered treatment related. There were no deaths in the study. No clinically significant abnormal laboratory tests or ECGs were reported (post treatment lab and ECG tests were not required by the protocol unless medically indicated).

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Table 12: Adverse events in study 1048 (adapted from table 6.1 and 6.4, Study 1048 report)

Treatment-emergent adverse event (AE)	E40 (N=835)	S100 (N=849)	Placebo (N=429)
Subjects with all causality AEs	261(31%)	315 (37%)	145 (34%)
Subjects with treatment related AEs	135 (16%)	174 (20%)	38 (9%)
Subjects with severe all causality AEs	30 (3.6%)	28 (3.3%)	14 (3.3%)
Subjects with severe, treatment-related AEs	14 (1.7%)	13 (1.5%)	2 (0.5%)
Subjects with all causality serious AEs	1 (0.1%)	1 (0.1%)	0 (0%)

The most frequent treatment-emergent adverse events (reported with an incidence > 2% in one or more treatment groups) are summarized in Table 13. In the Sponsor's report, chest pain was less frequently reported in eletriptan-treated subjects than in sumatriptan-treated subjects. I verified this observation in my analysis (see below).

Table 13: Incidence of Treatment-Emergent Adverse Events

	E40	S100	P
Adverse Events, N (%)			
Nausea	99 (11.9%)	125 (14.7%)	54 (12.6%)
Vomiting	49(5.9%)	49(5.8%)	46(10.7%)
Photophobia	34(4.1%)	39(4.6%)	24(5.6%)
Asthenia	13(1.6%)	20(2.4%)	4(0.9%)
Chest pain	13(1.6%)	17(2.0%)	2(0.5%)
Paresthesias	9(1.1%)	20(2.4%)	0(0%)

2.6.3.2.1 Reviewer's analyses

I analysed the adverse.xpt dataset of study 1048. Of 399 reported AE terms, I identified two categories of terms possibly related to a cardiac origin (Table 14).

Table 14: AE terms possibly related to a cardiac origin

Chest and cardiac symptoms	Throat and jaw symptoms
chest tightness	throat tightness
palpitations	tightness in throat
heartburn	ache in jaw
tachycardia	discomfort in throat
feeling of pressure on the chest	burning sensation to back of throat
tightness of chest	feeling of constriction in the throat
breast soreness female	jaw ache
breast tenderness (female)	jaw pain
chest heaviness	jaw tightness
chest pressure	pain in the throat
chest tightness X 10 min	pressure in the throat
heart palpitation	throat pain
oppression in chest	tight jaw
pressure in the thorax	tightening of throat
retro sternal chest pain	tightening sensation along jaw
thoracic pressure 1-2 hours	tightness in throat (15 MINS)
tight chest	
tightness of thoracal area	
Chest pain	

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Chest and cardiac symptoms	Throat and jaw symptoms
Pain in back of chest	
Epigastric pain	
Mild epigastric discomfort	
Chest discomfort	

I selected subjects with AEs terms related to chest and cardiac symptoms. There were respectively 26/835 (3.1%), 24/849 (2.8%) and 6/429 (1.4%) AEs in eletriptan, sumatriptan and placebo subjects. This suggest a similar incidence of chest symptoms associated to sumatriptan and eletriptan in that study.

2.6.3.3 Foreign labeling and postmarketing data

2.6.3.3.1 Foreign labeling

Relpax was approved in 46 countries by April 29, 2002. The Sponsor provided the representative label for the EU (Germany), Central American countries, Australia, Israel, Singapore, Japan, South Africa, Switzerland, Hong Kong, Hungary, and Indonesia. Table 15 shows various approaches for dealing with CYP3A4 inhibitors around the world, from complete contraindication of eletriptan within 48 hours of taking CYP3A4 inhibitors to recommendation of “care” in Japan, where recommended dosages are much lower even without use of CYP3A4 inhibitors (In Japan, the total recommended daily dosage is 40mg. Contraindications for concomitant drugs in Japan are listed in Table 16). Overall, co-administration of eletriptan with CYP3A4 inhibitors is accompanied by some kind of limitation, either dose reduction or contraindication.

Table 15: Foreign labeling

	Max daily dose	CYP3A4 inhibitor recommendation	Recommended starting dose
EU (Germany), Israel, Hungary	80mg	Eletriptan “should not be used” together with potent CYP3A4 inhibitors (warning)	40 mg
Central America South Africa, Switzerland	160mg	Eletriptan dose reduced to a single dose of 20 mg and a total daily dose of 40mg	40 mg
Australia, Hong Kong, Indonesia	160 mg	Eletriptan contra-indicated within 48 hours of treatment with potent CYP3A4 inhibitors	40 mg
Singapore	160mg	Eletriptan contra-indicated within 48 hours and at the same time reduction to a single dose of 20 mg and a total daily dose of 40mg (?)	40mg
Japan	40 mg	Co-administration with CYP3A4 inhibitors allowed “with care”	20 mg

Table 16: Concomitant drugs contraindications in Japan

Drugs	Signs, Symptoms, and Treatment	Mechanisms / Risk Factors
Ergotamine Ergotamine tartrate Anhydrous caffeine (Cafergot) Derivatives of ergotamine Dihydroergotamine mesylate (Dihydroergot) Ergometrine maleate (Ergometrine F) Methylergometrine maleate (Metenarin)	Increased blood pressure or vasospasm may be intensified. If ergotamine or a preparation containing an ergotamine derivative is going to be administered after this drug has been administered, or vice versa, an interval of at least 24 hours is to be provided.	The effects of each drug (vasospasm) intensify those of the other, due to the pharmacologically additive effects with 5-HT _{1B/1D} receptor agonists
5-HT_{1B/1D} receptor agonists e.g., Sumatriptan succinate (Imigran), zolmitriptan (Zomig)	Increased blood pressure or vasospasm may be intensified. If another 5-HT _{1B/1D} receptor agonist is going to be administered after this drug has been administered, or vice versa, an interval of at least 24 hours is to be provided.	Concomitant use may result in the effects of each being intensified
HIV protease inhibitors Ritonavir, indinavir sulfate ethanolate, nelfinavir mesilate	Eletriptan metabolism may be inhibited, resulting in increased blood concentrations.	This drug is metabolized primarily by the metabolizing enzyme CYP3A4. Reduced clearance rate of eletriptan due to the presence of metabolizing enzyme inhibitors

2.6.3.3.2 Post-marketing experience

There were no spontaneous reports of cardiovascular SAE during the period June-October 2001 (on — Relpax tablets sold). Post-marketing safety data up to March 31, 2002 (—) eletriptan tablets sold), also showed no cardiovascular SAEs. This also holds for the 4-month safety update (— tablets sold from July 1, 2001 to May 31, 2002, see below,).

There was one spontaneous report of a SAE in a woman with a history of allergies, asthma and anaphylactic reactions to triptans who developed an apparent anaphylactic reaction to eletriptan. The subject also stated that she developed a severe asthma attack, a feeling of swelling in the throat and urticaria. She self administered salbutamol spray and loratidine tablets and the asthma attack and urticaria abated after 30 minutes. The subject discontinued eletriptan and has recovered.

In the annual report corresponding to the period May 1, 2001 to April 1, 2002, there were 12 spontaneous reports of non serious AEs in 5 subjects: fatigue (2), malaise (1), edema (1), dizziness (2), paraesthesia (2), vertigo (1), nausea (1), chest pain (1), somnolence (1).

2.6.3.3.3 Additional SAE (death) from pharmacovigilance, post safety update

An additional SAE (death) was reported by the Sponsor, independently of this submission.

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The information contained in this report was received via a spontaneous mechanism from a physician in France. A case of malaise and acute myocardial infarction (MI) leading to death, in a consumer who took both eletriptan and sumatriptan, is described below. The Sponsor also added the event term of accidental drug ingestion (off label use), as two different triptans were taken within a 24-hour period despite contraindication in the labeling.

Case 2002056903

This 58-year-old female had a medical history significant for ophthalmic migraine, hyperlipidemia, hypertension (since 1998, controlled on rilmenidine), menopause, hypothyroidism, and a family history significant for cardiac disease. On Sep 7, 2002, the patient presented to her physician for symptoms of migraine with nausea and vomiting. She received two injections of metopimazine (antiemetic) and one 40mg tablet of eletriptan at 8:00 AM while in the physician's office. She also received a prescription for sumatriptan 50mg tablets to be used if needed. The patient's mother confirmed that she saw her take one tablet of sumatriptan at 3:00 PM. A second 50mg sumatriptan tablet was missing from the packaging and the patient's mother considered that the patient ingested the second tablet. The patient remained in bed until 7:00 PM and got up around 8:00 PM complaining of malaise. The patient's mother called the EMS, which performed fibrinolysis. The patient later died at 11:00 PM of a massive myocardial infarction. No autopsy was performed. The patient had no history of a cardiac work up prior to death. She had not received triptans previously. Concomitant medications taken within two weeks prior to the onset of the event included estradiol, levo-thyroxine and rilmenidine. In the Sponsor's opinion, the myocardial infarction was most likely due to underlying coronary artery disease with multiple risk factors for coronary artery disease; however, a contributory role of sumatriptan and/or eletriptan could not be ruled out. The Sponsor attributed the symptoms to the MI and the accidental drug ingestion (off label use) to not following drug-labeling information. As of Sep 18, 2002, review of Pfizer's corporate SAE database revealed no other case of myocardial infarction leading to death in the eletriptan program.

COMMENT: the relation of the SAE to the triptans is possible in my opinion, but it is impossible to discriminate between the relative role of eletriptan and sumatriptan. I recommend that this event be reported in labeling.

2.6.3.4 Four month safety update

The four month safety update was submitted on September 27, 2002. In the reporting period of this 4 month safety update (April 30, 2002 though July 30, 2002), no deaths was reported. There were five cases of serious adverse events (SAEs). These five cases consisted of one report from a clinical study and four spontaneous reports. The Sponsor added a sixth case which was a reclassification of an earlier AE. They are described below. From July 1, 2001 to May 31, 2002 a total of _____ tablets (all doses) were sold.

Case 2002000136

A 26-year-old woman with a history of migraine and tension headache was being treated with eletriptan 40mg, as needed for migraine in study A1601081. The woman had a spontaneous abortion 16 days after receiving a tablet of eletriptan 40mg. An autopsy of the fetus was performed with the result of a chromosome aberration (trisomy 13). Comment: I concur that the event is unrelated to sumatriptan.

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Case 2002055186

After 2 days of treatment with eletriptan 160 mg daily, a 64-year-old woman was diagnosed with eye cancer. She received radiation therapy and has recovered. Comment: I concur that this event is unrelated to eletriptan.

Case 2002000218

A 27-year-old woman with a history of classical migraine experienced a syncope, classified as serious as hospitalization was required, and the non-serious adverse events of anxiety, malaise, paresthesia, chills and asthenia. Symptoms began 30 to 40 minutes after taking eletriptan (three 40 mg tablets within 24 hours) during the headache phase of a migraine with aura. Blood pressure was normal at hospital admission. Eletriptan was permanently discontinued and several hours after hospitalization she recovered spontaneously. The reporting physician did not provide information on causality. Comment: in my opinion, a relation to eletriptan is possible.

Case 2002000236

A 34-year-old woman with a history of migraine who was being treated with eletriptan (40mg) experienced the thoracic oppression (coded as chest pain) and throat tightness (coded as dysphagia) classified as SAE as they were considered important medical events by the reporting physician, and the adverse events of fatigue, hypotension and headache. The woman had experienced a migraine and took two units of dextropropoxyphene/paracetamol caffeine at 7:00 a.m., one gram of aspirin at 10:00 a.m., and one eletriptan 40mg tablet at 2:00 p.m. The symptoms began 20 minutes after taking eletriptan and regressed spontaneously four hours later with no corrective treatment. Eletriptan therapy was discontinued. The reporting physician did not provide information on causality. Comment: in my opinion, the relation to eletriptan is likely.

Case 2002000317

A 50-year-old woman with a history of migraine and psychiatric problems experienced multiple neurological symptoms (coded as neuropathy), classified as SAE as hospitalization was required, and the non-serious AEs of confusion, involuntary muscle contractions, ataxia and hypertension. Symptoms began after taking three 20mg tablets within 24 hours. No blood pressure measurements are available. The hypertension later resolved and she was discharged five hours after admission. The treating neurologist reported that the events were related to eletriptan. The confusion and involuntary muscle contractions resolved two days later, but mild paresis in the leg continued. Comment: this case is difficult to interpret. A relation to eletriptan is possible for the non-serious AEs of confusion, involuntary muscle contractions, ataxia and hypertension, but unlikely for the SAE of neuropathy.

Case 2002002019

A 54-year-old woman with a history of migraine received a single initial dose of eletriptan 40mg for basilar migraine and experienced arterial thrombosis in the lower limb. This was classified as SAE as hospitalization was required. The treating physician reported that the patient was not on any other medication, was not a smoker, had not had recent forced immobility and was free of any other medical history. In his opinion the event was due to eletriptan. Eletriptan was discontinued and she recovered. Comment: in my opinion, the relation to eletriptan is possible.

The Sponsor states that no new safety concerns have emerged since the resubmission of the NDA and that the conclusions regarding the safety of eletriptan expressed in the NDA are supported by this Safety Update. I concur with that assessment, but I recommend to monitor for the occurrence of other cases of arterial thrombosis.

2.6.3.5 Coronarography studies

2.6.3.5.1 Study A160-1072

2.6.3.5.1.1 Study protocol

Study A160-1072 was a placebo-controlled, double-blind, parallel group study to determine the effect of escalating plasma concentrations of iv eletriptan on coronary vascular responsiveness, as measured by quantitative coronary angiography (QCA), and to compare it with therapeutic doses of sc sumatriptan (6 mg) and iv and sc placebo. Subjects scheduled for diagnostic coronary angiography were invited to participate in the study. On the day of the angiographic procedure, subjects with no evidence of $\geq 20\%$ stenosis or other multiple luminal irregularities that the investigator considered abnormal were randomized to study drug. Subjects received study drug as a 40 minutes iv infusion and a single sc injection (double dummy). The sponsor planned to study 60 subjects, with a 1:1:1 randomization to placebo/placebo, eletriptan/placebo, and placebo/sumatriptan (iv/sc). Unblinded third parties prepared the sc and iv doses and provided them to investigators, blinded with respect to study drug allocation. Angiography times during infusion of study drug (5, 15 and 40 minutes) were selected to correspond to the expected C_{max} of the 20, 40 and 80 mg oral dose of eletriptan in the presence of a potent CYP3A4 inhibitor (114, 264 and 564ng/ml, respectively). An additional QCA was performed 10 minutes after discontinuation of the iv infusion (50 minutes timepoint). Two coronary arteries were evaluated: the mid-left anterior descending artery (LAD), and the posterior circumflex artery (PCA). The protocol permitted investigators to examine other coronary artery areas if they considered there was a clinical reason to do so. An independent laboratory, blind with respect to study drug allocation, analyzed up to three consecutive images to calculate the mean segment diameter (MSD) at each timepoint.

The Sponsor used a two-step infusion (higher infusion rate in the last 20 minutes) to achieve target drug levels at the appropriate timing (5, 15 and 40 minutes). The Sponsor replaced subjects who had a plasma eletriptan concentration $< 299\text{ng/ml}$ at 40 minutes post-start of infusion. Eletriptan infusion rate was based on results of Study A1601045. In that study, the mean C_{max} for oral eletriptan 80mg in the presence of ketoconazole was 491ng/ml, 2.7 fold higher than that obtained with oral eletriptan 80mg alone. The Sponsor chose to assume a three-fold difference and selected a target concentration of 564ng/ml. COMMENT: the Sponsor also predicted C_{max} for eletriptan administered during a migraine attack (lower eletriptan bioavailability). The sponsor calculated that, in the presence of a potent CYP3A4 inhibitor and during a migraine attack, eletriptan C_{max} after one 80mg tablet would be 330 ng/ml, and that eletriptan C_{max} after two 80mg tablets separated by two hours attack would be 598ng/ml. In a public health perspective, the actual measurements done in Study A1601045 are more relevant, since a number of patients are expected to take eletriptan outside of migraine attacks.

Safety assessments included monitoring of adverse events, heart rate, femoral artery and aortic blood pressure, and ECG at various timepoints during the study.

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The Sponsor defined a series of study populations. The main population used for data analysis was the “modified ITT (MITT) population”, defined as subjects who had baseline and any on treatment data and who also had a plasma eletriptan concentration above 299ng/ml at the last planned QCA.

The primary parameter was the difference between the logs of the minimum post-baseline mean segment diameter (MSD) and the baseline MSD at the mid-LAD coronary artery region. The primary analysis was to produce a 95% confidence interval (CI) for the difference between the means for the eletriptan and sumatriptan groups and anti-log the CI limit to permit comparison with the allowed margin of inferiority. For each subject, the Sponsor analyzed the log of the ratio of minimum MSD post-baseline divided by the MSD at baseline:

$$\text{Log} \left(\frac{\text{Minimum MSD}}{\text{MSD at baseline}} \right)$$

The difference between the means for the response to study drug for this variable when anti-logged produced the ratio of the geometric means:

$$\frac{\text{Eletriptan geometric mean} \left(\frac{\text{Minimum MSD}}{\text{MSD at baseline}} \right)}{\text{Sumatriptan geometric mean} \left(\frac{\text{Minimum MSD}}{\text{MSD at baseline}} \right)}$$

The Sponsor defined the allowable margin of inferiority as the following ratio:

$$\frac{\text{Minimum post-baseline MSD/Baseline MSD for eletriptan}}{\text{Minimum post-baseline MSD/Baseline MSD for sumatriptan}} \geq 0.9$$

The Sponsor repeated the analysis for the proximal circumflex coronary artery region.

The Sponsor also calculated, for the mid-LAD and proximal circumflex regions, the 95% CIs for the difference between eletriptan MSD ratio at 5, 15 and 40 minutes post-start of infusion and 10 minutes post-end of infusion divided by baseline MSD and the mean the sumatriptan minimum MSD divided by baseline sumatriptan MSD, using the same log/antilog algorithm. The protocol stated that the secondary analyses of eletriptan iv would be comparisons against sumatriptan 6mg sc results at the observed maximum concentration which was assumed to coincide with the minimum MSD. In the Sponsor analysis however, comparisons were made against the minimum MSD after sumatriptan 6mg sc irrespective of concentration. Comment: Importantly, this was a post-hoc protocol change. The data for these comparisons were corrected for the placebo effect, which is also a post-hoc change. This correction was a subtraction of the mean placebo logged ratio at the corresponding time-point from each data value.

2.6.3.5.1.2 Study results (from the Sponsor’s analysis, with reviewer’s comments)

Demographics

Of 162 subjects screened, 60 were randomized, had study drug and were analyzed for safety. Of the 24 subjects randomized to eletriptan, 23 (96%), completed the study and 1 (4%) discontinued. All 18 subjects randomized to sumatriptan and all 18 subjects randomized to placebo completed the study. The demographic characteristics were similar between the groups. Four subjects had a history of migraine.

Concomitant medications

Among concomitant populations taken prior to study drug and during the study (Table 17), many subjects received antihypertensives, β blockers and vasodilators, which may have confounded the coronary arteries response to the study drug.

Table 17: Confounding concomitant drugs

	Prior to study	During study
Antihypertensives*	15	18
β blockers	33	35
Nitrates	22	29

* Ace inhibitor, Alpha-adrenoceptor blocking drugs, Diuretics, Calcium-channel blockers, Angiotensin II receptor antagonists

Table 18 summarizes concomitant use of nitrates during the study. Six subjects received sublingual or iv nitroglycerin (NTG) up to 29 minutes pre-start of infusion. Five subjects had NTG within one hour post-end of infusion. Eleven subjects had NTG pre-start of infusion. As part of the investigator routine practice (as stated by the Sponsor), 8 subjects had NTG post-end of infusion. Of these, five (Subjects 2, 6, 35, 42 and 50) had reported vasoconstriction (asymptomatic). COMMENT: if this was truly part of routine practice, it is surprising that no patient on placebo and only three subjects of the sumatriptan group received nitrates post-infusion, whereas 10 subjects (41.6%) of the eletriptan group received it. The Sponsor definition of these periods is confusing since within 1 hour post end includes post-end, and up to 29 minutes pre-start includes pre-start. I assumed that pre-start and post-start mean immediately pre-start and post-end, and that the other 2 categories exclude the immediate pre-start and post-end periods. I also analyzed the use of nitrates in the dataset (see Table 32, in the “Reviewer’s analyses” section). This confirmed a higher use of nitrates in subjects randomized to eletriptan.

Table 18: Concomitant use of nitrates during the study

	Eletriptan (n=24)	Sumatriptan (n=18)	Placebo (n=18)
Up to 29 min pre-start	1	1	4
Pre-start	2	4	5
Total Pre-start	3 (12.5%)	5 (27.7%)	9 (50%)
Within 1 h post-end	4	1	0
Post-end	6	3	0
Total Post-start	10 (41.6%)	8 (16.6%)	0 (0%)

Dropouts

There was one single dropout in this study, in a patient randomized to eletriptan. Patient 0050 was a 53 year old African American female who received eletriptan for approximately 25 minutes. During the study procedure, the principal investigator felt that the subject had an approximate 50% increase in narrowing in the LAD, in addition to the baseline 20%. The baseline 20% occlusion was determined to be an anatomical aberration (myocardial bridge) during the QCA core lab analysis. The subject was clinically asymptomatic and had no ECG changes. The subject had a 10-15% increase in blood pressure (BP) during the infusion. The increased narrowing was initially noted after 15 minutes (12:16). After approximately 25 minutes (12:26), an unscheduled QCA was performed because of the narrowing observed at 15 minutes. The subject did not have any symptom or ECG changes at this time. The angiographer estimated that the subject had a 60-70% narrowing of the mid-LAD, and described this as a generalized narrowing. The QCA core laboratory only measured 39% and 17% narrowing in the mid-LAD and proximal circumflex, respectively. The study drug infusion was stopped as a result of the angiographer's estimate and 200mg of intracoronary nitroglycerin was administered at 12:28. The event was considered resolved at 12:31. Interestingly, that patient had a history of headache (migraine, tension, and cluster). The screening physical examination and ECG were unremarkable, and the termination physical examination and ECG showed no change. In the opinion of the investigator the event was moderate in intensity and due to the study drug. COMMENT: Unfortunately, this patient was discontinued before he could receive the full dose of eletriptan, and no QCA was done after discontinuation of eletriptan infusion, so that we have no data on how much additional narrowing may have occurred after discontinuation of eletriptan in this case.

Primary CAD results

Eletriptan met the non-inferiority criterion compared to sumatriptan 6mg (Table 19). The criterion required that the lower limit of the 95% CI was >0.90 for the MITT population.

Table 19: Relative effect of eletriptan and sumatriptan on CAD in the mid LAD region (from table 5.1.2.1, study 1072 report)

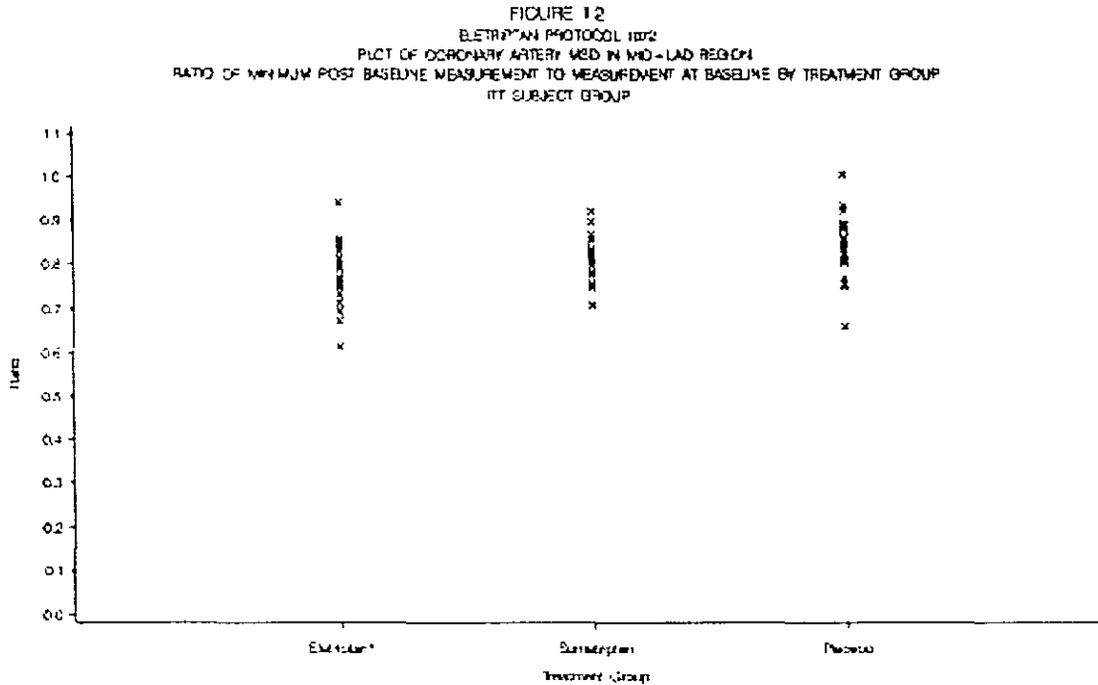
Drug	Pop	Geometric mean CAD ratio ^a	Ratio ^b	95% CI
Eletriptan iv Sumatriptan 6mg sc	ITT	0.78 0.81	0.96	0.91 to 1.02
Eletriptan iv Sumatriptan 6mg sc	EVAL	0.78 0.81	0.97	0.92 to 1.02

Source: Table 5.1.2.1; ^aantilog of the mean log (minimum MSD post-start of infusion/baseline MSD); ^beletriptan iv/sumatriptan 6mg sc; Pop=population.

Figure 1 shows the plot of ratio of minimum/baseline coronary artery MSD in mid LAD region for the three treatment groups.

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Figure 1: Plot of ratio of minimum/baseline coronary artery MSD in mid LAD region (from figure 1.2, page 173, Study 1072 report)



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Proximal circumflex region

For the proximal circumflex region, ele triptan also met the non inferiority criteria compared to sumatriptan 6mg for the MITT population (Table 20).

Table 20: Relative effect of ele triptan and sumatriptan on CAD in the proximal circumflex region (from table 5.2.2.1, Study 1072 report)

Drug	Geometric mean CAD ratio ^a	Ratio ^b	95% CI
Ele triptan iv	0.81	0.97	0.93 to 1.02
Sumatriptan 6mg sc	0.83		

Source: Table 5.2.2.1: ^aantilog of the mean log (minimum MSD post-start of infusion/baseline MSD); ^bele triptan iv/sumatriptan 6mg sc.

Comparisons at individual timepoints

For analysis by time-point for the Mid- Left Anterior Descending artery (LAD) and Proximal Circumflex Regions (PCA), the Sponsor corrected the data for placebo-effect (post-hoc protocol change).

LAD: eletriptan met the non inferiority criteria at each timepoint compared to sumatriptan 6mg at the minimum mean segment diameter (Table 21).

Table 21: Comparisons of the placebo 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 on coronary artery diameter in the mid-LAD

Drug	Time	Mean plasma concentration ng/ml ^a	Geometric mean CAD ratio ^b	Ratio ^c	95% CI
Eletriptan iv	5 mins post-start of infusion	186	0.96	1.00	0.96 to 1.05
Sumatriptan 6mg sc	Minimum MSD	67.9	0.96		
Eletriptan iv	15 mins post-start of infusion	297	0.99	1.02	0.98 to 1.07
Sumatriptan 6mg sc	Minimum MSD	67.9	0.96		
Eletriptan iv	40 mins post-start of infusion	660	0.95	0.98	0.93 to 1.04
Sumatriptan 6mg sc	Minimum MSD	67.9	0.96		
Eletriptan iv	10 mins post-infusion end	281	0.95	0.98	0.94 to 1.03
Sumatriptan 6mg sc	Minimum MSD	67.9	0.96		

Source: Tables 5.3.2 and 5.5. ^aMean peak plasma sumatriptan concentration at 15 minutes post-start of infusion, ^bthe ratio of the geometric means eletriptan iv/sumatriptan 6mg sc; ^cantilog of the mean log (minimum MSD post-start of infusion/baseline MSD).

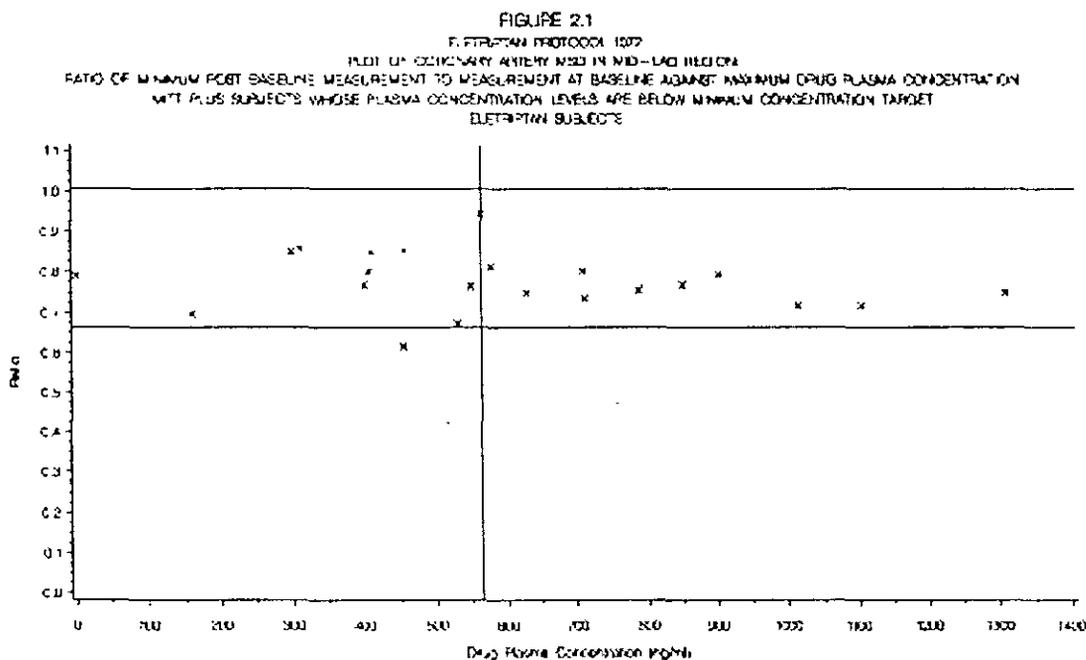
PCA: eletriptan also met the non inferiority criteria criteria at each timepoint compared to sumatriptan 6mg at the minimum mean segment diameter

Eletriptan PK/PD

Eleven subjects did not achieve the target plasma concentration of 564ng/ml and were excluded in the non-inferiority analysis. An additional two subjects had unknown concentrations at 40 minutes. This leaves only 11 subjects eligible for non-inferiority analysis, which raises questions about assay sensitivity for that very small population.

Figure 2 shows the plot of the ratio of minimum post-baseline measurement to measurement at baseline against maximum drug plasma concentration. The horizontal lines represent the range of ratio alues observed in the placebo group. The vertical line in the middle of the graph (originating just right from the “550 tick mark”) represents the target eletriptan peak concentration.

Figure 2: Plot of coronary artery mean segment diameter in MID-LAD region: ratio of minimum post-baseline measurement to measurement at baseline against maximum drug plasma concentration for all subjects with known eletriptan level at that timepoint (from figure 2.1, Study 1072 report)



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 Note: Horizontal reference lines are minimum and maximum of minimum post-baseline ratios for the Placebo Group
 Source: Section 11 Item 7, Table 4.1 & Section 13, Tables 11 and 12

The Sponsor states that all mean segment diameter reductions in eletriptan subjects were within the range of physiological variability (no definition provided) and that all except one reduction (Subject 50 at the mid-LAD region) was within the range of corresponding placebo results. The Sponsor contends that the higher reduction for Subject 50 was artifactual and due to an anatomical aberration. Comment: in support of that statement is the fact that the % reduction in the circumflex region at the same timepoint was within average in that patient. On the other hand, this demonstrates the possibility of eletriptan-induced constriction in subjects with anatomical variations.

Vital signs

In general, aortic diastolic blood pressure, aortic systolic blood pressure, femoral artery diastolic blood pressure and femoral artery systolic blood pressure increased with arterial plasma eletriptan concentration. This was consistent with the known pharmacological effects

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of triptans. There was no clear relationship between arterial plasma sumatriptan concentration and heart rate or arterial and femoral blood pressure for the subjects who received sumatriptan 6mg sc, although some subjects had blood pressure increases.

2.6.3.5.1.3 Reviewer’s analyses

I created a subset from the FDAeff.xpt dataset. From that subset, I defined several subgroups:

Subjects randomized to eletriptan with $C_{max} \geq 564$ ng/ml

This is the subgroup of subjects (n=11) where eletriptan C_{max} was ≥ 564 ng/ml, which is the plasma level expected with a 80mg tablet in the presence of a CYP3A4 inhibitor. The eletriptan plasma target level (564 ng/ml) was met at 40 minutes after baseline in all subjects of this subgroup. All subjects fell below plasma target level by 50 minutes after infusion start (10 minutes after infusion end). However, the maximum level of vasoconstriction was reached at the later timepoint (50 minutes after infusion start) for all but one patient.

The maximum lumen diameter reduction (vasoconstriction) was $\geq 20\%$ for the left anterior descending artery (LAD) territory and for the posterior circumflex artery (PCA) territory respectively in 8 and 4 subjects (Table 22). No patient had $\geq 30\%$ vasoconstriction.

Table 22: Maximum vasoconstriction in subjects with eletriptan $C_{max} \geq 564$ ng/ml

Patient ID	Plasma level	LAD % vasoconstriction (time)	PCA % vasoconstriction (time)
45			
118			
35			
113			
48			
37			
110			
42			
28			
31			
13			
Average	833 ± 234	22.35 ± 6.35	19.52 ± 6.25

Subjects randomized to eletriptan with C_{max} 264-563 ng/ml

This is the subgroup of subjects (n=9) where eletriptan C_{max} reached 264 ng/ml but did not exceed 563 ng/ml. 264 ng/ml is the plasma level expected with a 40 mg tablet in the presence of a CYP3A4 inhibitor. The eletriptan plasma level threshold (264 ng/ml) was met at 40 minutes after baseline in all subjects, except for patient 50 who was discontinued at 25 minutes post-baseline. All subjects fell below the threshold level by the 50 minutes timepoint after infusion start (10 minutes after infusion end).

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The maximum level of vasoconstriction was reached at the 40 minutes timepoint for four subjects, at the 50 minutes timepoint for three subjects and at 25 minutes for patient 50, who was discontinued. Vasoconstriction was $\geq 20\%$ in five subjects for the LAD territory, and in three subjects for the PCA territory. Two subjects had $\geq 30\%$ vasoconstriction in the LAD territory (Table 23).

Table 23: Maximum vasoconstriction in subjects with eletriptan C_{max} 264-563 ng/ml

Patient ID	Plasma level	LAD % vasoconstriction (time)	PCA % vasoconstriction (time)
50			
107			
52			
24			
19			
18			
10			
6			
2			
Average	424.1±85.7	19.1±4.04	18.9±3.8

Subjects randomized to eletriptan with $C_{max} < 264$ ng/ml or not available

This is the subgroup of subjects (n=4) where eletriptan C_{max} was below 264 ng/ml or was not available. Two subjects (101) had $\geq 20\%$ vasoconstriction in the LAD territory, and two subjects had $\geq 20\%$ vasoconstriction in the PCA territory. One patient (101) exceeded 30% constriction in the LAD territory, despite a low eletriptan plasma level.

Table 24: Maximum vasoconstriction in subjects with eletriptan $C_{max} < 264$ ng/ml or unknown C_{max}

Patient ID	Plasma level	LAD % vasoconstriction (time)	PCA % vasoconstriction (time)
8			
25			
101			
104			
Average		21±5.83	19.9±8.1