CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

NDA 10-151/
S-022, 029, 030, 032, 033, & 034

Name:	Dilantin Injection (Phenytoin Sodium Injection)
Sponsor:	Parke Davis
Approval Date:	11/20/2001

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APPLICATION NUMBER:

NDA 10-151/
S-022, 029, 030, 032, 033, & 034

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APPLICATION NUMBER:

NDA 10-151/
S-022, 029, 030, 032, 033, & 034

APPROVAL LETTER

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

NDA 8-762/S-020/021/022/026
NDA 10-151/S-022/029/030/032/033/034

Pfizer Pharmaceuticals
Attention: Rita A. Wittich
Drug Regulatory Affairs
235 East 42nd Street
New York, NY 10017-3184

Dear Ms. Wittich:

Please refer to your new drug applications submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Dilantin-125 (phenytoin oral suspension, USP) Suspension (NDA 8-762) and Dilantin (Phenytoin Sodium Injection, USP) Injection (NDA 10-151).

We additionally refer to the following supplemental applications:

NDA	Supplement	Dated
8-762	S-020	May 25, 1994, and amended on January 28, 1997
8-762	S-021	July 18, 1994
8-762	S-022	January 27, 1995
8-762	S-026	December 3, 1996
10-151	S-022	May 10, 1983 and amended on November 1, 1983
10-151	S-029	September 25, 1987, and amended on May 10, 1988
10-151	S-030	September 25, 1989
10-151	S-032	August 9, 1994
10-151	S-033	January 25, 1995, and amended on January 28, 1997
10-151	S-034	December 3, 1996

These applications provide for the following revisions to product labeling:

Dilantin-125 (phenytoin oral suspension, USP) Suspension

8-762/S-020

1. The addition and deletion of several inactive ingredients items under the **DESCRIPTION** section.
2. The deletion of several phenytoin products which are no longer marketed which include Dilantin 30 mg/5 ml suspension and Dilantin ampules throughout the labeling. We additionally note the deletion of several of the quantity sizes under the **HOW SUPPLIED** section since they are no longer marketed.
3. A complete revision to the **WARNINGS** section in regard to use during pregnancy and risks to the fetus to provide for updated information. The addition to the **PRECAUTIONS-General** section regarding adverse events associated with the combination use of phenytoin, cranial radiation, and reduction of corticosteroids.
4. The addition to the **PRECAUTIONS-Information for Patients** section reminding patients that they should use a calibrated measuring device.
5. The addition of the terms cimetidine, fluoxetine, ticlopidine, and paroxetine to the **PRECAUTIONS-Drug Interactions** section.
6. The addition of a new subsection under the **PRECAUTIONS** section entitled **Drug-Enteral Feeding/Nutritional Preparations Interaction.**
7. The addition of a cautionary statement under the **PRECAUTIONS-Drug/Laboratory Test Interactions** regarding immunoanalytical methods.
8. The addition of the statement "Pregnancy Category D" under the **PRECAUTIONS-Pregnancy** section.
9. The addition of a **Pediatric Use** section under the **PRECAUTIONS** section.

8-762/S-021

This supplement provides for the addition of fluoxetine to the **PRECAUTION-Drug Interactions** section as requested in an Agency letter dated February 3, 1994.

8-762/S-022

This supplement provides for revisions to the container labels as well as to the **PRECAUTIONS-Information for Patients** section stating that a calibrated measuring device should be used to measure the oral suspension.

8-762/S-026

This supplement provides for the following revisions:

1. The addition of a **Pediatric Use** subsection under the **PRECAUTIONS** section.
2. Several minor revisions to the **OVERDOSAGE** and **DOSAGE AND ADMINISTRATION** sections to conform to standard pediatric nomenclature.
3. Remove reference to the 5 ml unit dose pouches under the **HOW SUPPLIED** section since they are no longer marketed.

Dilantin (Phenytoin Sodium Injection, USP) Injection

10-151/S-022

This supplement provides for dosage recommendations for neonates in status epilepticus.

10-151/S-029
This supplement provides for revisions to the **PRECAUTIONS** and **ADVERSE REACTIONS** sections of labeling based upon your review of drug experience reports.

10-151/S-030
This supplement provides for revisions to the **DOSAGE AND ADMINISTRATION** section to strengthen the directions for the administration of parental Dilantin via the bolus method, and added instructions for the administration via the infusion method.

10-151/S-032
This supplement provides for the addition of fluoxetine to the **PRECAUTION-Drug Interactions** section as requested in an Agency letter dated February 3, 1994.

10-151/S-033
This labeling supplement is similar to that submitted for **8-762/SLR-020** (see above). We note that it was submitted by you in order to 1) update the labeling to add pertinent information from the Cerebyx labeling to the Dilantin labeling, and 2) assist the Agency in taking an action for the open labeling supplements.
10-151/S-034
This supplement provides for the following revisions:
1. The addition of a **Pediatric Use** subsection under the **PRECAUTIONS** section.
2. Several minor revisions to the **OVERDOSAGE** and **DOSAGE AND ADMINISTRATION** sections to conform to standard pediatric nomenclature.

We note that supplemental application 8-762/S-020 was submitted as a "prior approval" application and was amended on January 28, 1997. The amendment incorporates all of the revisions made in S-021/022/026 as well as strengthens the labeling to incorporate important safety changes already in the Cerebyx labeling.

Similarly, we note that supplemental application 10-151/S-033 was submitted as a "prior approval" application and was amended on January 28, 1997. The amendment incorporates all of the revisions made in S-022/029/030/032/034 as well as strengthens the labeling to incorporate important safety changes already in the Cerebyx labeling.

We have completed our review of these supplemental applications, as amended, and have concluded that adequate information has been presented to demonstrate that the drug product is safe and effective for use as recommended in your draft labeling submitted on January 28, 1997 except for your proposed addition to the **PRECAUTIONS-General** section regarding adverse events associated with the combination use of phenytoin, cranial radiation, and reduction of corticosteroids.

We are currently evaluating these data in conjunction with the Agency's Office of Postmarketing Drug Risk Assessment, and we will comment on these changes in a separate letter.

Accordingly, these supplemental applications are approved effective on the date of this letter.

The final printed labeling (FPL) for 8-762/S-020 and 10-151/S-033 must be identical to the draft labeling submitted on January 28, 1997, except for your proposed addition to the **PRECAUTIONS-General** section regarding adverse events associated with the combination use of phenytoin, cranial radiation, and reduction of corticosteroids.

Please submit the copies of final printed labeling (FPL) electronically to each application according to the guidance for industry titled *Providing Regulatory Submissions in Electronic Format - NDA* (January 1999). Alternatively, you may submit 20 paper copies of the FPL as soon as it is available but no more than 30 days after it is printed. Please individually mount ten of the copies on heavy-weight paper or similar material. For administrative purposes, these submissions should be designated "FPL for approved supplement NDA 8-762/S-020 and NDA 10-151/S-033." Approval of these submissions by FDA is not required before the labeling is used.

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, call Mr. Paul David, R.Ph., Senior Regulatory Project Manager, at (301) 594-5530.

Sincerely,

{See appended electronic signature page}

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

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

/s/

Russell Katz
11/20/01 08:05:22 AM

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 10-151/
S-022, 029, 030, 032, 033, & 034

MEDICAL REVIEW(S)

10/30/89

REVIEW AND EVALUATION OF CLINICAL DATA
NDA SUPPLEMENT - LABELING REVIEW

10-151 030

NDA 10-151

Sponsor: Parke-Davis

Drug: Dilantin (Phenytoin Sodium Injection USP)

Indication: Anticonvulsant

Date of Submission: September 22, 1989

Date Received: September 28, 1989

1.0 Proposed Labeling Change

In accordance with 21 CFR 314.70(b)(3), a revised package insert for Phenytoin Sodium Injection is submitted. The revision is intended to increase the safe use of parenteral Dilantin.

The major revision involves the addition of specific instructions regarding the method of administration in the DOSAGE AND ADMINISTRATION section. Specifically, it has strengthened the directions for the administration of parenteral Dilantin via the bolus method and added instructions for administration via the infusion method.

In the revised insert the directions for injection currently stated in paragraph 10 have been deleted and replaced by a subsection titled [ ]. This subsection parallels the original except that the revised instructions now state each injection should be [ ] followed by a flush of sterile saline [ ] [ ] and the reference to not using the infusion method of administration [ ]

Dosage and Administration:

[ ]

The second revision to this section involves the creation of a subsection titled [ ]. The directions for infusion administration are based on information contained in the published literature (see 2.2). [ ]

2.0 Literature Review

Previously, the package insert recommended against the addition of Dilantin to intravenous infusion, citing the lack of solubility and resultant precipitation. The firm now believes there is evidence from the following literature studies to support the proposed labeling revision.

2.1 Attachment A

Several articles detail major intravenous extravasation injuries, either generally (Upton, Mulliken, et al) (MacCara, M) or specifically to phenytoin (Ernest, Marx, et al), (Comer, J. 1984), (Kilarski, Buchana, et al), (Spengler, Arrowsmith, et al). This literature is familiar to me from previous reviews of this issue and will not be reviewed in detail at this time.

2.2 Attachment B

The following literature reports include several in vitro studies of phenytoin solubility and stability as well as several clinical studies:

2.21 Carmichael, R., Mahoney, C. and Jeffrey, L: Solubility and Stability of Phenytoin Sodium When Mixed With Intravenous Solutions, Am J Hosp Pharm, 37: 95-98,1980.

The solubility and stability of intravenous admixtures of DPH in D5W and NS was studied. The authors conclude that when direct IV injection of DPH is not practical, the drug may be infused over a period of no more than 1h if used immediately after dilution with no more than 50ml NS.

2.22 Salem, R., Yost, R., Torosian, G., et al.: Investigation of the Crystallization of Phenytoin in Normal Saline, Drug Intelligence & Clinical Pharmacy, 14: 605-608,1980.

The stability over 24h of five concentrations of DPH when admixed in NS was studied (1.0, 2.5, 5.0, and 7.5 mg/ml). Crystals formed as early as 18h in unfiltered samples, but took as long as 3 days in filtered solutions of the same concentration. The authors conclude that the admixture of DPH in NS yields colloidal solutions which appear to be stable for an undetermined period of time. If dilutions of DPH are used, it is advised that they be carefully observed for particulate matter and that the infusion be started as soon as possible after the admixture is made.

2.23 Pfeifle, C., Adler, D. et al.: Phenytoin Solubility in Three Intravenous Solutions, AM J Hosp Pharm 38: 358-361, 1981.

The solubility of DPH of two manufacturers was studies in NS, lactated Ringer's, D5W at concentrations 0.40, 0.98, 2.38, 4.55. It is concluded that NS and Ringer's lactate are acceptable diluents for IV DPH, but additional studies to identify all factors affecting DPH solubility in IV solution would be of interest. The appearance of precipitate in NS was inconsistent, scant, irregular, and particulate in nature, and occurred only with the Parke-Davis product.

2.24 Gannaway, W, Wilding, et al: Clinical Use of Intravenous Phenytoin Sodium Infusions, Clinical Pharmacy 2:135-138,1983.

93 doses of DPH 300mg in 50ml NS injection were administered to 28 adult patients in a neurosurgery ICU according to prospective hospital-approved guidelines, including concentration 1-10 mg/ml, administration over 30-60 min, initiation of infusion within 1h of solution preparation, and use of a 5-um in-line filter. There was a single occurrence of pain at the IV site requiring termination of the infusion; no cases of phlebitis were noted. It is concluded that careful infusion of DPH in NS is safe; written guidelines to govern important factors of preparation and administration are recommended.

2.25 Boike, M, Rybal, et al: Evaluation of a Method For Intravenous Phenytoin Infusion, Clinical Pharmacy 2:444-446, 1983.

24 emergency patients requiring a loading dose of DPH for seizure control received it as a small volume intravenous infusion. An IV dose of approximately 10mg/kg was mixed in 50ml NS to yield final concentration of 5.36 to 12.12mg/ml. An electronic infusion control device was used to infuse the DPH into a peripheral vein through a 0.22-um filter at an infusion rate of 33mg/min. The dose was administered within 2h after admixture; the primary IV administration set was flushed with 50ml NS immediately preceding and following phenytoin administration. A serum sample for DPH determination was obtained 60 min postinfusion. 2/24 patients were excluded from statistical analysis because adverse effects required premature termination of the infusion: one patient with lightheadedness, bradycardia, hypotension immediately after initiation of the infusion; another complained of intense arm pain during the infusion and refused further treatment. A total of 3 patients (13%), reported pain or burning at the injection site. Crystallization was not visible in any of the prepared DPH solutions. Actual increments in serum DPH concentrations were not significantly different from predicted increments; 20/22 patients were found to have serum drug increments within 3ug/ml(1 SD) of that predicted on the basis of actual or ideal body weight. The authors conclude that the high degree of predictability in attaining desired DPH serum concentrations after a given dose suggest little interference with the bioavailability of DPH by this method of administration.

2.26 Tuttle, B.: Guidelines for Phenytoin Infusions, The Canadian Journal of Hospital Pharmacy, 37 137-139,1984.

DPH infusions can be safely administered provided the injection is diluted in small volumes of saline solution and administered freshly prepared. Specific guidelines are given for the preparation and administration of DPH infusions: use a volume-control piggyback IV set with an in-line filter, flush all tubing before and after each infusion, administer 25-40mg/min at a rate not exceeding 50mg/min. Measure the peak serum DPH level 20-30 min following termination of a therapeutic loading dose or following any infusion where the pretreatment level is unknown.

2.27 Dela Cruz, F., et al: Efficacy of Individualized Phenytoin Sodium Loading Doses Administered by Intravenous Infusion, Clinical Pharmacy, 7:219-224, 1988.

The safety and efficacy of administering DPH loading doses by intravenous infusion were studied on 40 occasions in 37 adult patients having seizures. Doses were calculated based on an average volume of distribution (0.75 L/kg) and desired plasma phenytoin concentration. Total and free phenytoin concentrations were determined before and after the infusion. Phenytoin sodium doses of 225-1300mg were administered by intravenous infusion at a rate of 40mg/min after dilution in NS yielding concentrations ranging from 4.5 to 13.5 mg/mL. Infusion rates were reduced if adverse effects occurred.

The dosing method accurately achieved desired phenytoin concentrations (predicted mean ± S.D. concentration, 18.3 ± 1.6 ug/mL; observed mean concentration, 17.4 ± 2.5 ug/mL). Postinfusion concentrations of free phenytoin ranged from 0.8 to 3.6 ug/mL (mean ± S.D., 1.7 ± 0.6 ug/mL). Of 21 patients evaluated for efficacy, 16 responded. A total of 45% of patients experienced pain at the infusion site, which diminished when the infusion rate was reduced. No serious cardiovascular or neurological toxicities occurred. The authors conclude that the intravenous infusion method of administration is safe and effective and is useful for rapid achievement of therapeutic phenytoin concentrations in the emergency room setting.

2.28 Koren, J: Phenytoin Admixture Solutions: A Review Of The Literature With Recommendations, Hospital Pharmacy, 23:646-648, 1988.

The following guidelines are made with respect to administering DPH by IV infusion:

1. Phenytoin should be admixed with 50-100mL of sodium chloride 0.9% injection as a piggyback IV, with a maximum concentration of 10mg/mL.
2. Concentration of phenytoin in the admixture solution should be between 1-10mg/mL.
3. The dose should be administered over 20-60 minutes when possible (the <u>maximum</u> rate of administration is 50mg/min.
4. The infusion should begin within 1h of preparation, discarded 4h after preparation, and be kept unrefrigerated.
5. All tubing should be flushed with sodium chloride 0.9% injection before and after infusion. A 5 micron in-line filter is required as a final filter.

2.29 Earnest, M., et al. Complications of Intravenous Phenytoin for Acute Treatment Of Seizures. JAMA 249:762-765,1983.

200 emergency room patients were administered DPH (500 mg or more) in small volumes NS (100-500ml) given IV in a piggyback arrangement. Postinfusion DPH levels were obtained approximately 1h after completion of the infusion. Results: Dose of DPH ranged from 500(N=31) to 1,500(N=134) mg (mean, 887 mg). Volumes ranged from 50 to 500 ml (mean,312 ml; mode, 100 ml in 54 cases). The rates of administration varied widely, but the mean was 29.0 mg/min, and 2/3 (132) received rates between 15 and 50 mg/min. Post-treatment DPH levels for 134/145 patients who had pretreatment DPH levels of 0 is presented:

N	DOSE,mg	RANGE	MEAN
13	500	2-18	10.6
12	700-800	10-28	16.3
109	1000	1*-36	18.3

*one patient; the next lowest was 7 ug/ml

Eight excluded patients inexplicably had postinfusion DPH levels of 0 (!). In 5 patients the IV infusion was interrupted or otherwise inadequate.

There was a substantial incidence of occurrence of burning at the IV site. 29 patients complained of burning, aching, or other painful sensations in the arm at or near the IV site; 19/29 required adjustment of the infusion. Most commonly, when the rate was slowed the painful sensation resolved. However, in several cases the volume of the saline diluent was increased or the rate of the primary IV was increased.

3.0 COMMENT

In my opinion this labeling revision is an issue of safety rather than efficacy (although two of the clinical studies speak to this issue with data showing a high degree of predictability in attaining desired phenytoin serum concentrations after a given dose suggesting little effect on bioavailability by this method of administration). The revision proposes two ways to administer an intravenous loading dose of phenytoin, as a [ ] bolus injection [ ] [ ], and as an intravenous infusion given at a rate of 50 mg/min or less [ ] [ ]. The maximum recommended rates are thus identical; the infusion method may offer convenience <u>provided</u> that no complications occur. Of course, the rate may be more slower (25-40 mg/min), even less in the elderly or those with unstable cardiopulmonary function (5-10 mg/min).

It appears that the motivation behind this proposed labeling change is twofold while safety is cited, convenience also may be a factor, as the presence of a physician is not required. There is ample evidence that the insolubility and alkalinity of phenytoin results in its precipitation as crystals when diluted in common intravenous fluids. Several of the in vitro solubility studies (Carmichael, Salem, Pfeifle) provided in the literature review have explored the insolubility factors and conclude that despite them, phenytoin can be safely administered as an infusion provided certain guidelines are strictly followed. There are also several open clinical studies which reach the same conclusion that phenytoin sodium infusions can be safely administered provided the injection is diluted in small volumes of NS and administered promptly (although not necessarily uniform regarding the guidelines for concentration and rate).

Most of the studies have focused on the rate of administration, the total milligram dose, and the milligram per kilogram dose as being the important factors for study. They conclude that phenytoin toxicity, in part, relates to excessive rates of administration. Many patients do not tolerate the labeled maximum rate of (bolus) administration (50 mg/min) because of cardiovascular toxicity. Cranford at al. found that the administration of phenytoin by direct intravenous push had to be slowed because of hypotension in 24% of their patients. The mean rate of administration in these patients was 32 mg/min.

It is possible that slower and (theoretically) safer rates of administration are easier to achieve via the infusion. Thus, Gannaway (N=93) reports mean infusion rate 10 mg/min (range 3-20 mg/min) with an unspecified concentration although he recommends 1-10 mg/ml, Boike (N=24) employed a concentration 5.36-12.12 mg/ml with a rate of 33 mg/min, and Dela Cruz (N=40) used concentrations 4.5-13.5 mg/ml with a rate of 40 mg/min. There were insufficient details regarding concentration and rate of administration in the series of 200 patients reported by Earnest. This experience suggests that de facto administration rates for intravenous bolus vs infusion are in fact quite comparable.

I do not think the firm makes the case that the safety of an intravenous dose of phenytoin is better with the infusion than the bolus; in fact, complications which appear to be administration-rate related (in particular, local injection site reactions) appear to be as common, although meaningful incidence rates cannot be calculated for these open studies of relatively small power. Each of the clinical studies reported patients with pain necessitating interruption of the infusion. In Boike, 2/24 patients were terminated prematurely and subsequently excluded from statistical analysis due to adverse effects: one patient with lightheadedness,

bradycardia, hypotension immediately after initiation of the infusion; another complained of intense arm pain during the infusion and refused further treatment. A total of 3 patients (13%), reported pain or burning at the injection site. In Dela Cruz, 45% of 37 patients experienced pain at the infusion site, which diminished when the infusion rate was reduced. Earnest reported that 29/200 patients complained of burning, aching, or other painful sensations in the arm at or near the IV site; 19/29 required adjustment of the infusion.

In conclusion, the firm has revised labeling to provide for administration of phenytoin in NS via infusion as an alternative to administration by direct intravenous bolus push. The specific recommendations are supported by the literature references.

I would also recommend the following statement to be added:

4.0 Additional Revisions

In addition to the above, additional revisions previously made to the other phenytoin formulations (previously reviewed) are proposed. They are generally acceptable. Please refer to that review for comments.

5.0 Additional Recommended Revision: Drug Interaction

We have received an analysis from HFD-150 of a monitored adverse reaction report of decreased phenytoin levels associated with combination chemotherapy cisplatin, vinblastine, and bleomycin (see attached reviews). The following revision to DRUG INTERACTIONS is proposed:

Janeth Rouzer-Kammeyer, M.D.

cc/NDA 10-151
HFD-120
HFD-120/RKatz
JRouzer-Kammeyer
cso/SDecorte
ft/nb/8/30/89
DOC 1364n

11.1

REVIEW AND EVALUATION OF CLINICAL DATA

FEB 15 1988

NDA 8-762
Dilantin Suspension

NDA 10-151
Dilantin Injectable

[ ]

[ ]

Sponsor: Parke-Davis

Date of Supplement: September 25, 1987

Date of Review: February 8, 1988

Subject: Labeling Change Under 314.70(c)(2)
Re: Soft Tissue Injury, Toxic Epidermal Necrolysis

Submitted under 314.70(c)(2) to be placed into effect after 60 days are the following changes in labeling for Dilantin (phenytoin) products, to clarify and extend the Precautions and Adverse Reactions Sections of the Package Insert.

(1) To the PRECAUTIONS section of the Dilantin parenteral package insert.

(a) The following statement has been added:

> Parenteral Dilantin should be injected slowly (not exceeding 50mg per minute in adults), directly into a large vein through a large-gauge needle or intravenous catheter.

(b) This statement is followed by the present statements regarding saline flush, avoidance of continuous infusion, and the occurrence of soft tissue injury, such that this section now occurs at the opening of the Precautions (General) section.

(c) The information regarding instances of amputation has been added to the description of soft tissue irritation:

> Soft tissue irritation may vary from slight tenderness to extensive necrosis, sloughing, and in rare instances has led to amputation. Improper administration including subcutaneous and perivascular injection should be avoided to help prevent possibility of the above.

(d) The following statement is added to DOSAGE AND ADMINISTRATION section of the parenteral formulation:

> Parenteral drug products should be inspected visually for particule matter and discoloration prior to administration, whenever solution and container permit.

(2) The occurrence of toxic epidermal necrolysis has been added to the PRECAUTIONS AND ADVERSE REACTIONS sections of all Dilantin products package inserts (under Rash).

Comment:

These changes reflect the persistent activity in the periodic drug experience reports of soft tissue injury, both nonserious and serious since the labeling revision of June 6, 1984 concerning precautions of potential extravasation with phenytoin sodium injection and the use of the 50 mg/minute rate. During the period March 1, 1986 - February 28, 1987, of the 29 total reports submitted, there were 12 reports of soft tissue injury, 4 serious, including amputation, and 8 nonserious.

The addition of toxic epidermal necrolysis provides an alternate term for the well-desribed Stevens-Johnson syndrome.

Recommendation

These changes strengthen the labeling of Dilantin products with respect to these reactions. I recommend Approval.

Janeth Rouzer-Kammeyer, M.D.

cc:
Orig:NDAs 8-762
10-151
[ ]
HFN-120
HFN-120/RKatz
JRouzer-Kammeyer
ft/mb/2/15/88
DOC 0308n

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 10-151/
S-022, 029, 030, 032, 033, & 034

CHEMISTRY REVIEW(S)

MAR - 1 1990

CHEMIST'S REVIEW

1. ORGANIZATION: HFD-120
2. NDA NUMBER: 10-151
3. AF NUMBER:
4. SUPPLEMENT/NUMBERS/DATES: S-030
5. AMENDMENTS/REPORTS/DATES:
6. REC'D. BY CHEMIST: 10/2/89

7. APPLICANT NAME/ADDRESS:
Park - Davis
201 Tabor Road
Morris Plains, New Jersey 07950

8. NAME OF DRUG: Dilantin
9. NONPROPRIETARY NAME: phenytoin sodium
10. CHEMICAL NAME AND STRUCTURE:

11. DOSAGE FORM: Injection
12. POTENCY:
13. PHARMACOLOGICAL CATEGORY:
14. HOW DISPENSED: (RX) (OTC)
15. RECORDS AND REPORTS
CURRENT _____YES_____NO
REVIEWED_____YES_____NO
16. RELATED IND/NDA/DMF(s):
17. SUPPLEMENT(S) PROVIDES FOR: Revised package insert.

18. COMMENTS: The revisions are primarily clinical. With respect to chemistry manufacturing controls, the labeling is satisfactory.

19. CONCLUSIONS AND RECOMMENDATIONS: Recommend approval.

20. NAME	SIGNATURE	DATE COMPLETED
W. Brannon	William Brannon	3/01/90

Copies:
ORIG:NDA 10-151
HFD-120
HFD-120/WBrannon/3/1/90
INIT:RCShultz/3/1/90
ft/ET/3/1/90
DOC# 3910e

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APPLICATION NUMBER:

NDA 10-151/
S-022, 029, 030, 032, 033, & 034

ADMINISTRATIVE

MAR 13 1991

CSO REVIEW FOR NDA FINAL PRINTED LABELING (FPL)

NDA #: 10-151 Date of Submissions:	Type of Submission:
[redacted]	
11/01/83	S-022
[redacted]	
[redacted]	
04/02/86	Annual Report
04/21/86	S-026
04/22/87	Annual Report
09/25/87	S-029
05/09/88	Report
09/25/89	S-030

Related NDA's: 8-762, [redacted]

Date Review Completed: February 13, 1991

Applicant Name and Address: Parke-Davis
Division of Warner-Lambert Company
Attention: Deanna D. Thomas
201 Tabor Road
Morris Plains, New Jersey 07950

Product Name: Trade Name: Parenteral Dilantin
Generic Name: Phenytoin Sodium Injection, USP

Dosage Form and Strength: Injectable Solution 50mg/ml

Pharmacologic Category and/or Principle Indication:

Epilepsy (status epilepticus of the grand mal type and for seizures occurring during neurosurgery)

Material Reviewed:

1. Approved package insert: 121 875900 20 (March 1979).
2. [redacted]
3. Labeling proposed in S-022 submitted 11/01/83: 4475G022 (July 1983).
4. [redacted]
5. [redacted]
6. Package insert included in the 04/02/86 Annual Report: 4475G023 (January 1985).
7. Approved labeling in S-026 submitted 04/21/86 and approved 05/20/86: 4475G000 (March 1986).
8. Package insert included in the 04/22/87 Annual Report: 4475G024 (July 1986).
9. Labeling proposed in S-029 submitted 09/25/87: 4475G025 (September 1987).
10. A 05/09/88 report of ADR's.
11. Clinical review of S-029 dated 02/18/88.
12. Labeling proposed in S-030 submitted 09/25/89: 4475G026 (Revised March 1989).
13. Clinical Review on S-030 dated 09/30/89.
14. Chemistry Review on S-030 dated 03/01/90.

Background:

Several revisions in the labeling have been made since the last approved labeling (12/15/81, dated March 1979). [ ] [ ] [ ] and included draft labeling. S-022, [ ] and S-029 are Changes Being Effected Supplements. The labeling included in S-026, which was a chemistry supplement (that included new labeling) was approved by Mr. Shultz on May 20, 1986 A labeling review will be done on this supplement since none was done previously and for purposes of comparison. A Content and Format Review will be done on the last labeling submitted (S-030).

Organizational:

Since several revisions have been made since the approved labeling (approved December 15, 1981, version dated March 1979) and no labeling reviews completed, each revision in labeling will be compared to the previous labeling [ ] [ ] as follows:

Comparison	"Old" Labeling	"New" Labeling
A	Approved (March 1979)	S-022 (July 1983)
B	S-022 (July 1983)	[ ]
C	[ ]	AR 04/02/86 (January 1985)
D	AR 04/02/86 (January 1985)	S-026 (March 1986)
E	S-026 (March 1986)	AR 04/22/87 (July 1986)
F	AR 04/22/87 (July 1986)	S-029 (September 1987)
G	S-029 (September 1987)	S-030 (March 1989)
H		[ ]
I		Content and Format Review

Evaluation A:

Labeling included with this AR included the change in name from phenytoin to phenytoin USP. Additionally, a size previously included in the labeling has been deleted. The changes submitted in S-022 are minimal and warrant approval.

Review of the FPL for S-022 noted the following:

a. Points 1 and 3 provide for the addition of "USP" and point 7 provides for the addition of "Injection, USP" following "Phenytoin Sodium" at the top of each page of labeling.

b. The word, "ampoule" has been deleted in point 2.

c. A comma has been added as point 4.

d. Points 5 and 9 provide for the new revision number and date as follows: "4476G022" and "July 1983" from the previous "4475G020" and "Date Issued March 1979". Point 6 incorporates the deletion of a group of numbers, "121 875900 20".

e. The product: "N 0071-4475-40 (Steri-Dose 4475) Dilantin ready-mixed solution containing 50 mg phenytoin sodium per milliliter is supplied in a 5-ml sterile disposable syringe (22 gauge x 1 1/4 inch needle). Packages of ten individually cartoned syringes." has been deleted in point 8.

Evaluation B:

Redacted 6 page(s)

of trade secret and/or

confidential commercial

information from

Administrative : CSO Review (3/13/91)

Evaluation C:

Only minor editorial changes were noted in the labeling included in AR 04/02/86. Additionally, the statement noting that the drug can only be dispensed on the order of a prescription has been added.

a. Points 1 and 4 provide for the new revision number and date: "4475G023" and "January 1985".

b. The word "slowly", which was previously underlined, is now in italics under point 2.

c. The following sentence has been added as point 3: "Caution--Federal law prohibits dispensing without prescription."

Evaluation D:

S-026 was approved by Mr. Shultz on 05/20/86. The supplement added two new dosage forms. A labeling review was never done.

a. Points 1 and 3 provide for the new revision number and date: "4475G000" and "March 1986".

b. Point 2 includes the two new dosage forms as follows:

N 0071-4488-45 Dilantin ready-mixed solution containing 50 mg phenytoin sodium

per milliliter is supplied in 2-mL steri-vials. Packages of ten.

N 0071-4475-45 Dilantin ready-mixed solution containing 50 mg phenytoin sodium per milliliter is supplied in 5-mL steri-vials. Packages of ten.

Evaluation E:

No changes of note were included in the labeling provided with AR 04/22/87.

a. Points 1 and 2 provide for the new revision number and date: "4475G024" and "July 1986".

Evaluation F:

S-029 includes changes which strengthen the labeling including ADR's, additional symptoms of overdosage and more detailed directions for use. The medical officer has recommended approval of this supplement.

a. Points 1 and 11 provide for the new revision number and date: "4475G025" and "September 1987".

b. The following paragraph has been moved from lower in the PRECAUTIONS Section to the position after the first paragraph in point 2:

> Each injection of intravenous Dilantin should be followed by an ingestion of sterile saline through the same needle of intravenous catheter to avoid local venous irritation due to the alkalinity of the solution. Continuous infusion should be avoided.
>
> Soft tissue irritation and inflammation has occurred at the site of injection with and without extravasation of intravenous phenytoin. Soft tissue irritation varying from slight tenderness to extensive necrosis and sloughing has been noted. Subcutaneous or perivascular injection should be avoided.

c. The following sentence has been added to the second paragraph of the PRECAUTIONS Section under General in point 3: "Parenteral Dilantin should be injected slowly (not exceeding 50 mg per minute in adults), directly into a large vein through a large-gauge needle of intravenous catheter."

d. "varying" has been changed to "may vary" in point 4.

e. An addition and change to the following sentence, "... sloughing has been noted." occurs in point 5 as follows: "...sloughing, and in rare instances has led to amputation."

f. The following sentence has been changed in point 6 from, "Subcutaneous or perivascular injection should be avoided." to, "Improper administration including subcutaneous or perivascular injection should be avoided to help prevent possibility of the above."

g. "or toxic epidermal necrolysis" and "and toxic epidermal necrolysis" have been added to the PRECAUTIONS and ADVERSE REACTIONS Sections under points 7 and 8, respectively.

h. Under OVERDOSAGE, "hyperflexia" has been changed to "hyperreflexia" in point 9.

i. The following statement has been added to the DOSAGE AND ADMINISTRATION Section under point 10: "Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit."

Evaluation G:

The Medical Officer should determine if the description listed in "k" below is adequate to replace periarteritis nodosa.

a. Points 1 and 26 provide for the new revision number and date: "447G026" and "Revised March 1989", respectively. Additionally, a copyright statement has been added as point 27: "1989,Warner-Lambert Co."

b. In point 2, "hydantoin products" has been changed to [ ].

c. The following statement has been removed from the General subsection of the PRECAUTIONS Section under point 3: "The addition of Dilantin solution to intravenous infusion is not recommended due to lack of solubility and resultant precipitation."

d. The phrase, [ ] has been added as point 4.

e. Under point 5, the injection should be [ ] followed by... has been added and the ..."an injection" has been changed to [ ] as point 6.

f. The following paragraph has been added under point 7 to the General subsection:

g. The sentence, "Serum level determinations for phenytoin are especially helpful when possible drug interactions are suspected." has been added to the Drug Interactions subsection in point 8.

h. Under 1. in the Drug Interactions subsection, [ ] has been added in point 9. Additionally, "tagament" has been replaced with the broader [ ] and "ethosuximide" has been replace with the more general [ ] in points 10 and 11 respectively. Also, point 12 provides for the listing of drugs in alphabetical order rather than in order of occurrence as extrapolated from 21 CFR 201.56(g).

i. [ ] has been added as a drug which may decrease phenytoin levels in point 13, and [ ] have been added as drugs whose efficacy is impaired by phenytoin under point 14.

j. In the Gastrointestinal subsection of ADVERSE REACTIONS, [ ] [ ] have been added as point 15.

k. The Other subsection has been changed to [ ] and revised from:

> Systemic lupus erythematosus, periarteritis nodosa, toxic hepatitis, liver damage, and immunoglobulin abnormalities.

to:

[ ]

in point 16. N.B. The [ ] seems to describe periarteritis nodosa, however, the Medical Officer should determine if this replacement is adequate.

l. "hypertensive" has been changed to [ ] in point 17. This is consistent with labeling change approved for the suspension dosage form.

m. Under the DOSAGE AND ADMINISTRATION Section, point 18 includes changed from the following paragraphs:

> The addition of Dilantin solution to intravenous infusion is not recommended due to lack of solubility and resultant precipitation.
>
> Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit.
>
> The solution is suitable for use as long as it remains free of haziness and precipitate. Upon refrigeration or freezing, a precipitate might form; this will dissolve again after the solution is allowed to stand at room temperature. The product is still suitable for use. Only a clear solution should be used. A faint yellow coloration may develop; however, this has no effect on the potency of the solution.
>
> Parenteral Dilantin should be injected slowly and directly into a large vein through a large-gauge needle or intravenous catheter. Each injection of intravenous Dilantin

should be followed by an injection of sterile saline through the same needle or catheter to avoid local venous irritation due to alkalinity of the solution. Continuous infusion should be avoided; the addition of Parenteral Dilantin to intravenous infusion fluids is not recommended because of the likelihood of precipitation.

to:

Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit. [ ] [ ] a precipitate might form; this will dissolve again after the solution is allowed to stand at room temperature. [ ] A faint yellow coloration may develop; however, this has no effect on the potency of the solution.

n. In point 19, ...toxic doses "of" this drug... has been changed to ...toxic doses [ ] this drug.

o. [ ]

p. Descriptions of the packages have now been eliminated. They previously were listed as "(Ampoule 1488)" (point 28), "(Steri-Dose 4488)" (point 21), and "(Ampoule 1475)" (point 22).

q. [ ]

r. In point 25, all of the references to Section title have been capitalized, (e.g., from "Warnings" to "WARNINGS").

Evaluation H: Evaluation H will not be reviewed at this time, but will be reviewed once the consult from HFD-110 has been completed.

Evaluation I:

Evaluation I is a content and format labeling review. All of the changes described below should be implemented upon concurrence with the group leader.

a. The type of dosage form and the route of administration is not listed under point 1 in the DESCRIPTION Section as required by 21 CFR 201.57(a)(1)(ii).

b. In point 2, a statement that the product is sterile has not been included as required in 21 CFR 201.57(a)(1)(iv).

c. The pharmacologic or therapeutic class has been omitted in point 3 and is required under 21 CFR 201.57(a)(1)(v).

d. In point 4, "...is indicated for the control..." is not in compliance with 21 CFR 201.57(c)(1), where a product must be indicated for the treatment, prevention, diagnosis or relief of symptoms of a disease.

e. An Information for patients subsection should be included under point 5, as required by 21 CFR 201.57(f)(2).

f. A pregnancy category should be specified in point 6 as required by 21 CFR 201.57(e)(6)(i). The pharmacologist should verify that category D is appropriate.

Summary:

Evaluations A,C, and E illustrate no changes of substance, therefore, the labeling provided in AR 04/02/86 and 04/22/87, and the changes outlined in S-022 should be approved.

Evaluation D covers a supplement that has already been approved; the labeling changes in S-026 are not substantive.

Evaluation F encompasses changes submitted in a Changes Being Effected supplement (S-029). These changes are consistent with the provisions for Changes Being Effected supplements, and should be approved.

Evaluation G discusses a Package Change supplement (S-030) which also includes a safety issue. The Medical Officer has recommended approval with the addition of two paragraphs in the appropriate sections of the labeling. I would suggest (upon concurrence with the Medical Officer and Group Leader) that S-030 be approvable provided the two sections be included in FPL. The

Medical Officer should also address the issue of periarteritis nodosa (see "k" in Evaluation G).

Since Evaluation H was not completed at this time, no recommendations for S-020 are made at this time.

The requests made in Evaluation I should be incorporated into letter discussed above (under Evaluation B).

Recommendation:

A letter should issue informing the firm of the following:

1. S-022 and S-029 are approved.

2. [ ]

3. S-030 should be approvable with the addition of the two paragraphs described above included in FPL.

Susan M. DeCorte
Susan M. DeCorte
Project Manager

cc:
Orig. NDA
HFD-120
HFD-120/Leber
/Katz/Rouzer-Kammeyer
/Purvis/DeCorte
02/13/91
10151lrs.030

J Purvis
3/13/91

20 page(s) of draft labeling has been removed from this portion of the review.

Administrative Documents –
CSO Review (3/13/91)

REGULATORY PROJECT MANAGER
LABELING REVIEW

Date: September 28, 2001
DRUG/NDA: Dilantin-125 (phenytoin oral suspension, USP) Suspension (NDA 8-762) & Dilantin (Phenytoin Sodium Injection, USP) Injection (NDA 10-151)
Sponsor: Pfizer
Indication: Antiepileptic
Supplements:

NDA	Supplement	Dated	Action
Dilantin-125 (phenytoin oral suspension, USP) Suspension (NDA 8-762)			
8-762	SLR-019	9-5-89	Approved on 3-23-90 Label Code: 2214G108
8-762	SLR-020	5-25-94, and amended on 1-28-97	Open
8-762	SLR-021	7-18-94	Open
8-762	SLR-022	1-27-95	Open
8-762	SLR-026	12-3-96	Open
Dilantin (Phenytoin Sodium Injection, USP) Injection (NDA 10-151)			
10-151	SLR-015	10-19-78	Open
10-151	SLR-019	6-30-81	Approved on 12-15-81 Label Code: 4475G020
10-151	SPD-022	5-10-83 and amended on 11-1-83	Open
[			]
10-151	SLR-029	9-25-87, and amended on 5-10-88	Open
10-151	SLR-030	9-25-89	Open
10-151	SLR-031	10-14-93	AP letter 11-22-95
10-151	SLR-032	8-9-94	Open
10-151	SLR-033	1-25-95, and amended on 1-28-97	Open
10-151	SLR-034	12-3-96	Open

Notes of interest:

1. The labeling for Dilantin suspension and injection are separate and not combined formulation labeling. Although, as may be expected, many sections are identical. Therefore, this labeling review encompasses both products although not all of the changes were submitted to each of the NDAs.
2. Upon administrative review of the open labeling supplements, I noted that an approval letter dated 11-30-78 issued for 10-151/SLR-015 but the COMIS field was never updated. The DDR has been informed to update this field with the correct information. Therefore, 10-151/SLR-015 does not need to be reviewed.
3. The administrative code, SPD, which was used to code labeling supplement 10-151/SPD-022, is an older code that is no longer used by the Document Room but it was used to denote changes to the labeling.
4. [ ]
5. I have included, in the above table, supplement 10-151/SLR-031 dated 10-14-93 and approved on 11-22-95 solely for the sake of completeness. This supplement provides for the addition of an ozone (CFC-12) warnings statement in the labeling, and the AP letter was signed off by the CMC Team Leader, Dr. Blum. For comparison purposes, the parenteral Dilantin labeling will be compared to the last fully approved labeling, 10-151/SLR-019.

REVIEW

Dilantin-125 (phenytoin oral suspension, USP) Suspension

8-762/SLR-020
Date: 5-25-94, and amended on 1-28-97
CBE: No, Prior Approval
Label Code No: Draft Labeling
Reviewed by Medical Officer: No review on file

The original labeling supplement dated 5-25-94, was submitted, as a prior approval supplement, at the request of the Agency as a way for the sponsor to receive feedback from the Division on several labeling issues that have remained pending throughout the years. The amendment to SLR-020, dated 1-28-97, is intended to completely replace the proposed labeling originally submitted on 5-25-94, to incorporate additional updates to the product labeling in order to make the labeling more consistent with the Cerebyx labeling. Additionally, this amendment incorporates all of the previous supplemental labeling applications which have not been acted on in order to assist the Agency in taking an action. These previous supplemental applications, fully described below, include 8-762/SLR-021/SLR-022/SLR-026.

Specifically, the changes are to the following sections:
1. The addition and deletion of several inactive ingredients items under the **DESCRIPTION** section.

2. The deletion of several phenytoin products which are no longer marketed which include Dilantin 30 mg/5 ml suspension and Dilantin ampoules throughout the labeling. The sponsor also deleted several of the quantity sizes under the **HOW SUPPLIED** section since they are no longer marketed.
3. A complete revision to the **WARNINGS** section in regard to use during pregnancy and risks to the fetus to provide for updated information. The addition to the **PRECAUTIONS-General** section regarding adverse events associated with the combination use of phenytoin, cranial radiation, and reduction of corticosteroids.
4. The addition to the **PRECAUTIONS-Information for Patients** section reminding patients that they should use a calibrated measuring device.
5. The addition of the terms cimetidine, fluoxetine, ticlopidine, and paroxetine to the **PRECAUTIONS-Drug Interactions** section.
6. The addition of a new subsection under the **PRECAUTIONS** section entitled **Drug-Enteral Feeding/Nutritional Preparations Interaction.**
7. The addition of a cautionary statement under the **PRECAUTIONS-Drug/Laboratory Test Interactions** regarding immunoanalytical methods.
8. The addition of the statement "Pregnancy Category D" under the **PRECAUTIONS-Pregnancy** section.
9. The addition of a **Pediatric Use** section under the **PRECAUTIONS** section.

8-762/SLR-021
Date: 7-18-94
CBE: Yes
Label Code No: 2214G124
Reviewed by Medical Officer: No review on file

- This supplement provides for the addition of fluoxetine to the **PRECAUTION-Drug Interactions** section as requested in an Agency letter dated 2-3-94. These changes comply with the Agency letter dated 2-3-94.

8-762/SLR-022
Date: 1-27-95
CBE: Yes
Label Code No: 2214G025
Reviewed by Medical Officer and Chemist: Yes, acceptable.

- This supplement provides for revisions to the container labels as well as to the **PRECAUTIONS-Information for Patients** section stating that a calibrated measuring device should be used to measure the oral suspension.

8-762/SLR-026
Date: 12-3-96
CBE: Yes
Label Code No: 2214G129
Reviewed by Medical Officer: Yes, acceptable.

This supplement provides for the following revisions:

1. The addition of a **Pediatric Use** subsection under the **PRECAUTIONS** section.
2. Several minor revisions to the **OVERDOSAGE** and **DOSAGE AND ADMINISTRATION** sections to conform to standard pediatric nomenclature.
3. Remove reference to the 5 ml unit dose pouches under the **HOW SUPPLIED** section since they are no longer marketed.

Dilantin (Phenytoin Sodium Injection, USP) Injection

10-151/SPD-022
Date: 5-10-83 and amended on 11-1-83
CBE: Yes
Label Code No: 4475G022
Reviewed by Medical Officer: Yes, acceptable

I cannot definitively determine what this supplement exactly provides for. There is a notation in the files of a conference all between Dr. Russell Katz and a representative from Parke-Davis in which it is implied that the supplement provides for new dosage recommendations for neonates in status epilepticus. However, a labeling review of this supplement by Ms. Susan DeCorte, former PM, indicates that the changes are minor. The labeling review also indicates that this supplement was submitted under CBE. There is also a notation that the supplement is acceptable to the medical officer.

10-151/SLR-029
Date: 9-25-87, and amended on 5-10-88 (providing for FPL)
CBE: Yes
Label Code No: 4475G025
Reviewed by Medical Officer: Yes, acceptable.

This supplement provides for revisions to the **PRECAUTIONS** and **ADVERSE REACTIONS** sections of labeling based upon the sponsor's review of drug experience reports.

10-151/SLR-030
Date: 9-25-89
CBE: No, Prior approval
Label Code No: 4475G026
Reviewed by Medical Officer: Yes, acceptable but add paragraph to **PRECAUTIONS-Drug Interactions** section

This supplement provides for revisions to the **DOSAGE AND ADMINISTRATION** section to strengthen the directions for the administration of parental Dilantin via the bolus method, and added instructions for the administration via the infusion method.

10-151/SLR-032
Date: 8-9-94
CBE: No, Prior Approval
Label Code No: 4475G0340
Reviewed by Medical Officer: No review on file

This supplement provides for the addition of fluoxetine to the **PRECAUTION-Drug Interactions** section as requested in an Agency letter dated 2-3-94. These changes comply with the Agency letter dated 2-3-94.

10-151/SLR-033
Date: 1-25-95 and amended on 1-28-97
CBE: No, Prior Approval
Label Code No: Draft Labeling
Reviewed by Medical Officer: No review on file

This labeling supplement is similar to that submitted for **8-762/SLR-020** (see above). It was submitted by the sponsor in order to 1) update the labeling so that it conformed to the Cerebyx labeling, and 2) assist the Agency in talking an action for the open label supplements. It incorporates all of the revisions made in all of the open labeling supplements which include 10-151/SPD-022/SLR-024/SLR-030/SLR-032/SLR-034, as well as adding pertinent information from the Cerebyx labeling to the Dilantin labeling.

10-151/SLR-034
Date: 12-3-96
CBE: Yes
Label Code No: 4475G372
Reviewed by Medical Officer: Yes, acceptable.

This supplement provides for the following:
1. The addition of a Pediatric Use subsection under the **PRECAUTIONS** section.
2. Several minor revisions to the **OVERDOSAGE** and **DOSAGE AND ADMINISTRATION** sections to conform to standard pediatric nomenclature.

CONCLUSIONS

1. In regards to the Dilantin Oral Suspension, NDA 8-762, the medical officer has reviewed SLR-022 and SLR-026, and they are acceptable. The medical officer has not reviewed SLR-021. However, SLR-021, although not reviewed, provides for changes, verbatim, as requested in an Agency letter dated 2-3-94. SLR-020 incorporates all of the revisions made in SLR-021/022/026 as well as strengthening the labeling to incorporate important safety changes already in the Cerebyx labeling. Attachment 1 of this review contains the revisions to labeling submitted to SLR-020. If the medical officer concurs with these changes, I recommend that an approval action issue for all four open labeling supplements, SLR-020/021/022/026.

2. In regards to the Dilantin Parenteral NDA, 10-151, the medical officer has reviewed SPD-022, SLR-029, SLR-030, and SLR-034, and they are acceptable. SLR-032, although not reviewed, provides for changes, verbatim, as requested in an Agency letter. SLR-033 incorporates all of the revisions made in S-022/029/030/032/034 as well as strengthening the labeling to incorporate important safety changes already in the Cerebyx labeling. Attachment 2 of this review contains the revisions to labeling submitted to SLR-033. If the medical officer concurs with these changes, I recommend that an approval action issue for all 6 open labeling supplements, SLR-022/029/030/032/033/034.

3. I have attached, as Attachment 3, the current labeling for Cerebyx.

4. Additionally, below are labeling changes documented by the Agency but never conveyed to the sponsor:

   a) Dr. Rouzer notes in her review of 10-151/SLR-030, that the Division received an analysis from HFD-150 of a [ ]
   [ ]
   Dr. Rouzer suggested specific additions to the **PRECAUTIONS-Drug Interactions** section.
   b) Dr. Feeney, in a review dated 2-2-00, recommends specific revisions to the parenteral Dilantin labeling related to [ ]

   I recommend that the action letter also incorporate a request for a CBE supplement requesting the above revisions to labeling.

Paul David, R.Ph., Regulatory Project Manager

Robbin Nighswander, R.Ph., Supervisory Consumer Safety Officer

Attachment 1: Dilantin Suspension Labeling, NDA 8-762/SLR-020
Attachment 2: Dilantin Parenteral Labeling, NDA 10-151/SLR-033
Attachment 3: Cerebyx Labeling

22 page(s) of draft labeling has been removed from this portion of the review.

Administrative Documents- PM Labeling Review

MEMORANDUM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE: November 15, 2001

TO: NDA FILES

FROM: Paul A. David, Senior Regulatory Project Manager

SUBJECT: **Dilantin Open Labeling Supplements**
NDA 8-762/S-020/021/022/026, Dilantin-125 (phenytoin oral suspension, USP) Suspension
NDA 10-151/S-022/029/030/032/033/034 Dilantin (phenytoin sodium injection, USP) Injection

I have reviewed the open labeling supplements submitted to the Dilantin-125 suspension and the Dilantin Injection NDAs in a review dated 9-28-01. One of the recommendations, in the 9-28-01 review, was to request that the sponsor incorporate labeling changes documented by the Division but never conveyed to the sponsor.

The action package for these open labeling supplements was reviewed by Dr. John Feeney, Neuropharm Team Leader, and he decided that a separate letter should issue requesting specific labeling revisions since the approval letter to close out these open applications was not tied to revisions to the product labelings.

Therefore, the approval letter has been revised to not request a supplement with specific labeling changes. This action will be done at a later time.

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

/s/

Paul David
11/15/01 08:00:35 AM
CSO

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 10-151/
S-022, 029, 030, 032, 033, & 034

CORRESPONDENCE

201 Tabor Road Phone: 201-540-2000
Morris Plains, NJ
07950

ORIGINAL

NDA SUPPL AMEND
SLR-033(84)

PARKE-DAVIS
People Who Care

January 28, 1997

NDA 10-151
Dilantin® Injection (phenytoin sodium Injection, USP)

Re: Draft Labeling
Amendment to Supplement S-033

I have reviewed the proposed changes and find them appropriate to proceed.
NA1
CBM
2/19/97

FOR DRUG
JAN 29 1997
HFD-120
EVALUATION AND RESEARCH

Paul 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 10-151 for Dilantin® Injection (phenytoin sodium injection, USP).

Reference is also made to Labeling Supplement S-033, submitted January 25, 1995. This supplement provided for a general update of the package insert for Dilantin Injection including all revisions that had been made to the most recent FDA approved package insert. This update came at the suggestion of your Division as a way for Parke-Davis to receive feedback on several labeling submissions that have remained pending over recent years.

During labeling discussions for Cerebyx® (fosphenytoin sodium injection), NDA 20-450, (approved August 5, 1996), it was agreed that subsequent to approval, the Dilantin labeling should be updated with the most current information for phenytoin. We are hereby submitting an amendment to Supplement S-033 which incorporates updated information regarding phenytoin that is included in the package insert for Cerebyx®.

In as much as the draft package insert that was submitted in S-033 is being significantly revised, this amendment is intended to replace the January 25, 1995, submission in its entirety.

The following documentation is provided in this amendment:

Attachment 1	Summary of Revisions - A line listing of all revisions in the proposed draft package insert.
Attachment 2	Draft Package Insert - 4 copies in WordPerfect 6.1 format with all revisions marked. The additions are made in shaded lettering and the deleted items are presented in strikeout type in the typed text version.
Attachment 3	Diskette (WordPerfect 6.1) that contains the text of the draft insert as presented in Attachment 2.
Attachment 4	Current Package Insert for Dilantin® (specification #4475G341).
Attachment 5	Current Package Insert for Cerebyx® (specification #4007G030).
Attachment 6	Labeling Supplement dated September 25, 1989 (Expedited Review Requested).
Attachment 7	Special Supplement-Changes Being Effected (S-034) dated December 3, 1996.
Attachment 8	References to support addition of a statement to PRECAUTIONS section regarding cranial irradiation used in combination with phenytoin therapy.
Attachment 9	References to support addition of ticlopidine and paroxetine to the Drug Interactions subsection.
Attachment 10	References to support addition of a statement regarding Drug-Enteral Feeding/Nutritional Preparations Interaction to the PRECAUTIONS section.

The diskette has been scanned for all known computer viruses using McAfee Virus Scan version 2.2.9.

Please note that we are submitting, under separate cover, a similar amendent to NDA Supplement (S-020) for Dilantin Suspension (NDA 8-762).

If you have any questions or require additional information, please do not hesitate to contact me at 201/540-5529 or by FAX 201/540-5972.

Sincerely,

Patricia Carlson

Patricia A. Carlson
Manager
Advertising and Labeling
Worldwide Regulatory Affairs

PC\sv\rm
t:\nda\10-151\012397.pc

Attachments

1811

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

Date DEC 16 1996

NDA No. 10-151

Parke-Davis Pharmaceutical Research
201 Tabor Road
Morris Plains, NJ 07950

Attention: Patricia A. Carlson

Dear Sir/Madam:

We acknowledge receipt of your supplemental application for the following:

Name of Drug: **DILANTIN-INJECTION**

NDA Number: 10-151

Supplement Number: S-034

Date of Supplement: December 3, 1996

Date of Receipt: December 4, 1996

Unless we find the application not acceptable for filing, this application will be filed under Section 505(b)(1) of the Act on February 2, 1997 in accordance with 21 CFR 314.101(a).

All communications concerning this NDA should be addressed as follows:

Center for Drug Evaluation and Research
Division of Neuropharmacologic Drug Products
Attention: Document Control Room
5600 Fishers Lane, HFD-120
Rockville, MD 20857

Sincerely yours,

Jacqueline H. Wade

(FOR) John Purvis

Chief, Project Management Staff
Division of Neuropharmacologic Drug Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

FORM FDA 3217b (11/95)

201 Tabor Road Phone: 201-540-2000
Morris Plains, NJ
07950

ORIGINAL

NDA NO. 20-151 REF. NO. SLR-034

NDA SUPPL FOR Labeling

PARKE-DAVIS
People Who Care

I have reviewed these changes and agree with them. MAY Proceed
AFA. CDM 12/20/96

December 3, 1996

NDA SUPPLEMENT

NDA 10-151
Dilantin® Injection (phenytoin sodium injection, USP)

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 Office Center 2
1451 Rockville Pike
Rockville, Maryland 20852

CENTER FOR DRUG EVALUATION AND RESEARCH
REC'D
DEC 24 1996
HFD-120

Dear Dr. Leber:

Reference is made to our approved NDA for Dilantin® Injection (phenytoin sodium injection, USP).

We are making the following revisions to our package insert for Dilantin Injection :

1. Adding a "Pediatric Use" subsection to the PRECAUTIONS section to conform to the December 13, 1994 Final Rule regarding pediatric use. We are revising this section under 21 CFR 201.57(f)(9)(vii) with the statement:

   Pediatric Use - See DOSAGE AND ADMINISTRATION

2. Making other wording changes in the OVERDOSAGE and DOSAGE AND ADMINISTRATION sections to conform to the nomenclature for pediatric patient age groups as specified in the above mentioned Final Rule.

A draft copy of the package insert, indicating these revisions, is enclosed.

This change is effective immediately and will be included in the next printing of the package insert.

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

Sincerely,

Patricia A. Carlson

Patricia A. Carlson
Manager
Advertising and Labeling
Worldwide Regulatory Affairs

PC\sv\rm
t:\nda\10-151\112696.pc

Attachments

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

Date January 27, 1995

NDA No. 10-151

Parke-Davis Pharmaceutical Research
201 Tabor Road
Morris Plains, NJ 07950

Attention: James A. Parker, Jr.

Dear Sir/Madam:

We acknowledge receipt of your supplemental application for the following:

Name of Drug: DILANTIN - Injection

NDA Number: 10-151

Supplement Number: S-033

Date of Supplement: January 25, 1995

Date of Receipt: January 26, 1995

All communications concerning this NDA should be addressed as follows:

Center for Drug Evaluation and Research
Attention: Document Control Room 10B-20
5600 Fishers Lane, HFD-120
Rockville, MD 20857

Sincerely yours,

Arthur Sandra

(for) John Purvis
Supervisory Consumer Safety Officer
Division of Neuropharmacologic Drug Products
Center for Drug Evaluation and Research

CSO: PiAS

FORM FDA 3217b (3/91)

201 Tabor Road
Morris Plains, NJ
07950
Phone: 201-540-2000

ORIGINAL NDA SUPPLEMENT

PARKE-DAVIS
People Who Care

January 25, 1995

NDA 10-151
Dilantin® Injection (phenytoin sodium injection, USP)

Re: Draft Labeling

NDA NO. 10151 REF. NO. SLR 033
NDA SUPPL FOR Draft Labeling

Paul 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

CENTER FOR DRUG EVALUATION AND RESEARCH
REC'D
JAN 2 6 1995
HFD-120

Dear Dr. Leber:

Reference is made to our approved NDA 10-151 for Dilantin® Injection (phenytoin sodium injection, USP).

Reference is also made to my telephone conversation on April 16, 1993, with Ms. Nancy Chamberlain of your Division regarding our request to remove the reference to the Dilantin® with Phenobarbital product from the DOSAGE AND ADMINISTRATION section of the package insert. Ms. Chamberlain stated this revision could not be done through an Annual Report. She stated that we should submit a labeling supplement for FDA review and approval. During our conversation, I explained to Ms. Chamberlain that we had submitted other labeling revisions to the agency over the years for which we had no formal approval or feedback. She suggested that we submit the most recent FDA approved package insert for Dilantin Injection and include all the labeling revisions to date.

According to our records, the last FDA approved package insert for Dilantin Injection was specification number 4475G000, in March 1986. For ease of review, we have retyped this version in text form with each line numbered. Four copies are included herein as Attachment 1 (specification number 4475G341DR); updates to this version are noted. The additions are made in shaded lettering and the deleted items are presented in strikeout type in the typed text version. A printed copy of the current package insert, specification number 4475G341, dated September 1994, is included, for reference, as Attachment 2.

The following listing of labeling revisions represent those changes that have been implemented and are reflected in the current package insert. Package insert specifications numbers and revision dates precede each label change. The revisions with numerical line references are as follows:

-4475G000 (3/86) revised to 4475G024 (7/86):

Changes are made to the HOW SUPPLIED section. Products N 0071-4488-45 and N 0071-4475-45 are supplied in packages of 25. This replaces packages of 10. [Lines 469, 472].

-4475G024 (7/86) revised to 4475G025 (9/87):

Reference is made to the Parke-Davis September 25, 1987 "Special Supplement: Changes Being Effected" and to the submission dated May 10, 1988 that provided the final printed labeling for 4475G025. The changes clarified and added to the PRECAUTIONS and ADVERSE REACTIONS sections, and include the following:

The "INDICATION" section is renamed "INDICATIONS AND USAGE". [Line 67].

A statement regarding the injection procedure is clarified with the addition of the instruction that each injection should be preceded by a flush of sterile saline and the statement is moved within the PRECAUTIONS, General subsection. [Lines 166 - 169 from lines 203 - 205]. A sentence is added to describe injection procedure. [Lines 164 - 166].

The paragraph regarding soft tissue irritation is moved within the PRECAUTIONS, General subsection. Editorial changes are made to the paragraph to improve clarity. A statement regarding rare instance of amputation is added. [Lines 171 - 175 from lines 207 - 210].

A statement regarding the occurrence of toxic epidermal necrolysis is added to the PRECAUTIONS, General subsection, [Line 186] and to the ADVERSE REACTIONS, Integumentary System subsection. [Line 299].

A sentence regarding information on visual inspection is added to the DOSAGE AND ADMINISTRATION section. [Lines 371 - 372].

-4475G025 (9/87) revised to 4475G027 (8/91):

The product N 0071-4475-35 (Ampoule 1475) is deleted from the HOW SUPPLIED section. [Lines 461 - 463].

-4475G027 (8/91) revised to 4475G028 (5/92):

The package insert was revised to incorporate the new Parke-Davis image.

-4475G028 (5/92) revised to 4475G029 (7/93):

The CFC warning statement is added (S-031) [Lines 478 - 479].

The products N 0071-4488-05 (Ampoule 1488) and N 071-4475-08 (Ampoule 1475) are deleted from the HOW SUPPLIED section. [Lines 454 - 455 and 465 - 466].

-4475G029 (7/93) revised to 4475G340 (6/94):

Deleted "AHFS Category 28:12" as per FDA letter of August 26, 1993 [Line 1].

In accordance with FDA letter dated February 3, 1994, the Drug Interactions subsection in PRECAUTIONS, under number 1: "Drugs which may increase phenytoin serum levels include:" has been revised to include "fluoxetine" (S-032) [Line 233].

-4475G340 (6/94) revised to 4475G341 (9/94):

Reference is made to the September 25, 1989 "Expedited Review Requested" submission from Parke-Davis that proposes a major revision to the DOSAGE AND ADMINISTRATION section to strengthen the directions for the administration of parenteral Dilantin via the bolus method and added instructions for the administration via the infusion method (Attachment 3).

The revision is intended to increase the safe use of parenteral Dilantin. Numerous additional changes were also made. To date, no response has been received from the Agency regarding this submission. Therefore, these proposed revisions have not been incorporated into the current Dilantin package insert. The revisions include:

Lines 55 - 56	A statement concerning [ ] is added to the CLINICAL PHARMACOLOGY section.
Lines 75-76	"Hydantoin products" is deleted and [ ] [ ] is added to the CONTRAINDICATIONS section.
Lines 113-114	A statement regarding the association of [ ] [ ] is added to the WARNINGS section.
Lines 161-162	The statement regarding Dilantin solution and [ ] [ ] is deleted in the PRECAUTIONS, General subsection.
Lines 164,167	Editorial changes are added to the paragraph to clarify and expand information regarding [ ] [ ] in the PRECAUTIONS, General subsection. Specifically, the statements [ ] [ ] and [ ] are added to the sentences, and "an injection" is deleted.
Lines 192-195	A [ ] [ ] is added to the PRECAUTIONS, General subsection.

Lines 229-256 225-226	Drug Interactions subsection is updated under points 1,2,3 and 5. Sentence 256 is edited and moved to lines 225-226.
Lines 293	[ ] are transferred to the ADVERSE REACTIONS, Gastrointestinal System subsection from the Other subsection in line 319.
Lines 315-320	A new [ ] subsection is added to the ADVERSE REACTIONS section. "Systemic lupus erythematosus", "periarteritis nodosa", and "immunoglobulin abnormalities" are transferred to the [ ] subsection from the Other subsection. The "Other" subsection is deleted.
Line 328	[ ] reaction is added and "hypertensive" reaction is deleted in the OVERDOSAGE SECTION.
Lines 350-351	A statement regarding the addition of Dilantin solution to the intravenous infusion is deleted in the in the DOSAGE AND ADMINISTRATION section.
Lines 353-369	Subsections titled [ ] and [ ] are added back to the DOSAGE AND ADMINISTRATION section.
Lines 373-376, 381-385	An updated section regarding storage replaces previous text.
Lines 411-416	Parenteral Dilantin injection procedure is deleted under the DOSAGE ADMINISTRATION, subsection because instructions were added earlier in this paragraph.

Finally, we are proposing that the revised package insert also remove products no longer marketed from the DOSAGE AND ADMINISTRATION section as follows:

Lines 393-395	Dilantin 30 Pediatric and Dilantin with Phenobarbital are deleted in the DOSAGE ADMINISTRATION section.
Lines 481-483	Date and specification number will be revised once this submission is approved.

As requested by Ms. Chamberlain, we are providing two diskettes (Word Perfect 6.0) that each contain the text of this package insert as presented in Attachment 1. These diskettes are included herein as Attachment 4.

Please note that we have submitted, under a separate NDA supplement, the last approved package insert with annotated changes for the Dilantin Suspension (NDA 8-762). This submission was dated May 25, 1994 (S-020).

If you have any questions regarding this submission, please do not hesitate to contact me at 201/540-3113.

Very truly yours,

James A. Parker, Jr.
Director
Advertising and Labeling
Worldwide Regulatory Affairs

JP/rp
dilantin.inj

Attachments

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

Date August 11, 1994

NDA No. 10-151

Parke-Davis Pharmaceutical Research
Division of Warner-lambert Company
201 Tabor Road
Morris Plain, NJ 07950

Attention: James A. Parker, Jr.

Dear Sir/Madam:

We acknowledge receipt of your supplemental application for the following:

Name of Drug: DILANTIN - Injection

NDA Number: 10-151

Supplement Number: S-032

Date of Supplement: August 9, 1994

Date of Receipt: August 10, 1994

All communications concerning this NDA should be addressed as follows:

Center for Drug Evaluation and Research
Attention: Document Control Room 10B-20
5600 Fishers Lane, HFD-120
Rockville, MD 20857

Sincerely yours,

Arthur Randolph

For John Purvis
Supervisory Consumer Safety Officer
Division of Neuropharmacologic Drug Products
Center for Drug Evaluation and Research

cso: Chamberlin

FORM FDA 3217b (3/91)

201 Tabor Road
Morris Plains, NJ
07950
Phone: 201-540-2000

ORIGINAL

PARKE-DAVIS
People Who Care

NDA NO. 10-151 REF. NO. 82R-032

August 9, 1994 NDA SUPPL FOR FPL

NDA 10-151
Dilantin® Injection (Phenytoin Sodium Injection, USP)

Re: Labeling

Paul D. Leber, M.D.
Director
Division of Neuropharmacological
Drug Products (HFD-120)
Document Control Room 10B-30
Center for Drug Evaluation and Research
Food and Drug Administration
5600 Fishers Lane
Rockville, Maryland 20857

CENTER FOR DRUG EVALUATION AND RESEARCH
RECD
AUG 10 1994
HFD-120

Dear Dr. Leber:

Reference is made to our approved NDA 10-151 for Dilantin® (Phenytoin Sodium Injection, USP).

Reference is also made to your letter dated February 3, 1994, which requested revision of the labeling for Dilantin Injection to include a reported interaction with fluoxetine. Your letter cites a number of cases where patients on stable doses of phenytoin develop typical signs and symptoms of phenytoin toxicity within approximately two weeks of initiating treatment with fluoxetine. You request that this revision be effected at the next printing but no later than six months from the date of your letter.

We have included this drug interaction in the PRECAUTIONS section, Drug Interactions subsection under heading number one: "Drugs which may increase phenytoin serum levels...", after "trazodone" at the end of the paragraph. Twelve final printed copies of this revised labeling, specification number 4475G340, revised June 1994, are included herein as Attachment 1. This labeling will be implemented immediately.

Finally, your letter states that it would be useful for Parke-Davis to further explore the mechanism and magnitude of this interaction. We believe the evidence for this interaction is strong enough that further characterization, at this time, is not necessary.

Should you have any questions regarding this submission, please contact me at 201/540-3113 or FAX 201/540-5972.

Sincerely,

James A. Parker, Jr.
Director
Advertising and Labeling
Worldwide Regulatory Affairs

JP/rp
m:\postmark\dilantin\8894.jp

Attachments

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

NDA # 10-151

October 02, 1989

PARKE-DAVIS
Division of Warner-Lambert Company
201 Tabor Rd.
Morris Plains, New Jersey 07950

Attention:

Deanna D. Thomas

Dear

We acknowledge receipt of your supplemental application for the following:

Name of Drug: Dilantin (Phenytoin Sodium Injection, USP)

NDA number: 10-151

Supplement Number: S-030

Date of Supplement: September 25, 1989

Date of Receipt: September 28, 1989

All communications concerning this NDA should be addressed as follows:

Center for Drugs and Biologics, HFD-120
Attention: Document Control, Room 10B-20
5600 Fishers Lane
Rockville, Maryland 20857

Sincerely yours,

(for) John S. Purvis
Chief, Project Management Staff
Division of Neuropharmacological
Drug Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

cc:
NDA file
HFD-120 file
CSO file

12.1

NDA NO. 10-151 REF. NO. SEP-030

NDA SUPPL FOR Package Change
Supplement -
Expedited Review Requested

SLR

PARKE-DAVIS
Division of Warner-Lambert Company

Regulatory Affairs

SEP 25 1989

changed per SCSO: by Barbe

Paul Leber, M.D., Director
Division of Neuropharmacological Drug Products
Office of Drug Evaluation I (HFD-120)
Center for Drug Evaluation & Research
Food & Drug Administration
5600 Fishers Lane
Rockville, Maryland 20857

CENTER FOR DRUGS AND BIOLOGICS
REC'D
SEP 28 1989
HFN-120

RE: NDA 10-151
Dilantin (Phenytoin Sodium Injection, USP)

Dear Sirs:

In accordance with 21 CFR 314.70(b)(3), we are hereby submitting for your approval a revised package insert for the above product. is submitted

The major revision involves the addition of specific instructions regarding the method of administration in the DOSAGE AND ADMINISTRATION section. Specifically, we have strengthened the directions for the administration of parenteral Dilantin via the bolus method and added instructions for administration via the infusion method. The rationale for these changes is detailed below. Due to the nature and importance of this revision, we are requesting an expedited review of this supplement.

This revision of the DOSAGE AND ADMINISTRATION section is intended to increase the safe use of parenteral Dilantin. Although the strengthening of the instructions for use may be accomplished under 21 CFR 314.70(c)(2)(iii) without prior FDA approval, we wish to obtain the agency's approval prior to implementation.

The directions for injection, as currently stated in the DOSAGE AND ADMINISTRATION section in paragraph 10, are:

> Parenteral Dilantin should be injected slowly and directly into a large vein through a large-gauge needle or intravenous catheter. Each injection of intravenous Dilantin should be followed by an injection of sterile saline through the same needle or catheter to avoid local venous irritation due to alkalinity of the solution. Continuous infusion should be avoided; the addition of parenteral Dilantin to intravenous infusion fluids is not recommended because of the likelihood of precipitation.

201 Tabor Road Morris Plains, New Jersey 07950 (201) 540-2000

In the revised insert this paragraph has been deleted and replaced by a subsection titled [ ]. This subsection parallels the original except that the revised instructions now state each injection should be [ ] followed by a flush of sterile saline (instead of only followed by) and the reference to not using the infusion method of administration has been deleted.

The second revision to this section involves the creation of a new subsection titled [ ].

As background, intravenous Dilantin has been known to cause soft tissue injury and inflammation, with or without extravasation, at the injection site. This has been documented in both adverse reaction reports received in house and in the literature. Selected references detailing this problem are included herein as Attachment 1.

It has been speculated that the reason for these reactions may be due to the alkalinity of the solution. Reports in the literature have suggested these adverse reactions may be minimized by the administration of parenteral Dilantin via the infusion method. Through dilution, the alkalinity of the solution decreases, resulting in less tissue damage.

Previously, the package insert recommended against the addition of Dilantin to intravenous infusion, citing the lack of solubility and resultant precipitation. Subsequent investigations however (as reported extensively in the literature) have revealed Dilantin to be compatible for a limited period of time in certain solutions, concentrations and storage conditions. Furthermore, we are aware that, in the field, physicians are often administering Dilantin by this method. Consequently, we believe that the regulatory requirement for adequate directions for use necessitate inclusion in the package insert of appropriate instructions for infusion administration.

The directions for infusion administration, as contained in the revised DOSAGE AND ADMINISTRATION section, are based on information contained in the published literature. [ ]

Selected references detailing the infusion method are included herein for your reference as Attachment 2. We trust this information is sufficient to support the proposed revision.

In addition to the above, we have made additional revisions which are detailed below. These additional revisions add to or strengthen certain warnings, precautions and adverse reactions, and include editorial changes for clarification. To facilitate your review, we are providing in Attachment 3 a side-by-side comparison of the previous and revised inserts, with the changes clearly marked. These revisions have already been made to our other anticonvulsant package inserts and were

have been previously reviewed!

END!

submitted as special supplements under 21 CFR 314.70(c)(2).

The specific additional revisions are as follows:

(1) Under "CLINICAL PHARMACOLOGY" add the following sentence at the end of paragraph five: [ ]

[ ]

(2) In the "WARNINGS" section add the following as the fourth paragraph: [ ]

[ ]

[ ]

(3) Under the section "PRECAUTIONS" make the following revisions:

(a) in the subsection "General" add the following as the fourth paragraph: [ ]

[ ]

(b) Under the subsection "Drug Interactions":

(i) add the following in the first paragraph: "Serum level determinations for phenytoin are especially helpful when possible drug interactions are suspected". This sentence was moved from the end of this subsection.

(ii) The paragraph under (1) has been alphabetized and updated with additional drugs which may increase phenytoin serum levels.

(iii) [ ] has been added to paragraph (2).

(iv) paragraph (3) has been revised to alphabetize the drugs listed in the first sentence.

(v) paragraph (5) has been revised to alphabetize the drugs listed and to add [ ].

(5) Under "ADVERSE REACTIONS" :

(a) In the subsection "Gastrointestinal System", [ ] [ ] have been added. Note: these two adverse reactions were transferred from the "Other" subsection which has been deleted.

(b) The subsection "Other" has been deleted and the information contained therein has been transferred to the existing gastrointestinal subsection and the two new subsections [ ] and [ ]. Please note the [ ] subsection also contains new information.

(6) Under the section "OVERDOSAGE" delete "hypertensive" in the first paragraph and add [ ].

(7) Add a storage statement at the end of the insert.

Twelve final printed copies of the revised insert (specification number 4475G026), dated March 1989) are included in Attachment 4.

If you have any questions or require additional information, please do not hesitate to contact me at (201) 540-4334.

Sincerely,

Deanna D. Thomas
Associate Director
Regulatory Affairs

Attachments

ORIG

SLR 029 AF
NDA SUPPL AMENDMENT

PARKE-DAVIS
Division of Warner-Lambert Company

Regulatory Affairs

May 10, 1988

Paul D. Leber, M.D., Director
Division of Neuropharmacology Drug Products (HFN-120) Rm #10B-45
Office of Drug Research and Review
Center for Drug Evaluation and Research
Document Control Room # 10B-30
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857

Special Supplement
Changes Being Effected

Re: NDA 10-151 Dilantin® (Phenytoin Sodium Injection, USP) Injectable
Revised Labeling (Package Insert) S-029

Dear Doctor Leber:

As promised in our September 25, 1987 letter (S-029), we are providing 12 copies of the final printed labeling which was submitted under 314.70(C)(2) for the aforementioned product. As stated in the letter, the labeling was placed into effect 60 days after our September 25th communication.

We are also providing your division, under separate cover, final printed labeling which was submitted under 314.70 (C)(2) for the following products: Dilantin Suspension (NDA 8-762), [ ]
[ ]

Please be advised that final printed labeling is also being forwarded to the Generic Drug Division covering the supplements made pursuant to 314.70(C)(2) for Dilantin Kapseals (NDA 84-349) and Dilantin Infatab (NDA 84-427).

Thank you for your cooperation.

Sincerely yours,

Milton R. Kaplan
Director
Regulatory Affairs

MRK:DD:ag/0979j/1

RECEIVED
NATIONAL CENTER
JUN 01 1988
HFN-120
FOR DRUGS & BIOLOGICS

201 Tabor Road Morris Plains, New Jersey 07950 (201) 540-2000

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

Date OCT 5 1987

NDA No. 10-151

Division of Warner-Lambert Co.
201 Tabor Road
Morris Plains, New Jersey
07950

Attention: M. R. Kaplan

Dear Sir/Madam:

We acknowledge receipt of your supplemental application for the following:

Name of Drug: Dilantin® Injectable

NDA Number: 10-151

Supplement Number: S-020

Date of Supplement: September 25, 1987

Date of Receipt: October 1, 1987

All communications concerning this NDA should be addressed as follows:

Center for Drugs and Biologics, HFN-120
Attention: Document Control, Room 10B-30
5600 Fishers Lane
Rockville MD 20857

Sincerely yours
Mark T. Cary
for John S. Parks
Division of Neuropharmacological Drug Products
Center for Drugs and Biologics

cc:
NDA File
HFN-120 File
CSO File

FORM FDA 3217b (2/86)

ORIGINAL

PARKE-DAVIS
Division of Warner-Lambert Company

NDA NO. 10-151 REF. NO. 5-029
NDA SUPPL FOR Labeling Rev

Regulatory and Medical Affairs

SEP 25 1987

Paul D. Leber, M.D., Director
Division of Neuropharmacology Drug Products (HFN-120) Rm #10B-45
Office of Drug Research and Review
Center for Drugs and Biologics
Document Control Room # 10B-30
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857

Duplicate Review is Other Vol.

Special Supplement
Changes Being Effected

Dear Doctor Leber:

Re: NDA 10-151 Dilantin® (phenytoin sodium injection, USP) Injectable
Revised Labeling (Package Insert)

We are submitting under 314.70(c)(2) to be placed into effect after 60 days, the following change in our labeling for Dilantin (phenytoin) products, to clarify and extend the Precautions and Adverse Reactions sections of our package insert. These changes are based on review of drug experience reports received and submitted to the agency. We believe these revisions represent important labeling information for the medical community which should be included in our package insert at the present time.

Additions have been made in the Precautions and Adverse Reactions sections as well as minor additions in the How Supplied section. Specifically, information regarding rare instances of amputation has been added to the precautions section of the Dilantin parenteral package insert and the occurrence of toxic epidermal necrolysis has been added to the precautions and adverse reactions sections of all Dilantin products package inserts.

Labeling is also being forwarded to the Generic Drug Division covering Dilantin Kapseals (NDA 84-349) and Dilantin Infatabs (NDA 84-427). Under separate cover we are forwarding to you labeling covering Dilantin Suspension (NDA 8-762) [ ].

RECEIVED
NATIONAL CENTER
OCT 01 1987
HFN-120
FOR DRUGS & BIOLOGICS

201 Tabor Road Morris Plains, New Jersey 07950 (201) 540-2000

Enclosed please find draft labeling reflecting these changes. Final printed labeling will be forwarded to you as soon as it is available. Thank you for your cooperation.

Sincerely,

M. R. Kaplan
Director
Regulatory Affairs

MRK:LF:ts/0858j/9-10