

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

21-016

ADMINISTRATIVE DOCUMENTS

14. PATENT CERTIFICATION

With respect to the drug, RELPAX™, which is the subject of this Application (NDA-21,016) and the U.S. patent(s) which are listed in Section 13 of this New Drug Application, Pfizer certifies that the drug, RELPAX™, and formulations and uses thereof are claimed by U.S. Patent No. 5,545,644.

Item 13

PATENT INFORMATION

[21 U.S.C. 355 (b) or (c)]

RELPATMX Tablets (NDA 21-016)

Cross-reference - see attachment to cover letter of original NDA 21-016 submission dated October 27, 1998

Item 14

PATENT CERTIFICATION
[21 U.S.C. 355 (b) (2) or (j) (2) (A)]

RELPATMX Tablets (NDA 21-016)

Cross-reference - see attachment to cover letter of original NDA 21-016 submission dated October 27, 1998

13. PATENT AND EXCLUSIVITY INFORMATION FOR ELETRIPTAN

1.	Active Ingredient:	(R)-3-(1-methyl-2-pyrrolidinylmethyl)-5-[2-(phenylsulfonyl)ethyl]-1 <i>H</i> -indole hydrobromide
2.	Strengths:	20 mg, 40 mg, 80 mg
3.	Trade Name:	RELPAK
4.	Dosage Form/Route of Administration:	Capsules / Oral
5.	Applicant Firm Name:	Pfizer Inc.
6.	NDA Number:	21-016
7.	Exclusivity Period:	
8.	Applicable Patent Numbers and Expiration Dates:	5,545,644 August 13, 2013

NDA: 21-016
Trade Name: Relpax Tablet
Generic Name: eletriptan benzoate
Applicant Name: Pfizer
Division: HFD-120
Project Manager: Lana Y. Chen, R.Ph.
Approval Date:

PART I

IS AN EXCLUSIVITY DETERMINATION NEEDED?

1. An exclusivity determination will be made for all original applications, but only for certain supplements. Complete Parts II and III of this Exclusivity Summary only if you answer "yes" to one or more of the following questions about the submission.

a. Is it an original NDA? Yes

b. Is it an effectiveness supplement? No
If yes, what type? (SE1, SE2, etc.)

c. Did it require the review of clinical data other than to support a safety claim or change in labeling related to safety? (If it required review only of bioavailability or bioequivalence data, answer "no.") Yes

If your answer is "no" because you believe the study is a bioavailability study and, therefore, not eligible for exclusivity, EXPLAIN why it is a bioavailability study, including your reasons for disagreeing with any arguments made by the applicant that the study was not simply a bioavailability study. N/A

If it is a supplement requiring the review of clinical data but it is not an effectiveness supplement, describe the change or claim that is supported by the clinical data: N/A

d. Did the applicant request exclusivity? Yes
If the answer "yes," how many years of exclusivity did the applicant request? 5yrs,
6mo

IF YOU HAVE ANSWERED "NO" TO ALL OF THE ABOVE QUESTIONS, GO DIRECTLY TO THE SIGNATURE BLOCKS.

2. Has a product with the same active ingredient(s), dosage form, strength, route of administration, and dosing schedule previously been approved by FDA for the same use? No

If yes, what is NDA number

If yes, what is Drug Name

IF THE ANSWER TO QUESTION 2 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS.

3. Is this drug product or indication a DESI upgrade? No

IF THE ANSWER TO QUESTION 3 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS (even if a study was required for the upgrade).

APPEARS THIS WAY
ON ORIGINAL

APPEARS THIS WAY
ON ORIGINAL

PART II

FIVE-YEAR EXCLUSIVITY FOR NEW CHEMICAL ENTITIES

(Answer either #1 or #2, as appropriate)

1. Single active ingredient product.

No

Has FDA previously approved under section 505 of the Act any drug product containing the same active moiety as the drug under consideration? Answer "yes" if the active moiety (including other esterified forms, salts, complexes, chelates or clathrates) has been previously approved, but this particular form of the active moiety, e.g., this particular ester or salt (including salts with hydrogen or coordination bonding) or other non-covalent derivative (such as a complex, chelate, or clathrate) has not been approved. Answer "no" if the compound requires metabolic conversion (other than deesterification of an esterified form of the drug) to produce an already approved active moiety.

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

2. Combination product.

N/A

If the product contains more than one active moiety (as defined in Part II, #1), has FDA previously approved an application under section 505 containing any one of the active moieties in the drug product? If, for example, the combination contains one never-before-approved active moiety and one previously approved active moiety, answer "yes." (An active moiety that is marketed under an OTC monograph, but that was never approved under an NDA, is considered not previously approved.)

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

IF THE ANSWER TO QUESTION 1 OR 2 UNDER PART II IS "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS. IF "YES," GO TO PART III.

PART III

THREE-YEAR EXCLUSIVITY FOR NDA'S AND SUPPLEMENTS

To qualify for three years of exclusivity, an application or supplement must contain "reports of new clinical investigations (other than bioavailability studies) essential to the approval of the application and conducted or sponsored by the applicant." This section should be completed only if the answer to PART II, Question 1 or 2, was "yes."

1. Does the application contain reports of clinical investigations? (The Agency interprets "clinical investigations" to mean investigations conducted on humans other than bioavailability studies.) If the application contains clinical investigations only by virtue of a right of reference to clinical investigations in another application, answer "yes," then skip to question 3(a). If the answer to 3(a) is "yes" for any investigation referred to in another application, do not complete remainder of summary for that investigation.

IF "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS.

2. A clinical investigation is "essential to the approval" if the Agency could not have approved the application or supplement without relying on that investigation. Thus, the investigation is not essential to the approval if 1) no clinical investigation is necessary to support the supplement or application in light of previously approved applications (i.e., information other than clinical trials, such as bioavailability data, would be sufficient to provide a basis for approval as an ANDA or 505(b)(2) application because of what is already known about a previously approved product), or 2) there are published reports of studies (other than those conducted or sponsored by the applicant) or other publicly available data that independently would have been sufficient to support approval of the application, without reference to the clinical investigation submitted in the application.

For the purposes of this section, studies comparing two products with the same ingredient(s) are considered to be bioavailability studies.

- a. In light of previously approved applications, is a clinical investigation (either conducted by the applicant or available from some other source, including the published literature) necessary to support approval of the application or supplement?

If "no," state the basis for your conclusion that a clinical trial is not necessary for approval **AND GO DIRECTLY TO SIGNATURE BLOCKS.**

- b. Did the applicant submit a list of published studies relevant to the safety and effectiveness of this drug product and a statement that the publicly available data would not independently support approval of the application?

If the answer to 2(b) is "yes," do you personally know of any reason to disagree with the applicant's conclusion? If not applicable, answer NO.

- 1) If yes, explain:
- 2) If the answer to 2(b) is "no," are you aware of published studies not conducted or sponsored by the applicant or other publicly available data that could independently demonstrate the safety and effectiveness of this drug product?

If yes, explain:

If the answers to (b)(1) and (b)(2) were both "no," identify the clinical investigations submitted in the application that are essential to the approval:

Investigation #1, Study #:

Investigation #2, Study #:

Investigation #3, Study #:

3. In addition to being essential, investigations must be "new" to support exclusivity. The agency interprets "new clinical investigation" to mean an investigation that 1) has not been relied on by the agency to demonstrate the effectiveness of a previously approved drug for any indication and 2) does not duplicate the results of another investigation that was relied on by the agency to demonstrate the effectiveness of a previously approved drug product, i.e., does not redemonstrate something the agency considers to have been demonstrated in an already approved application.

- a. For each investigation identified as "essential to the approval," has the investigation been relied on by the agency to demonstrate the effectiveness of a previously approved drug product? (If the investigation was relied on only to support the safety of a previously approved drug, answer "no.")

Investigation #1

Investigation #2

Investigation #3

If you have answered "yes" for one or more investigations, identify each such investigation and the NDA in which each was relied upon:

NDA: Study:

NDA: Study:

NDA: Study:

- b. For each investigation identified as "essential to the approval," does the investigation duplicate the results of another investigation that was relied on by the agency to support the effectiveness of a previously approved drug product?

Investigation #1

Investigation #2

Investigation #3

If you have answered "yes" for one or more investigations, identify the NDA in which a similar investigation was relied on:

NDA: Study:

NDA: Study:

Investigation #3

Explain:

Notwithstanding an answer of "yes" to (a) or (b), are there other reasons to believe that the applicant should not be credited with having "conducted or sponsored" the study? (Purchased studies may not be used as the basis for exclusivity. However, if all rights to the drug are purchased (not just studies on the drug), the applicant may be considered to have sponsored or conducted the studies sponsored or conducted by its predecessor in interest.)

If yes, explain:

/S/

Lana Y. Chen, R.Ph.
Project Manager
DNDP, HFD-120

/S/

Russell Katz, M.D.
Acting Director
DNDP, HFD-120

c:\wpfiles\leletrip.nda\exclusv1.sum

Final: July 27, 1999

cc:

Original NDA
Division File
HFD-120/Chen
HFD-85/Holovac

EXCLUSIVITY SUMMARY for NDA # 21-016 SUPPL # _____

Trade Name Relpax Generic Name eletriptan

Applicant Name Pfizer HFD- 120

Approval Date _____

PART I: IS AN EXCLUSIVITY DETERMINATION NEEDED?

1. An exclusivity determination will be made for all original applications, but only for certain supplements. Complete Parts II and III of this Exclusivity Summary only if you answer "YES" to one or more of the following questions about the submission.

a) Is it an original NDA? YES/ x / NO / ___ /

b) Is it an effectiveness supplement? YES / ___ / NO / x /

If yes, what type(SE1, SE2, etc.)? _____

c) Did it require the review of clinical data other than to support a safety claim or change in labeling related to safety? (If it required review only of bioavailability or bioequivalence data, answer "NO.")

YES / x / NO / ___ /

If your answer is "no" because you believe the study is a bioavailability study and, therefore, not eligible for exclusivity, EXPLAIN why it is a bioavailability study, including your reasons for disagreeing with any arguments made by the applicant that the study was not simply a bioavailability study.

If it is a supplement requiring the review of clinical data but it is not an effectiveness supplement, describe the change or claim that is supported by the clinical data:

d) Did the applicant request exclusivity?

YES / ___ / NO / x /

If the answer to (d) is "yes," how many years of exclusivity did the applicant request?

e) Has pediatric exclusivity been granted for this Active Moiety?

YES / ___ / NO / x /

IF YOU HAVE ANSWERED "NO" TO ALL OF THE ABOVE QUESTIONS, GO DIRECTLY TO THE SIGNATURE BLOCKS ON Page 9.

2. Has a product with the same active ingredient(s), dosage form, strength, route of administration, and dosing schedule previously been approved by FDA for the same use? (Rx to OTC Switches should be answered No - Please indicate as such).

YES / ___ / NO / x /

If yes, NDA # _____ Drug Name _____

IF THE ANSWER TO QUESTION 2 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON Page 9.

3. Is this drug product or indication a DESI upgrade?

YES / ___ / NO / x /

IF THE ANSWER TO QUESTION 3 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON Page 9 (even if a study was required for the upgrade).

PART II: FIVE-YEAR EXCLUSIVITY FOR NEW CHEMICAL ENTITIES

(Answer either #1 or #2, as appropriate)

1. Single active ingredient product.

Has FDA previously approved under section 505 of the Act any drug product containing the same active moiety as the drug under consideration? Answer "yes" if the active moiety (including other esterified forms, salts, complexes, chelates or clathrates) has been previously approved, but this particular form of the active moiety, e.g., this particular ester or salt (including salts with hydrogen or coordination bonding) or other non-covalent derivative (such as a complex, chelate, or clathrate) has not been approved. Answer "no" if the compound requires metabolic conversion (other than deesterification of an esterified form of the drug) to produce an already approved active moiety.

YES / / NO / /

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA # _____
NDA # _____
NDA # _____

2. Combination product.

If the product contains more than one active moiety (as defined in Part II, #1), has FDA previously approved an application under section 505 containing any one of the active moieties in the drug product? If, for example, the combination contains one never-before-approved active moiety and one previously approved active moiety, answer "yes." (An active moiety that is marketed under an OTC monograph, but that was never approved under an NDA, is considered not previously approved.)

YES / / NO / /

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA # _____
NDA # _____
NDA # _____

IF THE ANSWER TO QUESTION 1 OR 2 UNDER PART II IS "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON Page 9. IF "YES," GO TO PART III.

PART III: THREE-YEAR EXCLUSIVITY FOR NDA'S AND SUPPLEMENTS

To qualify for three years of exclusivity, an application or supplement must contain "reports of new clinical investigations (other than bioavailability studies) essential to the approval of the application and conducted or sponsored by the applicant." This section should be completed only if the answer to PART II, Question 1 or 2, was "yes."

1. Does the application contain reports of clinical investigations? (The Agency interprets "clinical investigations" to mean investigations conducted on humans other than bioavailability studies.) If the application contains clinical investigations only by virtue of a right of reference to clinical investigations in another application, answer "yes," then skip to question 3(a). If the answer to 3(a) is "yes" for any investigation referred to in another application, do not complete remainder of summary for that investigation.

YES /___/ NO /___/

IF "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON Page 9.

2. A clinical investigation is "essential to the approval" if the Agency could not have approved the application or supplement without relying on that investigation. Thus, the investigation is not essential to the approval if 1) no clinical investigation is necessary to support the supplement or application in light of previously approved applications (i.e., information other than clinical trials, such as bioavailability data, would be sufficient to provide a basis

for approval as an ANDA or 505(b)(2) application because of what is already known about a previously approved product), or 2) there are published reports of studies (other than those conducted or sponsored by the applicant) or other publicly available data that independently would have been sufficient to support approval of the application, without reference to the clinical investigation submitted in the application.

For the purposes of this section, studies comparing two products with the same ingredient(s) are considered to be bioavailability studies.

- (a) In light of previously approved applications, is a clinical investigation (either conducted by the applicant or available from some other source, including the published literature) necessary to support approval of the application or supplement?

YES /___/ NO /___/

If "no," state the basis for your conclusion that a clinical trial is not necessary for approval **AND GO DIRECTLY TO SIGNATURE BLOCK ON Page 9:**

- (b) Did the applicant submit a list of published studies relevant to the safety and effectiveness of this drug product and a statement that the publicly available data would not independently support approval of the application?

YES /___/ NO /___/

- (1) If the answer to 2(b) is "yes," do you personally know of any reason to disagree with the applicant's conclusion? If not applicable, answer NO.

YES /___/ NO /___/

If yes, explain: _____

(2) If the answer to 2(b) is "no," are you aware of published studies not conducted or sponsored by the applicant or other publicly available data that could independently demonstrate the safety and effectiveness of this drug product?

YES /___/ NO /___/

If yes, explain: _____

(c) If the answers to (b)(1) and (b)(2) were both "no," identify the clinical investigations submitted in the application that are essential to the approval:

Investigation #1, Study # _____

Investigation #2, Study # _____

Investigation #3, Study # _____

3. In addition to being essential, investigations must be "new" to support exclusivity. The agency interprets "new clinical investigation" to mean an investigation that 1) has not been relied on by the agency to demonstrate the effectiveness of a previously approved drug for any indication and 2) does not duplicate the results of another investigation that was relied on by the agency to demonstrate the effectiveness of a previously approved drug product, i.e., does not redemonstrate something the agency considers to have been demonstrated in an already approved application.

(a) For each investigation identified as "essential to the approval," has the investigation been relied on by the agency to demonstrate the effectiveness of a previously approved drug product? (If the investigation was relied on only to support the safety of a previously approved drug, answer "no.")

Investigation #1 YES /___/ NO /___/

Investigation #2 YES /___/ NO /___/

Investigation #3 YES /___/ NO /___/

If you have answered "yes" for one or more investigations, identify each such investigation and the NDA in which each was relied upon:

NDA # _____ Study # _____
 NDA # _____ Study # _____
 NDA # _____ Study # _____

(b) For each investigation identified as "essential to the approval," does the investigation duplicate the results of another investigation that was relied on by the agency to support the effectiveness of a previously approved drug product?

Investigation #1 YES /___/ NO /___/
 Investigation #2 YES /___/ NO /___/
 Investigation #3 YES /___/ NO /___/

If you have answered "yes" for one or more investigations, identify the NDA in which a similar investigation was relied on:

NDA # _____ Study # _____
 NDA # _____ Study # _____
 NDA # _____ Study # _____

(c) If the answers to 3(a) and 3(b) are no, identify each "new" investigation in the application or supplement that is essential to the approval (i.e., the investigations listed in #2(c), less any that are not "new"):

Investigation #__, Study # _____
 Investigation #__, Study # _____
 Investigation #__, Study # _____

4. To be eligible for exclusivity, a new investigation that is essential to approval must also have been conducted or sponsored by the applicant. An investigation was "conducted or sponsored by" the applicant if, before or during the conduct of the investigation, 1) the applicant was the sponsor of the IND named in the form FDA 1571 filed with the Agency, or 2) the applicant (or its predecessor in interest) provided substantial support for the study. Ordinarily, substantial support will mean providing 50 percent or more of the cost of the study.

(a) For each investigation identified in response to question 3(c): if the investigation was carried out under an IND, was the applicant identified on the FDA 1571 as the sponsor?

Investigation #1 !
IND # _____ YES /___/ ! NO /___/ Explain: _____
! _____
! _____
!

Investigation #2 !
IND # _____ YES /___/ ! NO /___/ Explain: _____
! _____
! _____
!

(b) For each investigation not carried out under an IND or for which the applicant was not identified as the sponsor, did the applicant certify that it or the applicant's predecessor in interest provided substantial support for the study?

Investigation #1 !
YES /___/ Explain _____ ! NO /___/ Explain _____
! _____
! _____
!

Investigation #2 !
YES /___/ Explain _____ ! NO /___/ Explain _____
! _____
! _____
!

Item 16

DEBARMENT CERTIFICATION

[FD&C Act 306(k)(1)]

RELPAX™ Tablets (NDA 21-016)

Pfizer hereby certifies that it did not and will not use in any capacity the services of any person debarred under section 306 of the Federal Food, Drug, and Cosmetic Act in connection with this application.



Signature of Company Representative

6/3/02

Date

DEBARMENT STATEMENT

In accordance with the requirement of the Generic Drug Enforcement Act of 1992, and in connection with this application, Pfizer Inc did not use in any capacity the services of any person debarred under Section 306 of the Federal Food, Drug and Cosmetic Act.

8.1. Compliance Statement

The New Drug Application supports the approval of eletriptan hydrobromide for the acute treatment of migraine with or without aura in adults with the following clinical study reports:

<u>TYPE OF STUDY</u>	<u>PROTOCOL NUMBER</u>
ACUTE MIGRAINE (With or Without Aura)	
Double-Blind, Placebo Controlled, Single Attack (non-U.S.)	307, 314
Double-Blind, Placebo Controlled, Multiple Attack (U.S.)	102, 104
Double-Blind, Placebo Controlled, Multiple Attack (non-U.S.)	305, 318
SUPPORTIVE STUDIES	
Double-Blind, Placebo Controlled, Multiple Attack (U.S.)	103
OTHER CLINICAL STUDIES (U.S.)	
An Open-Label Single Dose	101
Double-Blind Placebo Controlled Adolescent	105
Ongoing Open-Label, Comparative - Long Term Treatment (U.S.)	108
OTHER CLINICAL STUDIES (non-U.S.)	
Double-Blind Placebo Controlled Single Dose	301
Double-Blind Placebo Controlled Single Dose	303
Double-Blind, Placebo Controlled, Single Attack (non-U.S.)	302
Double-Blind, Placebo Controlled During Aura Phase (non-U.S.)	306
Ongoing Double-Blind, Double Dummy (non-U.S.)	316
Ongoing Open Label Comparative - Long Term Treatment(non-U.S.)	317
Extension Studies (non-U.S.)	302A, 302C
CLINICAL PHARMACOLOGY STUDIES (U.S.)	001, 002, 003, 004
CLINICAL PHARMACOLOGY STUDIES (non-U.S.)	201, 202/202A, 203, 204, 205, 207, 208, 211, 212, 213, 214, 215, 216, 220, 222, 224, 225, 226, 227, 228, 229, 299, 230, 231, 232, 701, 701A, 702, 703

To assure that the data generated in the Pfizer-sponsored clinical studies were accurate, complete and reliable and that patient compliance with dosing regimens within these studies was acceptable, the following measures were taken in accord with standard operating procedures:

CONCLUSION

As a result of the above cited activities, the data and conclusions presented in this New Drug Application have been generated through adequate and, as identified well controlled clinical trials. Where deviations from standard procedures or protocol requirements have occurred, they are described and accounted for in both the appropriate study reports and data presentations.

PEDIATRIC PAGE

(Complete for all original application and all efficacy supplements)

NDA/BLA Number:	<u>21016</u>	Trade Name:	<u>RELPAK (ELETRIPTAN HYDROBROMIDE)</u> <u>20/40/80</u>
Supplement Number:		Generic Name:	<u>ELETRIPTAN HYDROBROMIDE</u>
Supplement Type:		Dosage Form:	<u>Tablet; Oral</u>
Regulatory Action:	<u>AE</u>	Proposed Indication:	<u>Treatment of Acute Migraine</u>

ARE THERE PEDIATRIC STUDIES IN THIS SUBMISSION?

YES, Pediatric data exists for at least one proposed indication, but is inadequate to support pediatric approval

What are the INTENDED Pediatric Age Groups for this submission?

NeoNates (0-30 Days) Children (25 Months-12 years)
 Infants (1-24 Months) Adolescents (13-16 Years)

Label Adequacy Adequate for ALL pediatric age groups
Formulation Status
Studies Needed
Study Status

Are there any Pediatric Phase 4 Commitments in the Action Letter for the Original Submission? NO

COMMENTS:

This Page was completed based on information from a PROJECT MANAGER/CONSUMER SAFETY OFFICER,
 LANA CHEN

/s/
 Signature

7/27/99
 Date

Add New Pediatric Information to this Submission

User Information

Preparer	LANA CHEN
Title	PROJECT MANAGER/CONSUMER SAFETY OFFICER
Division	HFD-120

Application Information

Application Number	021016
Application Clock Date	1998-10-27 00:00:00
Application Type	N
Applicant Sponsor	PFIZER
Drug Trade Name	RELPAK (ELETRIPTAN HYDROBROMIDE)20/40/80
Drug Generic Name	ELETRIPTAN HYDROBROMIDE
(leave Supplement Type, Number and Date blank, ON you are entering an original application)	
Supplement Type	
Supplement Number	
Supplement Date	
Proposed Indication(s)	Treatment of Acute Migraine
Has Proposed Indication been Approved?	<input type="checkbox"/> Check for YES
Adequacy of proposed label for Pediatric Dosing	Adequate for ALL pediatric age groups <input checked="" type="checkbox"/>
Regulatory Action	Approvable <input checked="" type="checkbox"/>
Is there a Pediatric Phase 4 Commitment in the Action Letter for the Original Submission?	<input type="checkbox"/> Check if YES
Comments & Recommendations (please date)	
Is there Pediatric Studies in this Submission? Select One	<input checked="" type="radio"/> YES, Pediatric data exists for at least one proposed indi which supports pediatric approval <input type="radio"/> YES, Pediatric data exists for at least one proposed indi but is inadequate to support pediatric approval <input type="radio"/> NO, no data was submitted for this indication, however, ongoing studies exist for pediatric patients <input type="radio"/> NO, Pediatric Studies are not necessary because of pedi <input type="radio"/> NO, No waiver and no pediatric data

<input type="button" value="Continue"/>	<input type="button" value="Clear"/>
---	--------------------------------------

PEDIATRIC PAGE

(Complete for all APPROVED original applications and efficacy supplements)

A/BLA #: 21-016 Supplement Type (e.g. SE5): _____ Supplement Number: _____

Stamp Date: _____ Action Date: _____

HFD -120 Trade and generic names/dosage form: Relpax (eletriptan) Tablets

Applicant: Pfizer Therapeutic Class: Migraine

Indication(s) previously approved: _____

Each approved indication must have pediatric studies: Completed, Deferred, and/or Waived.

Number of indications for this application(s): 1

Indication #1: Migraine

Is there a full waiver for this indication (check one)?

- Yes: Please proceed to Section A.
- No: Please check all that apply: Partial Waiver Deferred Completed
- NOTE: More than one may apply
- Please proceed to Section B, Section C, and/or Section D and complete as necessary.

Section A: Fully Waived Studies

Reason(s) for full waiver:

- Products in this class for this indication have been studied/labeled for pediatric population
- Disease condition does not exist in children
- Too few children with disease to study
- There are safety concerns
- Other: _____

If studies are fully waived, then pediatric information is complete for this indication. If there is another indication, please see Attachment A. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section B: Partially Waived Studies

Age/weight range being partially waived:

Min _____ kg _____ mo. _____ yr. 0 Tanner Stage _____
Max _____ kg _____ mo. _____ yr. 11 Tanner Stage _____

Reason(s) for partial waiver:

- Products in this class for this indication have been studied/labeled for pediatric population
- Disease condition does not exist in children
- Too few children with disease to study
- There are safety concerns
- Adult studies ready for approval
- Formulation needed
- Other: _____

If studies are deferred, proceed to Section C. If studies are completed, proceed to Section D. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section C: Deferred Studies

Age/weight range being deferred:

Min _____ kg _____ mo. _____ yr. 12 Tanner Stage _____
Max _____ kg _____ mo. _____ yr. 17 Tanner Stage _____

Reason(s) for deferral:

- Products in this class for this indication have been studied/labeled for pediatric population
- Disease/condition does not exist in children
- Too few children with disease to study
- There are safety concerns
- Adult studies ready for approval
- Formulation needed

Other: _____

Date studies are due (mm/dd/yy): 12/31/2005

If studies are completed, proceed to Section D. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section D: Completed Studies

Age/weight range of completed studies:

Min _____ kg _____ mo. _____ yr. _____ Tanner Stage _____
Max _____ kg _____ mo. _____ yr. _____ Tanner Stage _____

Comments:

If there are additional indications, please proceed to Attachment A. Otherwise, this Pediatric Page is complete and should be entered into DFS.

This page was completed by:

{See appended electronic signature page}

Lana Chen, RPh
Regulatory Project Manager

{See appended electronic signature page}

Armando Oliva, MD
Neurology Team Leader

NDA 21-016

Page 3

cc: NDA

HFD-950/ Terrie Crescenzi

HFD-960/ Grace Carmouze

(revised 9-24-02)

FOR QUESTIONS ON COMPLETING THIS FORM CONTACT, PEDIATRIC TEAM, HFD-960
301-594-7337

Attachment A

(This attachment is to be completed for those applications with multiple indications only.)

Indication #2: _____

Is there a full waiver for this indication (check one)?

- Yes: Please proceed to Section A.
- No: Please check all that apply: ___ Partial Waiver ___ Deferred ___ Completed

NOTE: More than one may apply

Please proceed to Section B, Section C, and/or Section D and complete as necessary.

Section A: Fully Waived Studies

Reason(s) for full waiver:

- Products in this class for this indication have been studied/labeled for pediatric population
- Disease/condition does not exist in children
- Too few children with disease to study
- There are safety concerns
- Other: _____

If studies are fully waived, then pediatric information is complete for this indication. If there is another indication, please see Attachment A. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section B: Partially Waived Studies

Age/weight range being partially waived:

Min _____	kg _____	mo. _____	yr. _____	Tanner Stage _____
Max _____	kg _____	mo. _____	yr. _____	Tanner Stage _____

Reason(s) for partial waiver:

- Products in this class for this indication have been studied/labeled for pediatric population
- Disease/condition does not exist in children
- Too few children with disease to study
- There are safety concerns
- Adult studies ready for approval
- Formulation needed
- Other: _____

If studies are deferred, proceed to Section C. If studies are completed, proceed to Section D. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section C: Deferred Studies

Age/weight range being deferred:

Min _____ kg _____ mo. _____ yr. _____ Tanner Stage _____
Max _____ kg _____ mo. _____ yr. _____ Tanner Stage _____

Reason(s) for deferral:

- Products in this class for this indication have been studied/labeled for pediatric population
- Disease/condition does not exist in children
- Too few children with disease to study
- There are safety concerns
- Adult studies ready for approval
- Formulation needed
- Other: _____

Date studies are due (mm/dd/yy): _____

If studies are completed, proceed to Section D. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section D: Completed Studies

Age/weight range of completed studies:

Min _____ kg _____ mo. _____ yr. _____ Tanner Stage _____
Max _____ kg _____ mo. _____ yr. _____ Tanner Stage _____

Comments:

If there are additional indications, please copy the fields above and complete pediatric information as directed. If there are no other indications, this Pediatric Page is complete and should be entered into DFS.

This page was completed by:

{See appended electronic signature page}

Regulatory Project Manager

cc: NDA
HFD-960/ Terrie Crescenzi
(revised 1-18-02)

FOR QUESTIONS ON COMPLETING THIS FORM CONTACT, PEDIATRIC TEAM, HFD-960
594-7337

MEMORANDUM

DATE: December 23, 2002

FROM: Director
Division of Neuropharmacological Drug Products/HFD-120

TO: File, NDA 21-016

SUBJECT: Recommendation for action on NDA 21-016, for the use of eletriptan hydrobromide (Relpax) in the treatment of acute migraine headache

NDA 21-016, for the use of eletriptan hydrobromide (Relpax) in the treatment of acute migraine headache, was submitted by Pfizer on 10/27/98. The application has been the subject of 2 Approvable letters (10/27/99 and 12/1/00). Briefly, eletriptan is metabolized by CYP3A4, and potent inhibitors of this enzyme can increase C_{max} about 3 fold, and AUC about 6 fold. In addition, an early angiography study suggested a dose related increase in coronary artery constriction. Further, studies have established the effectiveness of single doses of 20, 40, and 80 mg of eletriptan, with no important increased benefit of the 80 mg dose compared to the 40 mg dose. Given these facts, the Agency requested, in the second, 12/1/00 Approvable letter, that the sponsor perform a coronary angiography study comparing the effects on coronary vasoconstriction of plasma levels associated with the sponsor's proposed maximum dose (80 mg in the presence of a potent 3A4 inhibitor) to placebo and sumatriptan. At the time of this Approvable letter, the Agency was proposing that potent 3A4 inhibitors be contraindicated, and that the 80 mg dose not be approved, but we wanted reassurance that plasma levels associated with this use would not result in an unacceptable degree and/or frequency of important coronary vasospasm, given that we presumed that such off-label use might occur.

As a result, the sponsor performed Study 1072, in which patients who were undergoing coronary angiography for cardiac symptoms were randomized to a 40 minute infusion of eletriptan, a 6 mg subcutaneous dose of sumatriptan, or placebo. Only patients with no significant coronary artery obstruction were treated in this study. Plasma levels were obtained at 5, 15, 40, and 50 minutes after the start of the infusion. The blinded angiographer also took pictures at these times, which were reviewed by a panel of blinded reviewers. The primary comparisons were to be measurements at the mid Left Anterior Descending artery (LAD) and the proximal circumflex artery (PCA).

The results of this study were submitted by the sponsor on June 27, 2002, and this submission was considered a Complete Response to the 12/1/00 Approvable letter. This response has been reviewed by Dr. Eric Bastings, medical officer (review dated 12/10/02), Dr. Sharon Yan, statistician (review dated 12/20/02), and Dr. Armando Oliva, Neurology Team Leader (memo dated 12/10/02). Both

Drs. Bastings and Oliva recommend that the application be approved, but that the 80 mg tablet not be approved (and that the 80 mg single dose not be recommended in labeling), and that CYP3A4 inhibitors be contraindicated. I will briefly review some relevant findings of Study 1072, and then offer the Division's recommendation for action.

In Study 1072, 24 subjects received eletriptan, 18 received sumatriptan, and 18 received placebo. As it turned out, only 11 eletriptan patients achieved the target plasma level (564 ng/ml) or greater at the end of the infusion. Interestingly, the maximum degree of vasoconstriction in essentially all patients occurred at the 50 minute timepoint, 10 minutes after the end of the eletriptan and placebo infusions, and 50 minutes after the sc injection of sumatriptan. This phenomenon was also noted in the placebo patients.

As Dr. Bastings describes, the primary outcome measure, according to the sponsor's protocol, was to be the difference between the logs of the minimum post-baseline mean segment diameter (MSD) and the baseline MSD at the mid-LAD. The sponsor calculated the Log (minimum MSD/baseline MSD), and then examined the ratio of the geometric means of eletriptan and sumatriptan as follows:

$$\text{Minimum MSD}_{\text{ele}}/\text{Baseline MSD}_{\text{ele}}/\text{Minimum MSD}_{\text{suma}}/\text{Baseline MSD}_{\text{suma}}$$

The sponsor calculated the power of the study to permit a 10% worsening of eletriptan compared to sumatriptan (the lower bound of the 95% CI of the ratio was not to be below 90).

The following tables display the important results for the mid-LAD:

Drug	Geometric Mean Ratio	Ratio	95% CI
Eletriptan	.78		
Sumatriptan	.81	0.96	0.91-1.02

For the ratios of the Geometric Means for eletriptan and sumatriptan, as well as the ratios of these ratios, at the 4 different time-points (corresponding to different plasma levels), I refer the reader to Dr. Yan's review, page 9. These analyses reveal that the Geometric Mean ratios range from .95-.99, and the ratios of the ratios range from 0.98-1.02; the lower limit of the CIs never falls below .98. By these results, the sponsor contends that eletriptan has been demonstrated to be "non-inferior" to sumatriptan.

Dr. Bastings performed several additional analyses, in which he examined constriction in the subset of eletriptan patients who achieved plasma levels associated with an 80 mg dose and a CYP3A4 inhibitor (the target level of 564 ng/ml or above; HD), and those who achieved plasma levels below this (LD).

According to his analyses, the Pbo-HD comparison of the median maximum percent constriction in the LAD was significant ($p=0.01$), but the Pbo-LD comparison was not ($p=0.12$). For the PCA, both comparisons were significant ($p=0.01$ and 0.009 , respectively). For neither artery was the comparison between HD and LD eletriptan arms significant. Further, neither group was significantly different from the sumatriptan group, but there were trends for the degree of constriction to be greater in the HD eletriptan arm than in the sumatriptan arm (in particular for the LAD; see Dr. Bastings' Figures 9 and 10, pages 57 and 58 of his review).

Of additional interest was the finding that the study angiographers reported 8 events of "vasoconstriction" during the angiogram; all 8 were reported in eletriptan-treated patients. No such events were reported for either the sumatriptan or placebo-treated patients. There was little documentation in the record as to what the degree of constriction was felt to be, but it was recorded as mild in 7 cases and moderate in one. The sponsor asserted that the blinded film reviewers examined the same data that the angiographers had (in particular that the blinded reviewers not only examined the protocol specified primary areas of interest, but that they also examined the entire coronary tree visualizable on the films), and that they had reported no important constriction. The sponsor acknowledged, however, that the blinded review panel did not examine the video of the angiogram, as had the angiographers. These 8 cases of reported constriction were not related to plasma level of eletriptan.

In addition, 2 patients experienced events of note, both in the eletriptan-treated group.

The first was a 53 year old black woman in whom the angiographer noted an approximate 50% increase in narrowing of the LAD at 15 minutes. An unscheduled observation was made at 25 minutes because of the 15 minute finding, and the angiographer noted increased constriction. For this reason, the infusion was stopped. The patient was not symptomatic, and there were no EKG changes. The blinded panel noted a 39% narrowing of the LAD. This patient was noted to have a myocardial bridge, in which abnormal myocardial tissue passes over the LAD; this presumably accounted for the patient's 20% constriction at baseline.

A second patient, a 42 year old white man, experienced asymptomatic transient ST elevations in leads II, III, and AVF at 40 minutes; this resolved by about 20 minutes after the end of the infusion.

A total of 9 (38%) of eletriptan patients were treated with nitroglycerin, compared to 4 (22%) of sumatriptan patients and 1 (6%) placebo patient. Of the eight eletriptan-treated patients reported to have had constriction, 5 were treated with nitroglycerin.

COMMENTS

Study 1072 poses a number of challenges in interpretation.

A number of observations raise concern about the possibility that the constrictive effects of eletriptan are greater than those of sumatriptan.

First, the angiographers noted 8 instances of coronary vasoconstriction during the angiogram, all of which were in the eletriptan-treated group. While the likelihood that this would have occurred by chance (if there were truly no difference between the groups) is very low, we do not have good documentation as to what the angiographers saw that was of concern. While the sponsor asserts that the blinded reviewers saw no important constriction in any patient (presumably not just at the mid-LAD and PCA), they acknowledge that these reviewers did not have access to the videos that the angiographers were seeing; the reviewers only examined the still films at 5, 15, 40, and 50 minutes after the start of the infusion.

Further, there was a dose-related (not significant) increase in the degree of constriction in the eletriptan-treated patients, with a numerical trend toward increasing constriction in the HD eletriptan patients compared to sumatriptan ($p=0.09$ for the LAD). With little power to detect a difference (recall that only 11 patients achieved the HD eletriptan), we might not expect this difference to achieve significance.

Finally, the two patients in whom potentially significant events (discontinuation of the infusion, ST elevations) were seen were in eletriptan-treated patients.

On the other hand, the fact that the maximum degree of constriction occurred in almost all cases at 50 minutes (10 minutes after the end of the infusion), in all treatment groups, is perplexing. While this might suggest a lag between the C_{max} and the maximum degree of constriction (indeed, Drs. Bastings and Oliva suggest that this finding might obscure an even greater difference between eletriptan and sumatriptan, because 50 minutes is much longer after the C_{max} of sumatriptan than it is after the C_{max} of eletriptan in this study, and therefore we haven't examined a long enough lag-time for the eletriptan), the fact that this occurred in the placebo group as well makes this less likely, in my view, although it does not rule it out.

Further, the fact that the reported cases of constriction show absolutely no relation to exposure also suggests that we need not worry about high levels of exposure to eletriptan.

The primary questions, I believe, relate to two related labeling issues: the doses that should be recommended in labeling, and whether or not the use of inhibitors of CYP3A4 should be contraindicated.

Recall that the second Approvable letter asked for the angiography study to examine plasma levels associated with high doses in the inhibited state because, even though we believed the high dose should not be approved, and that inhibitors should be contraindicated, we believed that such use might occur, and we were concerned that such use might be unacceptably unsafe.

The sponsor has proposed that inhibitors not be contraindicated, and that the maximum recommended dose be 80 mg, followed 2 hours later by another 80 mg, if necessary.

While I do not know how to interpret the 8 cases of angiographer-reported constriction (and the lack of exposure response), it seems that there is somewhat of an exposure response for constriction in the eletriptan-treated patients (this is not particularly unexpected). However, it should be noted that the actual degrees of constriction seen in Study 1072 are relatively small, and are of uncertain clinical meaning. I do believe that these results ought not to be over-interpreted. That is, I do not know what to conclude about any "quantitative" relationship between exposure and degree of constriction seen in this study, and what this may mean clinically. I believe the study suggests that increasing exposure may result in increasing constriction, and that this may, in some susceptible people, result in a serious adverse clinical event. I do not believe we can say anything meaningful about what the degrees of constriction actually observed in Study 1072 mean clinically; constriction of this degree may never result in an adverse clinical event. I believe that the study is best interpreted "qualitatively"; that is, as stated above, we can reasonably conclude that, in some patients, greater degrees of constriction than seen here may occur, more likely at higher exposures (doses), and that these events may be clinically significant.

As Dr. Bastings notes, in this regard, migraine is a "benign" condition, and there is no reason to expose patients to doses that may be associated with serious clinical events if there is no additional benefit. In this case, an 80 mg dose has not been shown to be superior to a 40 mg dose, and it seems prudent to minimize the risk of serious events by minimizing the exposure to levels not necessary for effectiveness.

Given these considerations, it seems prudent to restrict the availability to the 20 and 40 mg tablets; there seems to be no necessity to make the 80 mg tablet available.

An important goal of Study 1072 was to compare the vasoconstrictive effects of eletriptan to sumatriptan. The sponsor constructed the study so as to declare eletriptan "equivalent" to sumatriptan if eletriptan induced no more than a 10%

worsening on constriction than sumatriptan. It is worth noting that the division did not agree to this margin, and, indeed, we do not know what an appropriate margin would be in this setting. One could argue that 10% is entirely too large a margin, given the risk/benefit considerations for a treatment for migraine. Indeed, as Dr. Yan points out, any smaller margin than 10% would not have been ruled out. As previously noted, Dr. Bastings has shown that the median of maximum degree of constriction of the HD eletriptan patients is numerically greater, and almost significantly so ($p=0.09$), compared to sumatriptan. However, it is also worth noting that the ratios of the ratios of the geometric means in the HD eletriptan patients to the sumatriptan patients is essentially identical to those of all other sets of patients (see Dr. Yan's Table 1, page 11 of her review).

One could argue that labeling should attempt to restrict use of eletriptan to doses that result in levels no greater than those achieved by a single 40 mg dose, or perhaps to levels associated with 2, 40 mg doses, given 2 hours apart (the utility of a second dose in the face of recurrence after an initial, successful 40 mg dose, has been established). Such a label would contraindicate the use of any 3A4 inhibitors, because there would be no necessity to expose patients to these higher levels.

However, a number of factors militate against this conclusion.

First, there is a robust safety experience in the data base up to daily doses of 160 mg (given as 2, 80 mg doses given 2 hours apart). While it is absolutely true that the database, robust as it is, is entirely too small to have reliably produced even one true case of cardiac ischemia (if the incidence is reasonably similar to other triptans), and I see no reason to recommend this dose in labeling, nonetheless the data are reassuring as far as they go.

Further, as noted above, one important consideration about how restrictive labeling should be relates to the comparison to sumatriptan. If we could determine a dose (exposure level) of eletriptan that resulted in a degree of constriction that was comparable to that seen with, for example, a 6 mg sc dose of sumatriptan, it seems to me that such doses could be permitted in labeling.

Indeed, the exposures seen after a single dose of 40 mg in the face of minimal or moderate 3A4 inhibition are considerably lower (less than 200 ng/ml) than the levels at higher doses with potent inhibitors. Further, and importantly, there is little difference in the degree of constriction produced by these lower levels and the degree of constriction produced by the 6 mg sc dose of sumatriptan (refer again to Dr. Bastings' Figures 9 and 10, pages 57-8).

For these reasons, then, the Division recommends that the application be approved, but that the approval be limited to the 20 and 40 mg tablets, that 80

mg as a single dose not be recommended, and that labeling make clear that potent CYP3A4 inhibitors should not be used.

Russell Katz, M.D.

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this page is the manifestation of the electronic signature.**

/s/

Russell Katz
12/24/02 08:13:40 AM
MEDICAL OFFICER

MEMORANDUM

Date: December 18, 2002

To: Dr. Russell Katz
Director
Division of Neuropharmacologic Drug Products
HFD-120

From: Lisa Stockbridge, Ph.D.
Regulatory Reviewer
Division of Drug Marketing, Advertising, and Communications
HFD-42

Re: NDA 21-016
Relpax (eletriptan HBr) Tablets

Material Reviewed: June 2002 proposal of Prescribing Information (PI) and Patient Information leaflet (PPI).

Background

For the following recommendations, the current PI for Imitrex and the current format of PPIs were considered.

Recommendations

Prescribing Information

- In the Mechanism of Action subsection of the Clinical Pharmacology section, the details about the _____ of _____ is promotional and is not used in the Imitrex PI. This should be deleted.
- The Hepatic Impairment subsection of the Clinical Pharmacology section is inconsistent with the Contraindications section of the PI because Relpax is contraindicated in severe hepatic impairment. The directive to _____ implies that there is a way to dose Relpax for severe hepatic impairment. This directive should be deleted.
- In the Dosage and Administration section, the second sentence in the Hepatic Impairment subsection should be revised to read _____

Patient Information Leaflet

The proposed patient information leaflet is promotional in tone and inadequately conveys the risks associated with the use of Relpax. Furthermore, tables are not patient-friendly. The following revision to the PPI is suggested:

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

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this page is the manifestation of the electronic signature.**

/s/

Lisa Stockbridge
12/18/02 01:38:35 PM
CSO



MEMORANDUM

Date: December 10, 2002
From: Armando Oliva, MD
To: Russell Katz, M.D.
Subject: NDA 21-016 - Eletriptan Response to Approvable Letter

This NDA provides a complete response to the approvable letter dated 12/1/00 for eletriptan, a new 5HT_{1B/1D} agonist for migraine.

The efficacy of eletriptan (20mg, 40mg, 80mg) has been established in previous reviews. The principal barrier to approval of the product thus far has been the fact that eletriptan is primarily metabolized by the cytochrome P450 CYP 3A4 isozyme. Previous studies have shown that subjects exposed to eletriptan in the presence of the a potent CYP 3A4 inhibitor can achieve levels well in excess of those that have been shown to be safe in humans (e.g., concomitant use with ketoconazole results in an approximately 3x increase in C_{max} and a 6-fold increase in AUC).

We stated in the approvable letter that before eletriptan could be approved, we needed further reassurance that the risk of concomitant exposures with CYP 3A4 inhibitors is not unacceptable. We viewed this issue as critical because, even if we contradict their use in labeling, we cannot be confident that such use will not occur.

We suggested they conduct a study to measure coronary artery diameters in subjects exposed to eletriptan at levels similar to what would be achieved during maximum CYP 3A4 inhibition. This submission contains the results of this study (A160-1072, referred to as study 1072).

In addition, the sponsor has submitted the results of a second angiography study (160-309) and a clinical study (A160-1048). We did not specifically request these studies, but they do provide additional information. Finally, the submission includes a summary of the post-marketing experience with eletriptan in countries where it is currently marketed.

Dr. Bastings performed the clinical review. We also obtained a consultative review of study 1072 from the Division of Cardioresenal Drug Products (DCRDP). Dr. Bastings and DCRDP conclude that study 1072 lacked assay sensitive to provide the reassurance that we seek. Furthermore, the additional two studies do not adequately address this concern. However, the post-marketing experience in other countries (amounting to ~~1~~ tablets sold), he concludes, does support the approval of eletriptan up to a maximum dose of 40mg daily.

Dr. Bastings recommends approval of the 20mg and 40mg dose, with a maximum daily dose of 40mg. He recommends non-approval of the 80mg dose as there is no clear evidence that 80mg is superior to 40mg, and it is associated with higher incidence of

adverse events, and has a greater potential to reach toxic levels when taken jointly with CYP 3A4 inhibitors.

In this memo, I discuss Dr. Bastings review. I then present my own interpretation of the results.

Study A160-1072

Study 1072 was designed with Agency input. It was a quantitative coronary angiography (QCA) study performed in subjects undergoing diagnostic coronary angiography who were subsequently found to have less than 20% arterial stenosis (this included subjects with essentially "clean" coronaries).

It was a double-blind, placebo-controlled, parallel-group study to determine the effects of escalating plasma concentrations of i.v. eletriptan on coronary vascular responsiveness. It studied i.v. eletriptan, subcutaneous sumatriptan, and placebo in a double-dummy 1:1:1 ratio. A total of 60 patients were treated with study medication.

Eletriptan was administered as a two-step 40 minute continuous intravenous infusion with the goal of achieving the expected concentrations that would be seen, during potent CYP 3A4 inhibition, of a 20mg dose at 5 minutes, 40mg at 15 minutes, and 80mg at 40 minutes (target concentrations were 114, 264, and 564 ng/ml, respectively). Sumatriptan was given as a single 6mg subcutaneous dose at the onset. The sponsor replaced any subject who failed to achieve a C_{max} of at least 299 ng/ml.

Quantitative coronary angiography of the mid Left Anterior Descending artery (mid-LAD) and the proximal Circumflex artery was conducted at these same time points: 5, 15, 40 minutes, as well as a final measurement at 50 minutes (10 minutes post-eletriptan infusion). Investigators could evaluate other arteries as well if visual inspection suggested evidence of vasoconstriction in other areas. Various additional safety measurements were also recorded (adverse events, heart rate, femoral artery and aortic blood pressure, ECG). Dr. Bastings provides more details on study design on page 42 of his review.

The primary analysis was the difference in the logarithms of the minimum post-baseline diameter and the baseline diameter (which was essentially the minimum ratio of post-infusion diameter to baseline). The sponsor defined the allowable margin of inferiority as >0.9 (see medical review for more details, page 43), and powered the study to demonstrate non-inferiority between eletriptan and sumatriptan. In our review of the analysis plan, we are on record that we consider this study a safety study and, as such, would perform a qualitative safety analysis of the data, and not necessarily rely on the results of the non-inferiority analysis exclusively, however adequately designed and executed.

In total, 24 subjects received eletriptan, 18 received sumatriptan, and 18 received placebo. All but one eletriptan patient completed the study (this dropout is discussed below).

Table 1 (medical review table 19, page 45) shows that eletriptan achieved numerically slightly lower diameters post-baseline than did sumatriptan, but these changes were within the non-inferiority margin (0.9) set by the sponsor.

Table 1: Study 1072 – Relative Effects on Minimum Coronary Artery Diameter at the mid-LAD and proximal Circumflex Regions (ITT Population)

	Geometric Mean CAD Ratio	Ratio	95% CI
<i>mid-LAD</i>			
Eletriptan i.v.	0.78	0.96	0.91 – 1.02
Sumatriptan 6mg SC	0.81		
<i>Prox-Circumflex</i>			
Eletriptan i.v.	0.81	0.97	0.93 – 1.02
Sumatriptan 6mg SC	0.83		

(Placebo Geometric Mean CAD Ratios were 0.84 for the mid-LAD and 0.92 for the prox-Circ, med review table 28, page 60)

When looking at individual time points post-baseline, eletriptan met the non-inferiority criteria at each time point, at both segments measured (medical review table 21, page 47, not shown here).

Eleven subjects failed to reach the targeted eletriptan concentration of 564 ng/ml and were excluded from the non-inferiority analysis. An additional 2 subjects had unknown plasma concentrations at 40 minutes. This left only 11 eletriptan-treated subjects for the analysis.

Dr. Bastings performed his own detailed analysis of the raw data. He confirms that only 11 eletriptan subjects achieved the target concentration of 564 ng/ml (which is estimated to be the concentration achieved by a subject taking an 80mg tablet in the presence of a potent CYP 3A4 inhibitor such as ketoconazole).

Mean maximum eletriptan-associated constriction seen in these subjects was 22% in the mid-LAD and 20% in the prox-circumflex (medical review table 22, page 49). No subject in the cohort had measurable vasoconstriction >30%. It is interesting to note that the 9 subjects who didn't achieve the target C_{max} mean maximum eletriptan-associated vasoconstriction was still about 20%, and included three subjects who experienced >30% vasoconstriction in the mid-LAD (including the one adverse dropout discussed below).¹ The degree of vasoconstriction observed after sumatriptan administration was similar, as would be expected given the results of the non-inferiority analysis (with the single exception of the adverse eletriptan dropout).

¹ Dr. Bastings' more formal analysis of this observation on page 59 of the medical review shows that the subjects with low eletriptan C_{max} (264-563 ng/ml) had maximum vasoconstriction that was not nominally different than dose with high C_{max} (564 ng/ml).

He notes that the maximum vasoconstriction achieved in either the LAD or circumflex artery occurred at 50 minutes in all but one measurement.² That is to say, the maximum pharmacodynamic effect (vasoconstriction) appeared to lag C_{max} by at least 10 minutes, and perhaps longer, although it is impossible to say how long since 50 minutes was the last angiographic observation time point in the experiment. Dr. Bastings illustrates this very nicely in figures 2 and 3 of his review (page 50 and 51). Although eletriptan levels clearly peaked at 40 minutes, vasoconstriction was still rising at 50 minutes. As he points out, placebo patients also experienced some vasoconstriction during the study, so this observation must be interpreted with caution.

In the sumatriptan subjects, C_{max} occurred 5-15 minutes post-baseline, yet the highest degree of vasoconstriction that was measured occurred at 50 minutes post-baseline. Dr. Bastings points out that this creates a potential bias in favor of eletriptan. If this pharmacodynamic lag is real, because sumatriptan subjects had a much shorter T_{max} than eletriptan subjects, they had a substantially longer period post- T_{max} for vasoconstriction to set in. Dr. Bastings again nicely shows (in figures 5 and 6, page 54 of his review) that vasoconstriction is still on the rise in sumatriptan subjects at 50 minutes, even though T_{max} was much earlier. This again suggests a temporal dissociation (lag) between maximum pharmacodynamic effect and C_{max} .

The interesting observation is that placebo patients also experienced vasoconstriction, albeit not as pronounced as in the eletriptan or sumatriptan treated subjects (16% in mid-LAD, and 13% in prox-circ, medical review table 27, page 57). The degree of vasoconstriction also seemed to be still rising at 50 minutes (medical review figures 7 and 8, page 56). This makes the observations of still-rising vasoconstriction in the triptan-treated groups difficult to interpret.

The one dropout is worthy of discussion. This was a 53 y/o African-american female who received eletriptan for approximately 25 minutes. At the time of angiography, the investigator felt that the patient had an approximate 50% constriction of the LAD compared to baseline (which was already 20% narrowed due to a "myocardial bridge" – a normal variant where myocardial tissue completely surrounds the coronary artery). The investigator noted the asymptomatic narrowing at 15 minutes and an unscheduled measurement at 25 minutes showed persistent narrowing. The infusion was stopped and she was given intravenous nitroglycerin. The mid-LAD was later measured to be 39% narrowed by the central lab. The episode was asymptomatic and not accompanied by any ECG changes. Our cardiology consultant was not reassured by this event...citing the not uncommon occurrence of myocardial bridges in the normal population (5-86% in various autopsy series). If only 1/3 of patients with myocardial bridges had similar events when exposed to high doses of eletriptan, there would be reason for significant concern.

The review of adverse events in the study provide interesting additional data. There were eight patients reported to have "vasoconstriction" as an adverse event. All of these occurred in eletriptan-treated subjects. Dr. Bastings as well as the sponsor could not find

² This occurred in subject 13 at the LAD measurement at 40 minutes. The posterior-circumflex measurement in the same subject achieved a minimum diameter at 50 minutes).

a correlation between the clinical adverse event called "vasoconstriction" and actual vasoconstriction by quantitative measurements or with eletriptan blood levels (with the exception of one subject). Dr. Bastings reviewed the individual case report forms of all these eight subjects. "Vasoconstriction" appeared to be reported when the qualitative appearance of vasoconstriction was apparent to the investigator on the angiogram. Often, nitroglycerin was administered as a result of the observation. What was most interesting is that the vasoconstriction measured by quantitative angiography appeared to *increase* over time, even though the investigator in many instances reported that the vasoconstriction had resolved. The sponsor argued at the pre-NDA meeting that these examples illustrate the inability of investigators to diagnose vasoconstriction in the catheterization laboratory...as quantitative measurements did not correlate with the observations. However, this does not explain why *all* the reported cases of vasoconstriction as an adverse event occurred in the eletriptan group. Our consultant in DCRDP was also concerned about the large number of "vasoconstriction" adverse events reported in the eletriptan group (which amounted to one-third of all eletriptan-treated subjects). If these reports are to be believed, it suggests, but doesn't prove conclusively, that eletriptan may lead to increased rates of cardiac ischemic events when taken concomitantly with CYP 3A4 inhibitors.

Study 160-039

Study 160-039 investigated the effects of i.v. eletriptan on coronary artery diameter in subjects undergoing percutaneous transluminal coronary angioplasty (PTCA) for severe single vessel disease (>50% stenosis). The FDA did not specifically request this study. The study was conducted in Portugal and the U.K and treated 42 subjects (19 eletriptan, 17 sumatriptan, 10 placebo). It had a similar design to study 1072 with the exception that subjects had documented single vessel disease on angiography, the dose of i.v. eletriptan used was lower (6mg vs. up to 72mg in study 1072), the duration of eletriptan administration was shorter (15 minutes vs. 40 minutes in study 1072), investigators measured coronary artery diameters themselves (vs. a centralized lab), and only one vessel was measured (at the focal point of stenosis). As in study 1072, sumatriptan 6mg SC was used as an active control. Dr. Bastings provide other details in his review starting on page 71. The dose of eletriptan employed in this study produced C_{max} that were similar to those achieved after a single dose of 80mg.

The study showed a 2.6% dilatation with eletriptan and a 6.85% constriction with sumatriptan ($p=0.062$). Interestingly, placebo reduced coronary artery diameter more than eletriptan but less than sumatriptan, which is counter-intuitive given the known effects of the triptans and raises concerns regarding the validity of the study. However, there were no evidence of major coronary vasoconstriction with eletriptan. The study gives modest reassurance about the possible effects of eletriptan in those with coronary artery disease. It is limited by small sample size, and the absence of central readings of angiograms. The safety data raised no new concerns.

Study A160-1048

Study A160-1048 was a comparative efficacy study of eletriptan 40mg and sumatriptan 100mg for the acute treatment of migraine. It was a very large ($N=2421$), double-blind,

parallel-group, placebo-controlled multicenter study comparing a single dose of eletriptan 40mg, sumatriptan 100mg, and placebo (2:2:1 randomization). A second dose was permitted to treat recurrence. Enrollment criteria were typical of acute migraine studies. The primary efficacy endpoint was headache response at 2 hours, defined in the traditional manner (moderate/severe pain at baseline and mild/no pain at 2 hours). Of the 2421 subjects, 2113 received study medication. Two hour response rates were 67% for eletriptan, 59% for sumatriptan, and 26% for placebo. The p-value for the eletriptan vs. sumatriptan comparison was $p=0.0005$ (medical review table 2, page 24). Eletriptan was generally superior to sumatriptan 40mg in most secondary endpoints measured. One flaw in the design is that the study did not specifically exclude sumatriptan non-responders. Safety of eletriptan 40mg and sumatriptan 100mg were similar, which included similar incidences of cardiovascular-related adverse events (e.g., chest pain was 1.6% and 2.0%, 0.5% for eletriptan 40mg sumatriptan 100mg, and placebo, respectively).

Post-Marketing Safety

As of 4/29/02, eletriptan was approved in 46 countries, including the European Union, Australia, and Japan. Overall, — tablets have been sold world-wide between 7/1/01 to 5/31/02. Dr. Bastings includes a table of how various countries have dealt with the CYP 3A4 issue. I reproduce that table in Table 2 below. One can see various approaches to the problem, to include various dosing regimens, recommendation for dose reductions, and contraindications. /;

Table 2: 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

There have been 8 serious adverse events reported (one contained in this submission, and 6 during the safety update, and one via a separate report and also identified by our Office of Drug Safety (OSD)). Dr. Bastings reviews all of them. One is worthy of mention here. This was a fatal myocardial infarction in a patient who took both eletriptan 40mg and at least one dose (possibly two) doses of sumatriptan 50mg within 24 hours. Although an association with triptan use is evident, it is impossible to determine the relative role of each triptan.

Dr. Bastings concludes that this is a relatively benign post-marketing world-wide experience with eletriptan, given that doses up to 160mg/day are approved in some

countries. The sponsor did not break down exposures (or sales) according to dose. It is impossible to conclude, from these data alone, that ALL eletriptan doses are safe, from a post-marketing standpoint. Based on the available information, Dr. Bastings concludes that at least the lowest marketed total daily dose is safe (40mg). This forms the basis of his recommendation that the total dose of eletriptan be limited to 40mg daily.

Discussion

In the approvable letter dated 12/1/00, we suggested they conduct what eventually turned out to be study 1072 in the hopes of providing reassurance that eletriptan, when taken in the presence of potent CYP 3A4 inhibitors, would not pose an unreasonable risk from a cardiac safety standpoint. Although, on its face, study 1072 seems to show similar degrees of vasoconstriction between eletriptan and sumatriptan, closer review of the data fail to provide the degree of reassurance that we had hoped.

The first source of concern is the small number of eletriptan subjects that actually achieved high eletriptan levels (defined as a C_{max} of 564 ng/ml or greater; the C_{max} that one might see of an 80mg dose in the presence of a potent CYP 3A4 inhibitor such as ketoconazole). Only 11 subjects, of the 24 treated with eletriptan, actually reached these levels.

Secondly, there is a possible dissociation (*i.e.*, a time lag) between T_{max} and maximum pharmacodynamic effect (vasoconstriction), such that it is not clear that the actual maximum amount of vasoconstriction was ever observed because the last observation was made at 50 minutes. Since the placebo group also showed increasing vasoconstriction over time, this lag may be due to other factors unrelated to treatment, but unfortunately does not exclude the possibility that subjects may have achieved even greater vasoconstriction after the 50 minute time point (and that a separation between eletriptan and sumatriptan could have occurred, since T_{max} for sumatriptan was much shorter than for eletriptan in this study). We and the sponsor did not consider such a lag (or at least didn't consider that the lag could be so large) at the time that the protocol was discussed, but, nonetheless, this possibility cannot be dismissed now.

Thirdly and perhaps most importantly, it is indeed noteworthy that all eight adverse event reports of "vasoconstriction" occurred in eletriptan-treated subjects. Both the sponsor and Dr. Bastings agree that the clinical observations and reports called "vasoconstriction" did not correlate with the quantitative angiographic measurements made later at the central lab. Clearly one of them is wrong, but which one? The sponsor argues that the investigator's ability to diagnose vasoconstriction in the cath lab which is faulty. But, if true, one would expect a balanced distribution of "vasoconstriction" adverse events across the treatment groups. That all eight occurred in the eletriptan group and none in the sumatriptan group and none in the placebo group is remarkable. I think a more likely explanation is that eletriptan really was doing something to the coronary arteries that the quantitative coronary angiography methodology failed to detect, *i.e.*, it suggests that the primary endpoint measurements were not meaningful. This is not an unreasonable conclusion given the fact that systematic measurements were only recorded at two points along a complicated vascular structure. It assumes that the changes seen at these two

points are representative of changes occurring elsewhere. It is quite possible, if not likely (based on these reports) that this assumption is incorrect. There appears to be a need for better measures of coronary responsiveness.

Fourthly, the one significant adverse dropout occurred due to worrisome vasoconstriction after eletriptan treatment, and occurred in a patient with an anatomical variant: a myocardial bridge. Autopsy series put the incidence of myocardial bridges at anywhere from 5-86% (with lower numbers using angiography). Myocardial bridges are not that rare, yet ischemic events associated with them are. While it is still possible that myocardial bridging may have contributed to the vasoconstriction seen in this case, it is not particularly reassuring.

In summary, the data from study 1072 do not provide the reassurance that we had hoped. On the other hand, eletriptan is now marketed in many countries world-wide and the post-marketing pharmacovigilance profile is indeed benign. Post-marketing experience, by itself, is not sufficient to demonstrate safety for various reasons which I will not elaborate here. However, I agree with Dr. Bastings that the benign postmarketing experience thus far, along with the substantial amount of long-term clinical trial safety data at higher doses, suggests that at least the lower doses of eletriptan are reasonably safe. I agree that the 20mg and 40mg dose can be approved. I still have serious concerns about the 80mg dose, given my discussion above. There is still insufficient reassurance regarding the risk for a subject on a potent CYP 3A4 inhibitor who inadvertently takes an 80mg dose. Furthermore, as I discussed in my previous review, there is no convincing evidence that the 80mg provides additional benefit over the 40mg dose (bottom of page 10 in my 11/1/00 review). Dr. Bastings recommends that the maximum daily dose be limited to 40mg a day. Although his recommendation is reasonable and has merit, I would argue that remedication after 2 hours with a second dose of 40mg is reasonably safe. I provide my reasoning below.

The safety database for the NDA contains a substantial amount of safety data of patients who take two 80mg doses spaced at least 2 hours apart. In my 11/1/00 review (page 22), 688 subjects were stabilized on the 80mg dose in long-term studies. Of these, 496 treated at least 2 migraines a month, and 438 of these completed 6 months of treatment and 410 completed one year of treatment. Their safety profile was benign. Thirty percent of these attacks were treated with two doses of medication (since a second dose of 80mg was permitted after 2 hours). In total, 15,274 attacks were treated with a total daily dose of 160mg. The amount of safety data with the 160mg maximum daily dose is significant, and, if the CYP3A4 issue were not present, the safety database would ordinarily support this maximum daily dose.

It is difficult to say what maximum daily dose this database would support, given that the CYP3A4 issue is not completely resolved and given what we know about the post-marketing data. I would suggest that it is reasonable to propose a maximum daily dose of 80mg (*i.e.*, two 40mg tablets spaced at least 2 hours apart for recurrent pain³). This is an attempt to strike a balance based on what's known about the safety of the drug during

³ I did not find evidence for efficacy for persistent pain in my original NDA review.

pre-marketing testing and post-marketing experience vs. the potential risk to a patient who takes a 40mg dose in the presence of potent CYP3A4 inhibition. While one may argue that such a patient would still potentially be exposed to eletriptan levels in excess of the 160 mg total daily dose that subjects have seen in long-term studies, I don't believe these levels would be wildly in excess of what subjects have been exposed to before and is probably not an unreasonable risk (given the additional facts that that the labeling will contraindicate such use and we will not be making the 80mg dose available as a further precaution that such levels are not achieved).

For the reasons elaborated above, I recommend approval of eletriptan 20mg and 40mg doses, but not the 80mg dose. I would permit remedication after 2 hours for recurrence, with a maximum daily dose of 80mg a day. I would approve the same labeling in the 12/1/00 approvable letter with only minor changes, as evident in the marked-up labeling in the action package.

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/s/

Armando Oliva
12/10/02 12:09:05 PM
MEDICAL OFFICER



Memorandum

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH
DIVISION OF CARDIO-RENAL DRUG PRODUCTS

Date: November 15, 2002

From: Thomas A. Marciniak, M.D.
Medical Officer

Subject: Consult Regarding Eletriptan (NDA 21-016) and Coronary Vasoconstriction

Through: Douglas C. Throckmorton, M.D.
Division Director

To: Armando Oliva, MD
Neurology Team Leader
CDRH/ODE/DCRD

This memo addresses the questions in your consult to us dated October 3, 2002, regarding a coronary angiography study of eletriptan and coronary vasoconstriction. For ease of reference I have included below your excellent summary of the consult request followed by our summary of the study and finally your questions (in boldface) and our responses.

In the assessment of the cardiovascular safety of eletriptan, a new triptan class symptomatic treatment of migraine, the sponsor was requested to conduct a study with high doses of eletriptan in patients undergoing a heart catheterization and who were diagnosed with a coronary artery stenosis <20%. The issue is that eletriptan is metabolized almost exclusively by CYP3A4 and that in the presence of a CYP3A4 inhibitor, blood concentrations of eletriptan can be dramatically increased (about 300%), to a level at which cardiovascular safety needed to be evaluated.

Study 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, and to compare it with therapeutic doses of sc sumatriptan (as an active control) and iv and sc placebo.

The investigators invited subjects who were scheduled for diagnostic coronary angiography to participate in the study. The objectives of this study were to compare the effects of eletriptan with those of sumatriptan and placebo, to determine any concentration-dependent effects of eletriptan on CAD, to assess changes, if any, in mid- left anterior descending (LAD) and proximal circumflex coronary artery mean segment diameter (MSD) resulting from eletriptan

exposure; and to determine the potential effects on coronary arteries of an oral eletriptan 80mg administered in the presence of a potent CYP3A4 inhibitor.

The basics of the study are the following: Patients who underwent coronary angiography for a clinical indication and who at catheterization had no evidence of $\geq 20\%$ stenosis or other multiple luminal irregularities were randomized to double dummy placebo (n = 18), eletriptan 36, 52, or 72 mg by 40 minute infusion (n = 24), or sumatriptan 6 mg SC (n = 16). Quantitative coronary angiography (QCA) of the mid-LAD (primary endpoint) and proximal circumflex (secondary endpoint) and drug levels were done at 5, 15, 40, and 50 minutes from the start of infusion.

The eletriptan dosing was selected to achieve blood levels comparable to oral eletriptan dosing at 20, 40, and 80 mg in the presence of a potent CYP3A4 inhibitor. In a prior study the mean C_{max} for oral eletriptan 80 mg in the presence of ketoconazole was 491 ng/ml, 2.7 fold higher than that obtained with oral eletriptan 80 mg alone. The infusion was stepped at 20 minutes to administer 36% of the dose in the first 20 minutes and 64% in the final 20 minutes.

The sumatriptan dose is the maximum single recommended adult dose. In a similar study of the effect of sumatriptan on coronary artery diameter reported in the literature and cited by the sponsor to support the design of this study, sumatriptan 60 mg SC produced blood levels of 124 ng/ml at 10 minutes and 71 ng/ml at 30 minutes. (MacIntyre, Bhargava et al. 1993)

The primary hypothesis was a non-inferiority hypothesis that the quotient of the geometric mean ratios of the minimum post-baseline mean mid-LAD segment diameter (MSD) to the baseline MSD for eletriptan to the mean such ratios for sumatriptan is ≥ 0.9 . In addition to an intention-to-treat (ITT), as randomized analysis set, the sponsor defined various other analysis sets. The proposed primary efficacy analysis uses a modified ITT (MITT) set consisting of patients who had eletriptan blood levels at the last QCA measurements greater than the minimum target concentration (599 ng/ml? MITT has 20 eletriptan patients compared to 24 in ITT set.) Because the sponsor's presentation of the data is complex and somewhat confusing with its multiple analysis sets and adjustments, we analyzed the raw data.

The study achieved levels of eletriptan close to those projected as shown in the following table.

Table 1: Mean Drug Levels by Time in Minutes After Start

	5	15	40	50
eletriptan	152	282	625	272
sumatriptan	49	68	46	37

Sumatriptan levels appear to be slightly lower than those achieved in (MacIntyre, Bhargava et al. 1993).

Changes in the ratio of mid-LAD diameter to baseline were very similar in the three groups and appear to be dominated by a time trend towards lower ratios as shown in the following table.

Table 2: Mean Mid-LAD Ratios to Baseline by Time

	5	15	40	50
eletriptan	0.93	0.90	0.82	0.80
sumatriptan	0.94	0.90	0.86	0.81
placebo	0.96	0.91	0.87	0.84
Total	0.94	0.90	0.85	0.81

Results for the proximal circumflex are similar. The sponsor calculated a geometric mean minimum mid-LAD ratio to baseline of 0.78 for eletriptan and 0.81 for sumatriptan for quotient of eletriptan to sumatriptan ratios of 0.96, 95% confidence limits 0.91 to 1.02. The sponsor concludes non-inferiority of eletriptan.

The data do not show a clear drug effect of either eletriptan or sumatriptan upon coronary artery diameter. The time trend towards lower ratios observed with placebo dominates. In the study cited (MacIntyre, Bhargava et al. 1993) sumatriptan 60 mg SC produced a significant reduction in coronary artery diameter (17% at 30 minutes). This study was not placebo-controlled. A prior study by the same investigators of IV sumatriptan included placebo comparisons and did not show a placebo effect. (Macintyre, Bhargava et al. 1992) The methodology used by MacIntyre was similar to the present study, although MacIntyre evaluated multiple points (at least three) along each artery.

If one tries to adjust for the time trend by correcting the ratios on drug with the corresponding ratio on placebo at each timepoint, one does get a significant linear trend ($p = 0.043$ for LAD, $p = 0.013$ for proximal circumflex) in decreasing diameter with increasing drug level for eletriptan by multiple regression with adjusted ratio and time as independent variables. The linear trends for the same regression analysis with sumatriptan are not significant. However, overall we conclude that the study was negative for the primary endpoint of change in coronary artery diameter because it lacked assay sensitivity due to the time trend in coronary artery diameters (see response to Question 1).

As opposed to effects upon coronary artery diameters, the blood pressure (BP) recordings show that eletriptan and sumatriptan had expected physiologic effects. Eletriptan increased mean aortic systolic BP by about 18 mm Hg at 40 minutes and mean diastolic BP by about 10 mm Hg. Sumatriptan increased mean SBP by about 10 mm Hg at 20 minutes and mean diastolic BP by about 4 mm Hg at 30-40 minutes. Placebo showed small (-2 to +2 mm Hg), mostly random changes in BP.

More revealing than the primary endpoint results are the adverse events. The sponsor's tabulation of the cardiac adverse events is shown in the following table. Note that coronary vasoconstriction was reported only in the eletriptan group while the only report of chest pain was in a placebo patient. The sponsor emphasizes that the investigator reports of coronary vasoconstriction are unrelated to the primary endpoint QCA measurements. Rather than being reassuring, the lack of association confirms that the primary endpoint measurements are not meaningful.

Table 3: Cardiac Adverse Events by Treatment

Adverse event	Eletriptan iv	Sumatriptan 6mg sc	Placebo
Chest pain	0	0	1
ECG abnormal	1	0	0
Vasoconstriction (coronary)	8	0	0

Source: Table 6.2.3; ECG=electrocardiogram.

The one ECG abnormality was in one of the patients with coronary vasoconstriction. The patient was a 42 year-old male with a history of angina pectoris and a family history of ischemic heart disease. He was reported to have mild asymptomatic coronary vasoconstriction in the proximal LAD after 40 minutes of eletriptan infusion that resolved within 10 minutes. He had transient ST segment elevation and T-wave inversion for the first two minutes of the vasoconstriction. (Prinzmetal's angina or a history of coronary spasm was an exclusion criterion.)

The other cases of coronary vasoconstriction were asymptomatic and, with one exception, reported by the investigator as mild. The one case of vasoconstriction reported by the investigator as moderate was in a 53 year-old female with a history of migraine. She developed vasoconstriction at 15 minutes estimated by the investigator as 50% beyond a baseline 20% constriction in the mid-LAD. The investigator discontinued the infusion at 25 minutes and the vasoconstriction resolved by 30 minutes. The patient was asymptomatic and had no ECG changes. The sponsor notes that this patient had myocardial bridging. This case was the only discontinuation of study drug.

1. Was the methodology appropriate to achieve the study objectives (catheterization method, measurement sites and number of sites evaluated, quantitative coronary angiography technique)?

Most aspects of the methodology were excellent. In retrospect there appear to be three major flaws:

- Variations in coronary artery tone were not controlled. Contrast agents are known to dilate coronary arteries. (Jost, Hausmann et al. 1997; Baile, Pare et al. 1999) One investigator has suggested that nitrates should be administered during QCA to maximize dilation and minimize variability due to contrast agents. (Jost, Rafflenbeul et al. 1990) One can hypothesize that in this study the injection of contrast media during the scheduled coronary angiography that confirmed eligibility produced coronary vasodilation that gradually returned towards baseline during the time course of the QCA studies.
- Multiple measurements were not done as in the cited study. (MacIntyre, Bhargava et al. 1993) Multiple segment measurements should be useful in detecting effects that are localized rather than generalized. However, it is not clear whether MacIntyre et al. or this study provides the clearer picture of the effects of triptans on coronary artery diameter. This

study has some design aspects superior to Macintyre et al., such as concurrent placebo control.

- Due to the two flaws just discussed or to other unidentified problems the primary endpoint lacks assay sensitivity. This study failed to show a drug effect for the primary endpoint either with eletriptan or with the active control sumatriptan, so no information is provided by the primary endpoint results. The methodology failed for the primary endpoint.

2. What can be considered an acceptable level of vasoconstriction induced by a coronary procedure of this type?

The most relevant reference for this question is the American College of Cardiology/American Heart Association guidelines on coronary angiography, in particular this statement on coronary spasm: "Although vasomotion can result in as much as a 20% change in lumen diameter, coronary spasm is considered to be present when a reduction in lumen caliber of 50% occurs during a provocative test and reversal is achieved with intracoronary nitroglycerin." (Scanlon, Faxon et al. 1999) No patient in this study had a minimum artery diameter of <50%, although one eletriptan patient was discontinued after 25 minutes of infusion and had a maximum reduction of 38%. However, the primary endpoint may fail to detect localized spasm. The interpretation of small changes in artery diameter, such as were possibly shown in the Macintyre et al. study, is difficult. Such changes have not been linked to cardiac events.

3. After unblinding, the sponsor modified the protocol in order to perform a placebo correction "to eliminate a pronounced placebo effect" from the comparisons between eletriptan and sumatriptan at individual timepoints. Was this acceptable in your sense, since the effect related to the procedure and not to the study drug (as evaluated by the placebo group) was presumably similar in the eletriptan and sumatriptan groups?

The sponsor did not perform the placebo correction for the primary endpoint analysis. For some secondary analyses by time, the sponsor did correct for the placebo effect. For comparisons of eletriptan to sumatriptan we agree with you that correcting for a placebo effect is not appropriate. For estimating a dose-response relationship it is critical to try to adjust for the placebo effect. However, because of probable noise introduced by the adjustment, the post-hoc nature of it, and the secondary status of the analyses, interpretation is more difficult than that of the unadjusted primary endpoint.

4. Subject 50 was discontinued after 15 minutes of eletriptan infusion because of a 20% vasoconstriction, which peaked at 38% at 25 minutes post-start of the infusion. The sponsor argued that an anatomical aberration of myocardial bridging could partially account for this observation. Is this explanation justified? How frequent is that type of abnormality in the general population?

The investigator estimated the narrowing in the mid-LAD as 60-70%, about 50% greater than a baseline 20% narrowing, although the reference lab estimated about 39% narrowing from the QCA. By coincidence *Circulation* has a mini-review about myocardial bridging in the current issue. (Mohlenkamp, Hort et al. 2002) Myocardial bridging is muscle overlying an epicardial coronary artery. It is common, with prevalence ranging from 5% to 86% by autopsy and less by angiography—the recent review concludes that myocardial bridges are present in about one-third of adults. Myocardial bridges are located most frequently in the mid-LAD, as in this case. They have been associated with ischemic events. However, based on the frequency of bridges and the rarity of case reports linking them reasonably to ischemic events, ischemia is rare with bridges alone as the review notes. While myocardial bridging might partially account for the event in this case, we are not reassured. If similar events occurred in the one-third of adults with myocardial bridges taking eletriptan and CYP3A4 inhibitors, we would worry about an increased risk of ischemic events.

5. In this study, there is a large imbalance between the number of treatment related adverse events in the eletriptan group (n=8) versus the sumatriptan group (n=0). These adverse events were related to the observation of vasoconstriction, deemed clinically insignificant by the sponsor. However, the imbalance between both groups is striking. What is your impression about this observation?

The imbalance in vasoconstriction adverse events between eletriptan and both sumatriptan and placebo is striking and worrisome. The event rate with eletriptan is high (33%). While most of the events were mild, two of the events are concerning: the event associated with ECG changes and the moderately severe narrowing associated with the myocardial bridge. That symptoms or ischemic events did not develop is not completely reassuring: The patients in this study were selected because they had relatively clean coronary angiograms. One would be concerned about ischemic event rates in the more vulnerable general population, particularly older individuals with no history of ischemic heart disease but with diseased coronaries.

6. What is your perceived risk of eletriptan to cause coronary vasoconstriction?

The lack of difference in the primary endpoint among eletriptan, sumatriptan, and placebo is not informative. The vasoconstrictive adverse events occurring only in one-third of eletriptan patients are cause for concern. They suggest, but do not prove conclusively, that eletriptan may lead to increased rates of cardiac ischemic events. This study does not answer the question of what is the risk of cardiac ischemic events in patients exposed to high levels of eletriptan when taken concomitantly with a CYP3A4 inhibitor—answering the latter question is difficult and we do not have suggestions for additional studies.

We did not review the rest of the NDA data in detail, but we note that your original NDA review lists chest tightness in 4.3% of patients treated with eletriptan 80 mg, 2.3% of patients treated with 40 mg, 0.9% with 20 mg, and 0.8% with placebo. Your NDA review also commented that triptan-related myocardial infarctions are rarely seen during the development program but have

been observed after approval. Restrictive labeling may be sufficient, but you will have to weigh the potential increased risk of ischemic events with this drug against its established benefits.

References:

- Baile, E. M., P. D. Pare, et al. (1999). "Effect of contrast media on coronary vascular resistance: contrast-induced coronary vasodilation." Chest **116**(4): 1039-45.
- Jost, S., D. Hausmann, et al. (1997). "Influence of radiographic contrast agents on quantitative coronary angiography." Cardiovasc Intervent Radiol **20**(1): 5-9
- Jost, S., W. Rafflenbeul, et al. (1990). "Elimination of variable vasomotor tone in studies with repeated quantitative coronary angiography." Int J Card Imaging **5**(2-3): 125-34.
- Macintyre, P. D., B. Bhargava, et al. (1992). "The effect of i.v. sumatriptan, a selective 5-HT₁-receptor agonist on central haemodynamics and the coronary circulation." Br J Clin Pharmacol **34**(6): 541-6.
- MacIntyre, P. D., B. Bhargava, et al. (1993). "Effect of subcutaneous sumatriptan, a selective 5HT₁ agonist, on the systemic, pulmonary, and coronary circulation." Circulation **87**(2): 401-5.
- Mohlenkamp, S., W. Hort, et al. (2002). "Update on Myocardial Bridging." Circulation **106**(20): 2616-2622.
- Scanlon, P. J., D. P. Faxon, et al. (1999). "ACC/AHA guidelines for coronary angiography. A report of the American College of Cardiology/American Heart Association Task Force on practice guidelines (Committee on Coronary Angiography). Developed in collaboration with the Society for Cardiac Angiography and Interventions." J Am Coll Cardiol **33**(6): 1756-824.

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Thomas Marciniak
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MEDICAL OFFICER

Doug Throckmorton
11/15/02 03:47:53 PM
MEDICAL OFFICER

MEMORANDUM OF MEETING MINUTES

Meeting Date: February 27, 2001
Location: WOCII 4th Floor Conference Room
Application: NDA 21-016 Relpax (eletriptan) tablets
Type of Meeting: Advice
Meeting Chair: Russell Katz, MD
Meeting Recorder: Lana Chen, RPh

FDA Attendees

Russell Katz, MD Division Director
Armando Oliva, MD, Neurology Team Leader
Gerald Tremblay, MD Clinical Reviewer
Eric Bastings, MD Clinical Reviewer
Maria Sunzel, Clinical Pharmacology Reviewer
Ramana Uppoor, Clinical Pharmacology Team Leader
Lana Chen, RPh

External Constituent Attendees

Neville Jackson, Clinical
Verne Pitman, Clinical
Simon Kirby, Biostatistics
Philip Poole, Biostatistics
Ashley Milton, Clinical Pharmacology
Andrew Clair, Regulatory Affairs
Larry Paglia, Regulatory, Affairs

Meeting Objectives:

The Sponsor requests Agency guidance on the design of the cardiac safety protocol, a study requested in our December 1, 2000 Approvable Letter.

Background:

In the December 1, 2000 Approvable Letter, the Sponsor was requested to conduct a placebo-controlled study designed to assess the potential of eletriptan to constrict coronary arteries at eletriptan concentrations that are higher than those achieved in previous studies, and that are comparable to exposures seen with CYP3A4 inhibition. The requested study should also include active triptan controls.

The Sponsor requested this meeting to discuss the draft protocol submitted January 26, 2001.

Discussion Points (bullet format):

- The choice of the IV route of eletriptan administration limits the number of active controls that could be included in the study. Intravenous dosage form of eletriptan was chosen to minimize risk to patient safety during the invasive angiography procedure.
- The dose of IV eletriptan administered in this proposed study is postulated to achieve a C_{max} that should exceed the C_{max} achieved with oral eletriptan in the presence of CYP3A4 inhibition.
- For safety reasons, the Sponsor is asked to recalculate the proposed dose using a different (two-compartment) simulation approach.
- The Sponsor is also asked to evaluate the pharmacokinetic data from smaller batches of patients prior to expanding the study to a larger patient group.
- The choice of viewing LAD segment constriction as a surrogate marker for coronary constriction assumes uniform constriction across all coronary arteries. Because it is unknown whether the constriction is uniform, the Sponsor is asked to consider measuring constriction in other segments as well.
- Because migraineurs tend to be relatively young, the Sponsor is asked to consider limiting the maximum age of patients enrolled in this study. The Sponsor suggests a maximum of 60 years of age.
- The safety monitoring in this protocol should be revised as appropriate for this study.
- Eletriptan labeling regarding CYP3A4 inhibition will be reviewed and revised in light of the study results.
- The Sponsor's proposal to perform a third party, unblinded interim analysis to determine sample size will be reviewed by the Agency's statisticians.

Action Items:

The Sponsor will consider revising the protocol regarding the following:

1. dose of IV eletriptan based on other pharmacokinetic modeling
2. evaluating the pharmacokinetic data from smaller batches of patients prior to expanding the study to a larger patient group.

3. maximum age of patients enrolled will be revised, probably to a maximum of 60 years
4. viewing additional, proximal site(s) of coronary constriction other than the LAD
5. revising safety monitoring in this protocol as appropriate for this study

The Division will:

1. Consult the Agency's statisticians to review the Sponsor's proposal to perform a third party, unblinded interim analysis to determine sample size.

Minutes Preparer:

Lana Chen, R.Ph.
Project Manager, DNDP

Chair Concurrence:

Armando Oliva, MD
Team Leader, Neurology
(designated signatory)

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/s/

Armando Oliva
5/1/01 07:52:33 AM

MEMORANDUM

DATE: November 27, 2000

FROM: Director
Division of Neuropharmacological Drug Products/HFD-120

TO: File, NDA 21-016

SUBJECT: Divisional Recommendation for Action on NDA 21-0126, for the use of Relpax (eletriptan) in the acute treatment of acute migraine

NDA 21-016, for the use of Relpax (eletriptan) in the acute treatment of acute migraine headache, was submitted on 10/27/98 by Pfizer Incorporated. The application contained the results of a number of controlled trials that established the effectiveness of the drug, as well as sufficient numbers of patients to address the safety of the treatment. However, eletriptan is primarily metabolized via CYP3A4, and, prior to the original PDUFA due date of 10/27/99, the Agency became aware of the results of 2 interaction studies, one examining the effects of concomitant erythromycin on eletriptan levels, and one examining the effects of concomitant ketoconazole on eletriptan levels. In the latter case, preliminary results suggested that the C_{max} of eletriptan was increased by about 3 fold, with the AUC increased about 6 fold compared to when eletriptan is given alone. This raised concerns, given that there is a generally accepted view that there is a dose (plasma level) relationship between triptan levels and coronary artery constriction.

Based on these results, the Agency issued an Approvable letter on 10/27/99. In this letter, the Agency stated that the application could eventually be approved with labeling warning against the concomitant use of eletriptan and 3A4 inhibitors, if the sponsor adequately addressed the following concerns:

- 1) the complete report of the ketoconazole study was requested
- 2) the sponsor was asked to document that the increased eletriptan levels achieved in conjunction with 3A4 inhibitors did not produce an unacceptable risk, notwithstanding the fact that they would be contraindicated
- 3) the sponsor was requested to examine the interactions with 3A4 inhibitors considered to be less potent than either erythromycin or ketoconazole
- 4) the sponsor was requested to submit the results of long term safety data
- 5) the sponsor was asked to submit the results of pre-clinical learning and memory studies and a repeat rat fertility study.

The sponsor responded to the Approvable letter with a submission dated 6/1/00. The submission contained the requested long-term safety data and animal studies. In addition, the submission contained reports of the erythromycin and ketoconazole studies. Subsequent to the submission of the re-submission, the

sponsor submitted the preliminary (on 8/9/00) and final (on 10/13/00) results of an interaction study with verapamil. Verapamil was studied because it was considered a CYP3A4 inhibitor of intermediate potency. A finding of no important effect on eletriptan levels of such a moderate inhibitor would have been considered evidence that use of eletriptan with these inhibitors would not need to be contraindicated. The sponsor also subsequently performed and reported the (preliminary) results of an interaction study with fluconazole on 10/13/00, also considered to be a 3A4 inhibitor of intermediate potency, but without the capacity to increase blood flow alleged to be associated with verapamil use.

The re-submission has been reviewed by Dr. Armando Oliva, medical officer in the division (review dated 11/1/00), Dr. Maria Sunzel of the Office of Clinical Pharmacology and Biopharmaceutics (review dated 11/20/00), Dr. Sid Stolzenberg, pharmacologist (review dated 11/16/00), and Dr. Mona Zarifa, chemist (review dated 11/6/00). Critically, Dr. Oliva recommends that the application be considered Not Approvable, based on the results of the interaction studies and a study in which patients with suspected coronary artery disease undergoing angiography were given intravenous eletriptan. In this memo, I will briefly review the results of the relevant data, and offer the division's recommendation for action on the NDA.

Interaction Studies

As noted above, the sponsor has submitted the results of 4 interaction studies, which have been reviewed in detail by Dr. Sunzel. In brief, these studies examined the effects on plasma levels (C_{max} and AUC) of eletriptan of the following 3A4 inhibitors: erythromycin, ketoconazole, verapamil, and fluconazole. The following table gives the ratio of plasma levels of eletriptan_{inhibitor}/eletriptan_{alone}:

Inhibitor	C _{max}	AUC
Erythromycin	2	3.6
Ketoconazole	2.7	5.9
Verapamil	2.2	2.7
Fluconazole	1.4	2.0

In these studies, the inhibitor was given for several days, followed by a single 80 mg dose of eletriptan.

As noted earlier, verapamil was chosen because in vitro data suggested that it was a considerably less potent inhibitor than ketoconazole. Subsequently, the sponsor suggested that the unexpectedly marked increase in Cmax with verapamil was related to verapamil's effect on the increase in hepatic blood flow, an effect presumably not seen with fluconazole. As Dr. Sunzel notes however (page 10), verapamil's effect on hepatic blood flow in this study (as measured by indocyanine green clearance) was about 5%, a level not likely to have been responsible for the large increase in eletriptan levels. The half-life of eletriptan was not significantly increased, suggesting that the clearance was not importantly increased. Dr. Sunzel postulates that the effect of verapamil may be related to increasing eletriptan bioavailability (perhaps by inhibiting p-glycoprotein).

Long-term safety

As noted above, the sponsor was requested to submit the results of long-term safety data. Dr. Oliva has reviewed this data in detail. Briefly, the data derive from 3 studies: in 2 studies, patients were randomized in a 4:1 ratio to eletriptan:physician optimized therapy (POT) for 1-2 years. Patient could receive a maximum initial single dose of 80 mg/headache, with a second dose after 2 hours if the headache did not respond or recurred. In the third study, patients were randomized to receive either eletriptan (up to 80 mg/headache) or oral sumatriptan. Patients were treated for 18 months or 50 headaches, whichever was the longer period; apparently the protocol was amended to include treatment up to 3 years. According to Dr. Oliva (page 25), 865 patients were treated for at least 6 months and 758 were treated for at least 1 year with the 40 mg dose. A total of 464 were treated for at least 6 months and 399 were treated for at least 1 year with the 80 mg dose (for at least 2 headaches/month).

It is difficult to evaluate the dose response for adverse events in this experience, given the non-randomized nature of the dose groups. Dr. Oliva's Tables 16-18 (pages 28-30) list the ADRs seen in the first 2 trials described. As can be seen from Dr. Oliva's review, there were few serious events, and only 2 adverse events in this experience not seen before and of note:

- 1) a 32 year old woman treated with 40 mg had a miscarriage 2 months after discontinuation of the drug. I cannot tell from the review how long she had been pregnant, or if she had received eletriptan while she had been pregnant.
- 2) a 45 year old woman on eletriptan 80 mg with intermittent clumsiness and weakness in both hands on the day of dosing. An MRI and carotid ultrasound were normal; the neurologist diagnosed a transient ischemic attack (TIA) and the investigator considered the event related to eletriptan.

There seemed to be no clearly drug related noteworthy clinical laboratory abnormalities.

Coronary Angiography Studies

As noted above, the sponsor performed a study in which 10 patients with suspected coronary artery disease underwent angiography. During the procedure, patients received a 10 minute saline infusion, followed by a 15 minute infusion of eletriptan during which they received a total of 50 mcg/kg. This dose was calculated to produce a Cmax essentially equivalent to that achieved after a 40 mg single oral dose-about 88 ng/ml. In reality, the mean level achieved was 112 ng/ml.

In this study, coronary artery diameter was measured at 0, 15, 30, 45, and 60 minutes after the saline infusion ended. Each patient had 3 or 4 coronary artery segments measured at each time point. The sponsor had originally reported that the mean decrease in coronary artery diameter was about 6%. However, Dr. Oliva re-evaluated the data by examining the maximum decrease (compared to baseline) in diameter of any segment at any time point. He reasoned that the degree of coronary blood flow would be determined by the most constricted segment of coronary artery.

Given this, he constructed his Table 21 (page-39). It can be seen that only one patient did not have any segment that decreased in diameter. In the remaining 9 patients, the maximum decrease in diameter at any segment at any time ranged from 11% decreased to 66% decreased (the mean maximum decrease was about 18%). The patient with the 66% decrease had chest pain with a plasma level of 127 ng/ml, but no changes on EKG. Another patient had a maximum decrease of 24% (in the other 7 patients, the maximum decrease ranged from 11%-17%). None of the patients had angiographic evidence of coronary artery disease.

In an attempt to compare these results with other triptans, Dr. Oliva went back to the naratriptan and sumatriptan NDAs. In each of these applications, similar angiographic studies were performed.

In the naratriptan NDA, 10 patients with suspected coronary artery disease underwent angiography, during which they received a subcutaneous placebo injection, followed 10 minutes later by a subcutaneous injection of 1.5 mg of naratriptan (which resulted in a Cmax greater than that associated with the highest approved dose of oral naratriptan of 5 mg).

The results of the analysis analogous to that just described for eletriptan are presented as Dr. Oliva's Table 22 (page 41). All patients had at least one segment at at least one time point that was constricted; the mean maximum decrease was about 14%. The maximum decrease seen in any patient in any segment at any time was 18%, seen in 2 patients. Only one patient was