

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

21-016

CHEMISTRY REVIEW(S)

DIVISION OF NEUROPHARMACOLOGICAL DRUG PRODUCTS
Review of Chemistry, Manufacturing, and Controls

NDA#: 21-016

CHEMISTRY REVIEW: # 5

DATE REVIEWED: 17-DEC-02

Submission Type	Document Date	CDER Date	Assigned Date
ORIGINAL	27-OCT-98	27-OCT-98	28-OCT-98
RS	27-JUN-02		27-JUN-02

NAME AND ADDRESS OF APPLICANT: Pfizer Inc
50 Pequot Avenue
New London, CT 06320

DRUG PRODUCT NAME:

Proprietary: Relpax®
Nonproprietary/Established/USAN: Eletriptan hydrobromide [USAN Accepted September 1997]
Code Name/#: UK-116044-04
Chem. Type/Therapeutic Class: 1 S

PHARMACOLOGICAL CATEGORY / INDICATION: Migraine
DOSAGE FORM: Tablets
STRENGTH(S): 20, 40 mg, and 80 mg
ROUTE OF ADMINISTRATION: Oral
DISPENSED: XX Rx ___ OTC
SPECIAL PRODUCTS: No

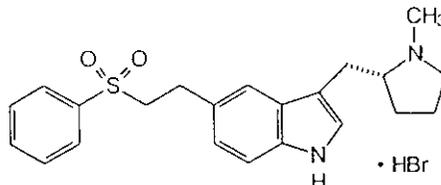
CHEMICAL NAME, STRUCTURAL FORMULA AND MOLECULAR FORMULA:

3-[[*(R)*-1-Methyl-2-pyrrolidinyl]methyl]-5-[2-(phenylsulfonyl)ethyl]indole, monohydrobromide

C₂₂H₂₆N₂O₂S HBr

CAS # 177834-92-3

Mol. Weight: 463.40



REMARKS / COMMENTS: This is a resubmission in response to the second Approvable letter dated December 1, 2000. The Approvable letter contained clinical deficiencies to be addressed by the sponsor and did not raise any CMC deficiencies. In this resubmission Pfizer provides a revised draft labeling package with instructions and other provisions for the all proposed strengths including the 80-mg Tablets (based on an additional clinical study recommended in the Approvable letter). No CMC changes have been made to the labeling as proposed in FDA's Approvable letter except for the addition of the 80-mg strength and a change in the How Supplied Section, where the presentation of the _____ s has changed to _____. The _____ are actually the originally proposed _____ embedded in paper push-through display cards (per sponsor's clarification by telephone on December 6, 2002). The sponsor notified the reviewer that the presentation's description will be revised to "blister cards" to avoid confusion.

The Methods Validation from the second FDA laboratory is still pending. The updated overall recommendation from the Office of Compliance is "Acceptable."

CONCLUSIONS AND RECOMMENDATIONS: As recommended in CMC Reviews #1, 2, and 3, and 4, NDA 21-016 may be approved for Chemistry based on adequate CMC information provided by Pfizer and satisfactory recommendation from the Office of Compliance.

cc: Orig NDA 21-016
HFD-120/Division File
HFD-120/Mzarifa/LChen
HFD-120/MGuzewska

Filename: n21016RS doc

Mona Zarifa, Ph.D., Review Chemist

6 page(s) have been removed because it contains trade secret and/or confidential information that is not disclosable.

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

/s/

Mona Zarifa
12/17/02 04:47:30 PM
CHEMIST

Maryla Guzewska
12/18/02 07:41:26 AM
CHEMIST

DIVISION OF NEUROPHARMACOLOGICAL DRUG PRODUCTS
Review of Chemistry, Manufacturing, and Controls

NDA#: 21-016

CHEMISTRY REVIEW: # 4

DATE REVIEWED: 27-NOV-00

Submission Type	Document Date	CDER Date	Assigned Date
ORIGINAL	27-OCT-98	27-OCT-98	28-OCT-98
AMENDMENT	01-JUN-00	02-JUN-00	27-NOV-00

NAME AND ADDRESS OF APPLICANT: Pfizer Inc.
Eastern Point Road
Groton, CT 06340

DRUG PRODUCT NAME:
Proprietary: Relpax™
Nonproprietary/Established/USAN: Eletriptan hydrobromide [USAN Accepted September 1997].
Code Name/#: UK-116044-04
Chem. Type/Therapeutic Class: 1 S

PHARMACOLOGICAL CATEGORY / INDICATION: Migraine
DOSAGE FORM: Tablets
STRENGTH(S): 20, 40 mg, and 80 mg
ROUTE OF ADMINISTRATION: Oral
DISPENSED: XX Rx ___ OTC
SPECIAL PRODUCTS: No

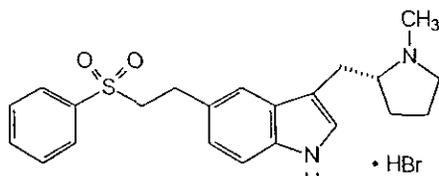
CHEMICAL NAME, STRUCTURAL FORMULA AND MOLECULAR FORMULA:

3-[[[(R)-1-Methyl-2-pyrrolidinyl]methyl]-5-[2-(phenylsulfonyl)ethyl]indole, monohydrobromide

C₂₂H₂₆N₂O₂S HBr

CAS = 177834-92-3

Mol. Weight. 463.40



REMARKS / COMMENTS: In their amendment dated June 1, 2000 Pfizer provides a final revised draft package with instructions and other provisions for the 80 mg tablets. In a meeting on November 27, 2000, the clinical reviewer recommended removal of the 80 mg tablets from the draft labeling. This review is in response to the clinical reviewer's recommendation. See CMC Review Notes for details and input to the action letter. The DTAAD laboratory has completed the validation of the regulatory methods and found these methods adequate (August 2, 2000). The Methods Validation from the second FDA laboratory is still pending. The latest satisfactory recommendation from the Office of Compliance was dated February 19, 1999 and is still valid (see attached EER and e-mail from EES Questions).

CONCLUSIONS AND RECOMMENDATIONS: As recommended in CMC Reviews #1, 2, and 3, NDA 21-016 may be approved for Chemistry based on adequate CMC information provided by Pfizer and satisfactory recommendation from the Office of Compliance. The Division of Biopharmaceuticals agrees with the proposed change in the original dissolution method. The dissolution specification to be accepted is Q = at 15 minutes using USP Apparatus 1 at 100 rpm in 900 mL 0.1M HCl at 37° C. Available stability results support the proposed expiration date of 24 months. See CMC Review Notes for CMC input to the action letter with regards to the proposed draft package insert and container/carton labels.

cc: Orig. NDA 21-016
HFD-120/Division File
HFD-120/Mzarifa/LChen
HFD-120/LChen
HFD-120/MGuzewska/R/D Init.by: MG
HFD-810/Jsimmons

Mona Zarifa, Ph.D., Review Chemist
Filename: n21016003.doc

7 page(s) have been removed because it contains trade secret and/or confidential information that is not disclosable.

/s/

Mona Zarifa
11/27/00 03:35:36 PM
CHEMIST

Maryla Guzewska
11/27/00 03:42:07 PM
CHEMIST

DIVISION OF NEUROPHARMACOLOGICAL DRUG PRODUCTS
Review of Chemistry, Manufacturing, and Controls

NDA#: 21-016

CHEMISTRY REVIEW: # 3

DATE REVIEWED: 06-NOV-00

Submission Type	Document Date	CDER Date	Assigned Date
ORIGINAL	27-OCT-98	27-OCT-98	28-OCT-98
AMENDMENTS	01-JUN-00	02-JUN-00	11-OCT-00

NAME AND ADDRESS OF APPLICANT: Pfizer Inc.
Eastern Point Road
Groton, CT 06340

DRUG PRODUCT NAME:
Proprietary: Relpax™
Nonproprietary/Established/USAN: Eletriptan hydrobromide [USAN Accepted September 1997].
Code Name/#: UK-116044-04
Chem. Type/Therapeutic Class: 1 S

PHARMACOLOGICAL CATEGORY / INDICATION: Migraine
DOSAGE FORM: Tablets
STRENGTH(S): 20, 40, and 80 mg
ROUTE OF ADMINISTRATION: Oral
DISPENSED: XX Rx ___ OTC
SPECIAL PRODUCTS: No

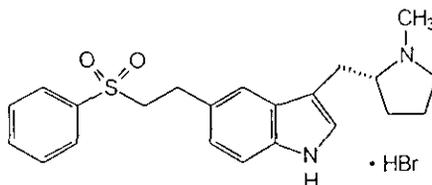
CHEMICAL NAME, STRUCTURAL FORMULA AND MOLECULAR FORMULA:

3-[[[(R)-1-Methyl-2-pyrrolidinyl]methyl]-5-[2-(phenylsulfonyl)ethyl]indole, monohydrobromide

C₂₂H₂₆N₂O₂S HBr

CAS # 177834-92-3

Mol Weight: 463.40



REMARKS / COMMENTS: AM June 1, 2000: Pfizer responds to the Approvable Letter dated October 27, 2000. No CMC issues were outstanding. A final draft package insert (version 3) is provided as well as copies of revised carton labels for the 80 mg tablets with instructions for the appropriate use of this strength. See CMC Review Notes for details and input to the action letter. The DTAAD laboratory has completed the validation of the regulatory methods and found these methods adequate (August 2, 2000). The Methods Validation from the second FDA laboratory is still pending. The latest satisfactory recommendation from the Office of Compliance was dated February 19, 1999 and is still valid (see attached EER and e-mail from EES Questions).

CONCLUSIONS AND RECOMMENDATIONS: AS recommended in CMC Reviews #1 and 2, NDA 21-016 may be approved for Chemistry based on adequate CMC information provided by Pfizer and satisfactory recommendation from the Office of Compliance. The Division of Biopharmaceuticals agrees with the proposed change in the original dissolution method. The dissolution specification to be accepted is Q = at 15 minutes using USP Apparatus 1 at 100 rpm in 900 mL 0.1M HCl at 37° C. Available stability results support the proposed expiration date of 24 months. See CMC Review Notes for CMC input to the action letter with regards to the proposed draft package insert and container/carton labels.

cc: Ong, NDA 21-016
HFD-120/Division File
HFD-120/Mzarifa/LChen
HFD-120/LChen
HFD-120/MGuzewska/R/D Init.by: MG
HFD-810/Jsimmons

Mona Zarifa, Ph.D., Review Chemist
Filename: n2101602.doc

2 page(s) have been removed because it contains trade secret and/or confidential information that is not disclosable.

FDA CDER EES
ESTABLISHMENT EVALUATION REQUEST
SUMMARY REPORT

Last Milestone: OC RECOMMENDATION
Milestone Date: 14-DEC-1998
Decision: ACCEPTABLE
Reason: BASED ON PROFILE

APPEARS THIS WAY
ON ORIGINAL

APPEARS THIS WAY
ON ORIGINAL

/s/

Mona Zarifa

== 11/13/00 04:22:33 PM

CHEMIST

Maryla Guzewska

11/13/00 04:29:08 PM

CHEMIST

chen

DIVISION OF NEUROPHARMACOLOGICAL DRUG PRODUCTS
Review of Chemistry, Manufacturing, and Controls

JUL 13 1999

NDA#: 21-016

CHEMISTRY REVIEW: # 2

DATE REVIEWED: 28-JUN-99

Submission Type	Document Date	CDER Date	Assigned Date
ORIGINAL	27-OCT-98	27-OCT-98	28-OCT-98
AMENDMENTS	17-JUN-99	21-JUN-99	21-JUN-99
	23-JUN-99	24-JUN-99	28-JUN-99

NAME AND ADDRESS OF APPLICANT: Pfizer Inc.
Eastern Point Road
Groton, CT 06340

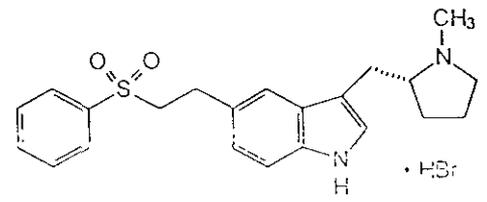
DRUG PRODUCT NAME:
Proprietary: Relpax™
Nonproprietary/Established/USAN: Eletriptan hydrobromide [USAN Accepted September 1997].
Code Name/#: UK-116044-04
Chem. Type/Therapeutic Class: 1 S

DESI/PATENT STATUS: Patent No. 5,545,644 expires in August 13, 2013
PHARMACOLOGICAL CATEGORY / INDICATION: Migraine
DOSAGE FORM: Tablets
STRENGTH(S): 20, 40, and 80 mg
ROUTE OF ADMINISTRATION: Oral
DISPENSED: XX Rx ___ OTC
SPECIAL PRODUCTS: No

CHEMICAL NAME, STRUCTURAL FORMULA AND MOLECULAR FORMULA:

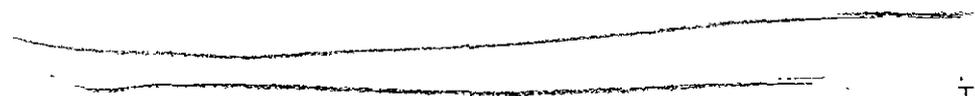
(R)-3-(1-methyl-2-pyrrolidinylmethyl)-5-[2-(phenylsulfonyl)-ethyl]-1H-indole hydrobromide

C₂₂H₂₆N₂O₂S HBr



Mol. Weight: 463.43

Remarks / Comments: AM June 17: Pfizer responds to our request to clarify the identity of the



The corrected list of

specifications for the drug substance is attached.

AM June 23: Pfizer makes editorial corrections to the Standard Methods Procedures. Copies of the corrected procedures have been included in the Methods Validation packages sent to the assigned FDA laboratories.

CONCLUSIONS AND RECOMMENDATIONS: As recommended in CMC Review #1, based on Office of Compliance recommendation and adequate CMC information provided by Pfizer, NDA 21-016 is adequate for approval with respect to CMC. The Division of Biopharmaceuticals agrees with the proposed change in the original dissolution method. The dissolution specification to be accepted is Q = ~~10~~ at 15 minutes using USP Apparatus 1 at 100 rpm in 900 mL 0.1M HCl at 37° C. Available stability results support the proposed expiration date of 24 months.

/S/

cc: Orig. NDA 21-016
HFD-120/Division File
HFD-120/MZarifa
HFD-120/LChen
HFD-120/MGuzewska/R/D Init.by: M.G
HFD-810/CHoiberg

/S/ 13.99

Mona Zarifa, Ph.D., Review Chemist
Filename: n2101600.doc

3 page(s) have been removed because it contains trade secret and/or confidential information that is not disclosable.

DIVISION OF NEUROPHARMACOLOGICAL DRUG PRODUCTS
Review of Chemistry, Manufacturing, and Controls

JUN 18 1999

NDA#: 21-016

CHEMISTRY REVIEW: # 1

DATE REVIEWED: 18-JUN-99

Submission Type	Document Date	CDER Date	Assigned Date
ORIGINAL	27-OCT-98	27-OCT-98	28-OCT-98
AMENDMENTS	27-APR-99	28-APR-99	28-APR-99
	27-MAY-99	28-MAY-99	28-MAY-99
	17-MAY-99	18-MAY-99	18-MAY-99

NAME AND ADDRESS OF APPLICANT: Pfizer Inc.
Eastern Point Road
Groton, CT 06340

DRUG PRODUCT NAME:

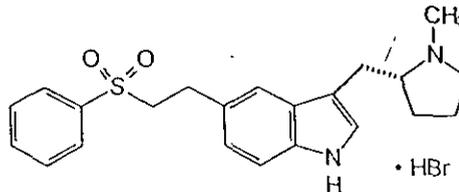
Proprietary: Relpax™
Nonproprietary/Established/USAN: Eletriptan hydrobromide [USAN Accepted September 1997]. See Attachment 3
Code Name/#: UK-116044-04
Chem. Type/Therapeutic Class: 1 S

DESI/PATENT STATUS: Patent No. 5,545,644 expires in August 13, 2013
PHARMACOLOGICAL CATEGORY / INDICATION: Migraine
DOSAGE FORM: Tablets
STRENGTH(S): 20, 40, and 80 mg
ROUTE OF ADMINISTRATION: Oral
DISPENSED: XX Rx ___ OTC
SPECIAL PRODUCTS: No

CHEMICAL NAME, STRUCTURAL FORMULA AND MOLECULAR FORMULA:

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

C₂₂H₂₆N₂O₂S HBr



Mol. Weight: 463.43

Remarks / Comments: Pfizer has provided adequate CMC information in accordance with the pre-NDA agreement of July 14, 1998. In the amendment dated April 27, 1999, the sponsor provides the pending stability data on the drug substance and drug product in accordance to Pfizer's commitment in the agreement. Updated 24-month stability data for the drug substance is provided in the May 27, 1999 amendment. All site inspection have been completed and Office of Compliance recommendation is "Acceptable." See Attachment 2 for EER report.

CONCLUSIONS AND RECOMMENDATIONS: Based on Office of Compliance recommendation and adequate CMC information provided by Pfizer, we recommend that NDA 21-016 is Approved. The Division of Biopharmaceuticals agrees with the proposed change in the original dissolution method: The dissolution specification to be accepted is Q = ∞ at 15 minutes using USP Apparatus 1 at 100 rpm in 900 mL 0.1M HCl at 37° C Available stability results support the proposed expiration date of 24 months.

cc: Orig. NDA 21-016
HFD-120/Division File
HFD-120/MZarifa
HFD-120/LChen
HFD-120/MGuzewska/R/D Init.by: MG
HFD-810/CHoiberg

151
Mona Zarifa, Ph.D., Review Chemist
Filename: n2101600.doc

44 page(s) have been removed because it contains trade secret and/or confidential information that is not disclosable.

ESTABLISHMENT EVALUATION REQUEST SUMMARY REPORT

Application: NDA 21016/000 Priority: Org Code: 120
 Stamp: 27-OCT-1998 Regulatory Due: 27-AUG-1999 Action Goal: District Goal: 28-JUN-1999
 Applicant: PFIZER Brand Name: RELPAX (ELETRIPTAN HYDROBROMIDE)20/40/80
 EASTERN POINT RD Established Name:
 GROTON, CT 06340 Generic Name: ELETRIPTAN HYDROBROMIDE
 Dosage Form: TAB (TABLET)
 Strength: 20,40,80 MG/ML

FDA Contacts: L. CHEN (HFD-120) 301-594-5529 , Project Manager
 M. ZARIFA (HFD-120) 301-594-2850 , Review Chemist
 M. GUZEWSKA (HFD-120) 301-594-5571 , Team Leader

Overall Recommendation:

ACCEPTABLE on 19-FEB-1999 by M. EGAS (HFD-322) 301-594-0095

Establishment:

DMF No:

AADA No:

Profile: TCM OAI Status: NONE
 Last Milestone: OC RECOMMENDATION
 Milestone Date 14-DEC-1998
 Decision: ACCEPTABLE
 Reason: BASED ON PROFILE

Responsibilities:

Establishment: 1211022
 PFIZER INC
 EASTERN POINT RD
 GROTON, CT 06340

DMF No:

AADA No:

Profile: CSN OAI Status: NONE
 Last Milestone: OC RECOMMENDATION
 Milestone Date 14-DEC-1998
 Decision: ACCEPTABLE
 Reason: BASED ON PROFILE
 Profile: CTL OAI Status: NONE
 Last Milestone: OC RECOMMENDATION
 Milestone Date 14-DEC-1998
 Decision: ACCEPTABLE
 Reason: BASED ON PROFILE

Responsibilities: DRUG SUBSTANCE
 MANUFACTURER
 FINISHED DOSAGE STABILITY
 TESTER

Establishment: 2410924
 PFIZER INC
 630 FLUSHING AVE

DMF No:

AADA No:

FDA CDER EES
ESTABLISHMENT EVALUATION REQUEST
SUMMARY REPORT

BROOKLYN, NY 11206

Profile: TCM OAI Status: NONE
Last Milestone: OC RECOMMENDATION
Milestone Date 19-FEB-1999
Decision: ACCEPTABLE
Reason: DISTRICT RECOMMENDATION

Responsibilities: FINISHED DOSAGE
MANUFACTURER
FINISHED DOSAGE PACKAGER
FINISHED DOSAGE RELEASE
TESTER
FINISHED DOSAGE STABILITY
TESTER

Establishment: 9610425
PFIZER LTD

DMF No:
AADA No:

SANDWICH KENT, , UK CT139NJ

Profile: CSN OAI Status: NONE
Last Milestone: OC RECOMMENDATION
Milestone Date 14-DEC-1998
Decision: ACCEPTABLE
Reason: BASED ON PROFILE

Responsibilities: FINISHED DOSAGE STABILITY
TESTER
INTERMEDIATE MANUFACTURER

Profile: CTL OAI Status: NONE
Last Milestone: OC RECOMMENDATION
Milestone Date 14-DEC-1998
Decision: ACCEPTABLE
Reason: BASED ON PROFILE

Establishment: 9611016
PFIZER PHARMACEUTICALS INC
RINGASKIDDY
COUNTY CORK, , EI

DMF No:
AADA No:

Profile: CSN OAI Status: NONE
Last Milestone: OC RECOMMENDATION
Milestone Date 14-DEC-1998
Decision: ACCEPTABLE
Reason: BASED ON PROFILE

Responsibilities: DRUG SUBSTANCE
MANUFACTURER

Establishment:



DMF No:
AADA No:

Profile: CTL OAI Status: NONE

Responsibilities: 

FDA CDER EES
ESTABLISHMENT EVALUATION REQUEST
SUMMARY REPORT

Last Milestone: OC RECOMMENDATION
Milestone Date 14-DEC-1998
Decision: ACCEPTABLE
Reason: BASED ON PROFILE

APPEARS THIS WAY
ON ORIGINAL

APPEARS THIS WAY
ON ORIGINAL

APPEARS THIS WAY
ON ORIGINAL

PK9

CDER LABELING AND NOMENCLATURE COMMITTEE

CONSULT #	1112	HFD#	120	PROPOSED PROPRIETARY NAME:	PROPOSED ESTABLISHED NAME:
ATTENTION:	Lana Y. Chen		Relpax		eletriptan oral tablets

A. Look-alike/Sound-alike

Potential for confusion:

Relafen	XXX	Low	Medium	High
Relaxin	XXX	Low	Medium	High
Keflex	XXX	Low	Medium	High
Z-Pak	XXX	Low	Medium	High
		Low	Medium	High

B. Misleading Aspects:

C. Other Concerns:

--	--

D. Established Name

Satisfactory
 Unsatisfactory/Reason

The USP does not include "oral" in the title of tablet monographs

Recommended Established Name

eletriptan tablets

E. Proprietary Name Recommendations:

ACCEPTABLE UNACCEPTABLE

F. Signature of Chair/Date

/s/

4/19/99