

CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

Application Number: 20450/S-001

**Trade Name: CEREBYX INJECTION 75 MG/ML (50
MG/ML PE)**

Generic Name: FOSPHENYTOIN SODIUM

**Sponsor: PARKE-DAVIS PHARMACEUTICAL
RESEARCH, DIVISION OF WARNER-
LAMBERT COMPANY**

Approval Date: 12/26/96

Indication(s): TREATMENT OF EPILEPSY

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION: 20450/S-001

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	Included	Pending Completion	Not Prepared	Not Required
Approval Letter	X			
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Final Printed Labeling	X			
Medical Review(s)				X
Chemistry Review(s)				X
EA/FONSI				X
Pharmacology Review(s)				X
Statistical Review(s)				X
Microbiology Review(s)				X
Clinical Pharmacology Biopharmaceutics Review(s)				X
Bioequivalence Review(s)				X
Administrative Document(s)/ Correspondence	X			

CENTER FOR DRUG EVALUATION AND RESEARCH

Application Number: 20450/S-001

APPROVAL LETTER

NDA 20-450/S-001

DEC 26 1996

Parke-Davis Pharmaceutical Research
Division of Warner-Lambert Company
Attention: James A. Parker
201 Tabor Road
Morris Plains, NJ 07950

Dear Mr. Parker:

We acknowledge your December 6, 1996 supplemental new drug application received on December 9, 1996 under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Cerebyx™ (fosphenytoin sodium) Injection 75 mg/mL (50 mg/mL PE).

The supplemental application provides for revision of the vial and carton labels to express the concentration in terms of phenytoin equivalent mg (PE) per mL instead of the current mg/mL. In addition, the following statement from the WARNINGS section of the package insert has been added to the carton labels.

DOSES OF CEREBYX™ ARE EXPRESSED AS THEIR PHENYTOIN SODIUM EQUIVALENTS (PE = phenytoin sodium equivalents).

We have completed the review of this supplemental application and it is approved effective on the date of this letter.

We are concerned, however, about the seemingly long interval over which Cerebyx™ product carrying the old and misleading labeling will remain available for use. You estimate that Cerebyx™ product bearing the newly approved label will not replace Cerebyx™ product bearing the older labeling until mid-April 1997 or later. In light of the fact that the old labeling is confusing and can, as reports from post-marketing experience already document, cause or contribute to the misuse of Cerebyx™, we urge that you take steps to remove/withdraw product carrying the old labeling from the market now.

Ideally, all supplies of the mislabeled product, including even single boxes stocked on emergency carts in health care facilities should be removed. While we are mindful of the effort and expense that would be involved in such a program, we strongly urge you to initiate such an effort promptly.

During the interval required to plan and initiate such a program, it is important that the letter you propose to issue to hospital pharmacists advising them of the labeling changes and the factors requiring the action also ask them to remove stocks of the product bearing the old label from distribution within their institution. There is no public health risk involved in

doing so, because if product bearing the revised labeling is not available, alternative sources of phenytoin injection are available.

Your prompt attention to this matter is important; we would appreciate learning as soon as possible of your plans. We will be happy to discuss the matter further with your representatives if you would find that helpful.

We remind you that you must comply with the requirements for an approved NDA set forth under 21 CFR 314.80 and 314.81.

If you have any questions, please contact:

Robbin Nighswander, R.Ph.
Regulatory Management Officer
(301) 594-2777

APPEARS THIS WAY
ON ORIGINAL

Sincerely yours.

/S/

12/24/96

APPEARS THIS WAY
ON ORIGINAL

Paul Leber, M.D.
Director
Division of Neuropharmacological Drug
Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

APPEARS THIS WAY
ON ORIGINAL

cc:

Original NDA 20-450

HFD-120/Div. files

HFD-120/Leber

/Katz/Feeney/S/

/Blum/Heiman.

/Nighswander

12/24/96

/S/ 12/24/96

APPEARS THIS WAY
ON ORIGINAL

HFD-101/L.Carter

HFD-810/C.Hoiberg

DISTRICT OFFICE

HF-2/Medwatch (with labeling)

HFD-80 (with labeling)

HFD-40/DDMAC (with labeling)

HFD-613 (with labeling)

HFD-735/(with labeling) - for all NDAs and supplements for adverse reaction changes.

HFD-560/D.Bowen (with labeling - for OTC Drug Products Only)

drafted: /December 16, 1996/

r/d Initials:rmn

final:12/24/96rmn

SUPPLEMENT APPROVAL

APPEARS THIS WAY
ON ORIGINAL

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: 20450/S-001

FINAL PRINTED LABELING

Labeling: SLK-001
NDA No: 20-450 Rec'd 12-9-96
Reviewed by /s/ [redacted] 12/26/96

APPROVED

DEC 26 1996

**APPEARS THIS WAY
ON ORIGINAL**

N.0071-4007-06
Each vial contains
phenytoin sodium 150 mg
equivalent to 100 mg
phenytoin sodium
Liquid Dosage. See
package insert.
© PARKE-DAVIS
Cerebyx®
(Phenytoin Sodium Injection)
50 mg PE/mL
(PE = phenytoin sodium equivalent)
For IM or IV use
2 mL Vial
4007G012

**APPEARS THIS WAY
ON ORIGINAL**

**APPEARS THIS WAY
ON ORIGINAL**

**APPEARS THIS WAY
ON ORIGINAL**

APPEARS THIS WAY
ON ORIGINAL

N 0071-4008-10

For IM or IV use.
Each vial contains fosphenytoin sodium 750 mg equivalent to 500 mg phenytoin sodium.
Usual Dosage—See package insert for full prescribing information.

Note—Administration differs from parenteral phenytoin. See Dosage and Administration. Store under refrigeration at 2°C to 8°C (36°F to 46°F).

STERI-VIAL®
Cerebyx®
(Fosphenytoin Sodium Injection)

50 mg PE/mL
(PE = phenytoin sodium equivalents)

Caution—Federal law prohibits dispensing without prescription.

10 mL Vial

PARKE-DAVIS
Morris Plains, N.J. 07950, U.S.A.
© 1986

4008G013

APPEARS THIS WAY
ON ORIGINAL

APPEARS THIS WAY
ON ORIGINAL

APPEARS THIS WAY
ON ORIGINAL

 PARKE-DAVIS

25 VIALS (2 mL each)

Caution—Federal law prohibits dispensing without prescription.

Cerebyx®
(Fosphenytoin Sodium Injection)
50 mg PE/mL
(PE = phenytoin sodium equivalents)

STERIL-VIAL®

N 0071-4007-05

For IM or IV Use.

Each vial contains fosphenytoin sodium, 150 mg equivalent to 100 mg phenytoin sodium, Trometamine, USP (TRIS) as a buffer, Hydrochloric Acid, NF or Sodium Hydroxide, NF to adjust the pH to 8.6 to 9, and sufficient Water for Injection, USP.

Usual Dosage—See package insert for full prescribing information.

Note—Administration differs from parenteral phenytoin. See Dosage and Administration Store under refrigeration at 2°C to 8°C (36°F to 46°F).

DOSE OF CEREBYX ARE EXPRESSED AS THEIR PHENYTOIN SODIUM EQUIVALENTS (PE = phenytoin sodium equivalent)

© 1986, Warner-Lambert Co.

PARKE-DAVIS
Div of Warner-Lambert Co/Morris Plains, NJ 07950 USA

APPEARS THIS WAY
ON ORIGINAL

APPEARS THIS WAY
ON ORIGINAL

APPEARS THIS WAY
ON ORIGINAL

4007C012

APPEARS THIS WAY
ON ORIGINAL

N 0071-4007-05

STERIL-VIAL®

Cerebyx®
(Fosphenytoin Sodium Injection)
50 mg PE/mL
(PE = phenytoin sodium equivalents)

Caution—Federal law prohibits dispensing without prescription.

25 VIALS (2 mL each)

APPEARS THIS WAY
ON ORIGINAL



25 VIALS
Caution—
dispensing

Cerebryx
(Fosphenytoin Sodium Injection)
50 mg PE/mL
(PE = phenytoin equivalents)

Contentment to 100 mg phenytoin sodium,
sodium salt, NF or Sodium Hydroxide, NF
Injection, USP
See Dosage and Administration
Section, USP
16-Ph.
PHENYTOIN SODIUM EQUIVALENTS

350 USA

APPEARS THIS WAY
ON ORIGINAL

4007C012


APPEARS THIS WAY
ON ORIGINAL

APPEARS THIS WAY
ON ORIGINAL

N 0071-4007-05
STERI-VIAL®
Cerebryx®
(Fosphenytoin Sodium Injection)
50 mg PE/mL
(PE = phenytoin sodium equivalents)
Caution—Federal law prohibits dispensing without prescription.
25 VIALS (2 mL each)

APPEARS THIS WAY
ON ORIGINAL

APPEARS THIS WAY
ON ORIGINAL


FOR POSITION ONLY
N 0071-4007-05

APPEARS THIS WAY
ON ORIGINAL

APPEARS THIS WAY
ON ORIGINAL

PARKE-DAVIS

10 VIALS (10 mL each)

Caution—Federal law prohibits dispensing without prescription.

50 mg PE/mL
(PE = phenytoin sodium equivalents)

Cerebyx®
(Fosphenytoin Sodium Injection)

STERIL-VIAL®

11-8008-1700 N

For IM or IV Use.

Each vial contains fosphenytoin sodium 750 mg equivalent to 500 mg phenytoin sodium, Tromethamine, USP (TRIS) as a buffer, Hydrochloric Acid, NF or Sodium Hydroxide, NF to adjust the pH to 8.6 to 9, and sufficient Water for Injection, USP.

Usual Dosage—See package insert for full prescribing information.

Note—Administration differs from parenteral phenytoin. See Dosage and Administration.

Store under refrigeration at 2°C to 8°C (36°F to 46°F).

DOSES OF CEREBYX ARE EXPRESSED AS THEIR PHENYTOIN SODIUM EQUIVALENTS
(PE = phenytoin sodium equivalent)

© 1996, Warner-Lambert Co.

PARKE-DAVIS

Div of Warner-Lambert Co/Morris Plains, NJ 07950 USA

4008C012

STERIL-VIAL®

Cerebyx®
(Fosphenytoin Sodium Injection)

50 mg PE/mL
(PE = phenytoin sodium equivalents)

Exp date and lot

APPEARS THIS WAY
ON ORIGINAL

N 09744908-10

STERIL-VIAL®

Cerebyx®
(Fosphenytoin Sodium Injection)

50 mg PE/mL
(PE = phenytoin sodium equivalents)

Caution—Federal law prohibits dispensing without prescription.

10 VIALS (10 mL each)

PARKE-DAVIS

APPEARS THIS WAY
ON ORIGINAL



STERIL VIAL 10

50 mg PE/ml

(Fosphenytoin sodium)

Cerebyx

STERILE

100 N

APPEARS THIS WAY
ON ORIGINAL

4008C012

N 0071-4008-10

STERIL VIAL®

Cerebyx®

(Fosphenytoin Sodium Injection)

50 mg PE/ml

(PE = phenytoin sodium equivalents)

Exp date and lot

STERIL VIAL®

Cerebyx®

(Fosphenytoin Sodium Injection)

50 mg PE/ml

(PE = phenytoin sodium equivalents)

Caution—Federal law prohibits dispensing without prescription.

10 VIALS (10 mL each)

PARKE-DAVIS



N 0071-4008-10

equivalent to 500 mg phenytoin sodium,
chloric Acid, NF or Sodium Hydroxide, NF
for Injection, USP.
Additional information:
phenytoin. See Dosage and Administration.
(69F).
PHENYTOIN SODIUM EQUIVALENTS

USA

APPEARS THIS WAY
ON ORIGINAL

APPEARS THIS WAY
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ON ORIGINAL

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: 20450/S-001

ADMINISTRATIVE DOCUMENTS/CORRESPONDENCE

ORIGINAL

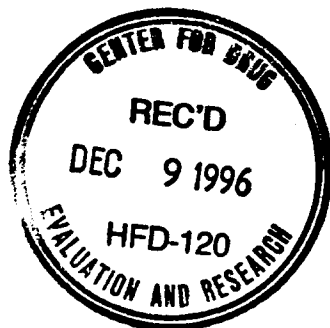
 **PARKE-DAVIS**
People Who Care

NDA NO. 20-450 REF. NO. SLR-001

NDA SUPPL FOR Labeling

December 6, 1996

NDA SUPPLEMENT



NDA 20-450
Reference No. 41
Cerebyx® (fosphenytoin sodium injection)

Re: Labeling
Special Supplement -
Changes Being Effected

Paul D. Leber, M.D.
Director
Division of Neuropharmacological
Drug Products (HFD-120)
Document Control Room 4037
Center for Drug Evaluation and Research
Food and Drug Administration
Woodmont 2
1451 Rockville Pike
Rockville, Maryland 20852

Dear Dr. Leber:

Reference is made to our approved NDA for Cerebyx® (fosphenytoin sodium injection) and to the November 26, 1996 telephone conversation between yourself and Irwin Martin of Parke-Davis.

In that conversation, Parke-Davis was requested to revise the current labels for Cerebyx due to a concern for possible confusion surrounding proper dosing for the product.

It was suggested that the vial and carton labels for Cerebyx be revised to express the concentration in terms of phenytoin equivalent mg (PE) per mL instead of the current mg/mL. In addition, the following statement from the WARNINGS section of the package insert was suggested as an addition to the carton labels:

DOSES OF CEREBYX ARE EXPRESSED AS THEIR PHENYTOIN SODIUM EQUIVALENTS (PE = phenytoin sodium equivalents).

No revision was requested to be made to the current package insert.

Paul D. Leber, M.D.
NDA 20-450
December 6, 1996
Page 2

**APPEARS THIS WAY
ON ORIGINAL**

On December 5, 1996, James Parker of Parke-Davis had a telephone conversation with Robin Nighswander of your Division. The purpose of this conversation was to clarify the agency's expectations regarding this labeling submission (e.g., prior approval required or Changes Being Effected). Mr. Nighswander stated we should submit the supplement as "Changes Being Effected" and give the agency a two to four week window for review prior to implementation.

**APPEARS THIS WAY
ON ORIGINAL**

Therefore, in accordance with 21 CFR 314.70(c)(2)(iii), we are submitting revised vial and carton labels as listed below. This labeling revision is designed to strengthen an instruction about the administration of the drug.

**APPEARS THIS WAY
ON ORIGINAL**

Attached are 16 copies of the Final Printed Labeling, with the revisions described above, for the following components:

- Attachment 1 Vial Label (2mL vial)- specification # 4007G012
- Attachment 2 Carton (2mL vial)- specification # 4007C012
- Attachment 3 Vial Label (10mL vial)- specification # 4008G013
- Attachment 4 Carton (10mL vial)- specification # 4008C012

**APPEARS THIS WAY
ON ORIGINAL**

Also included, as Attachment 5, is a draft copy of a "Dear Hospital Pharmacist" letter that we intend to distribute as notification of this labeling clarification. This submission, with a copy of the pharmacist letter, is also being sent concurrently to Dr. Leah Palmer, Branch Chief, DDMAC for her review. This letter will be mailed to the target audience on approximately the first of the new year.

**APPEARS THIS WAY
ON ORIGINAL**

The revised labels will be used for all product manufactured in the future. (Please be advised that the manufacturing site will be shutdown beginning December 19, 1996 through January 6, 1997. Therefore no production of Cerebyx is anticipated before the January 6, 1997).

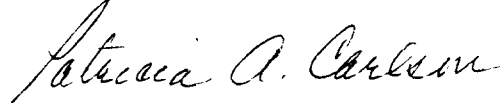
**APPEARS THIS WAY
ON ORIGINAL**

We anticipate that the current inventory of Cerebyx will be exhausted by mid-April 1997. At that time, product with the revised vial and carton labels will be available and will be used to replace the exhausted inventory.

Paul D. Leber, M.D.
NDA 20-450
December 6, 1996
Page 3

Should you have any questions or require any additional information, please contact me at 201/540-5529 or by FAX at 201/540/5972.

Sincerely,



Patricia A. Carlson
Manager
Advertising and labeling
Worldwide Regulatory Affairs

APPEARS THIS WAY
ON ORIGINAL

PC\sv\rm
t:\nda\20-450\120396.041

Attachments
Desk Copy: L. Palmer, DDMAC, HFD-40

APPEARS THIS WAY
ON ORIGINAL

cc:

Original NDA 20-450

HFD-120/Div. files

HFD-120/Leber

/Katz/Feeney

/Blum/Heimann

/Nighswander

/S/ 12/24/96
/S/ 12/24/96

APPEARS THIS WAY
ON ORIGINAL

HFD-101/L.Carter

HFD-810/C.Hoiberg

DISTRICT OFFICE

HF-2/Medwatch (with labeling)

HFD-80 (with labeling)

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drafted: /December 16, 1996/

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SUPPLEMENT APPROVAL

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