

CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

Application Number: 019445/S04/S06

**Trade Name: 25% DEXTROSE INJECTION IN PLASTIC
VIALS**

**Generic Name: 25% DEXTROSE INJECTION IN
PLASTIC VIALS**

**Sponsor: ABBOTT LABORATORIES, HOSPITAL
PRODUCTS DIVISION**

Approval Date: 11/23/98

**Indication(s): SOURCE OF CARBOHYDRATES FOR
NEONATES AND INFANTS**

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION: : 019445/S04/S06

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| | Included | Pending Completion | Not Prepared | Not Required |
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| Approval Letter | X | | | |
| Tentative Approval Letter | | | | X |
| Approvable Letter | | | | X |
| 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 | X | | | |
| Biopharmaceutics Review(s) | | | | |
| Bioequivalence Review(s) | | | | X |
| Administrative Document(s)/ Correspondence | X | | | |

CENTER FOR DRUG EVALUATION AND RESEARCH

Application Number: : 019445/S04/S06

APPROVAL LETTER

NDA 19-445/S-004, S-006

NOV 23 1998

Abbott Laboratories
Hospital Products Division
Attention: Thomas F. Willer, Ph.D.
Assistant Director, Regulatory Affairs
D-389 Bldg. AP30
200 Abbott Park Road
ABBOTT PARK, ILLINOIS 60064-3537

Dear Dr. Willer:

Please refer to your supplemental new drug applications (S-004 and S-006) dated November 21, 1997, received November 25, 1997, submitted pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act for Dextrose 50% Injection in PET Abboject Vials.

For administrative purposes the change described in supplement S-005, which provided for manufacture of a new strength, 25% Dextrose in a new 10 mL Ansyr plastic syringe has been incorporated in S-004 and S-006. Supplement 005 has been canceled.

We acknowledge receipt of your submissions dated April 3 and 8, May 11, July 23, October 16, and November 18 and 19, 1998.

The user fee goal date for these applications is November 25, 1998.

These supplemental new drug applications provide for the use of a new strength of Dextrose 25% Injection in a new container, a 10 mL Ansyr plastic syringe as follows:

- S-004: This supplement provides for a new sub-population - neonates and infants for approved use as a minimal source of carbohydrates and calories in this population.
- S-006: This supplement provides for a new indication in the treatment of acute symptomatic episodes of hypoglycemia in the neonate and older infant to restore depressed blood glucose levels and control symptoms.

We have completed the 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 the agreed upon labeling text. Accordingly, the supplemental applications are approved effective on the date of this letter.

The final printed labeling (FPL) must be identical to the enclosed labeling (immediate container and carton labels) and submitted draft labeling (package insert submitted November 19, 1998, immediate container and carton labels submitted November 19, 1998). Marketing the product with FPL that is not identical to the approved labeling text may render the product misbranded and an unapproved new drug.

Please submit 20 copies of the FPL as soon as it is available, in no case 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, this submission should be designated "FPL for approved supplements NDA 19-445/S-004, 006." Approval of this submission by FDA is not required before the labeling is used.

In addition, please submit three copies of the introductory promotional materials that you propose to use for this product. All proposed materials should be submitted in draft or mock-up form, not final print. Please submit one copy to this Division and two copies of both the promotional materials and the package insert directly to:

Division of Drug Marketing, Advertising, and Communications, HFD-40
Food and Drug Administration
5600 Fishers Lane
Rockville, Maryland 20857

If a letter communicating important information about this drug product (i.e., a "Dear Health Care Practitioner" letter) is issued to physicians and others responsible for patient care, we request that you submit a copy of the letter to this NDA and a copy to the following address:

MEDWATCH, HF-2
FDA
5600 Fishers Lane
Rockville, MD 20857

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

NDA 19-445/S-004, 006
Page 3

If you have any questions, contact Steve McCort, Project Manager, at (301) 827-6415.

Sincerely,

/S/ 11/23/98

APPEARS THIS WAY
ON ORIGINAL

Solomon Sobel, M.D.
Director
Division of Metabolic
and Endocrine Drug Products, HFD-510
Office of Drug Evaluation II
Center for Drug Evaluation and Research

ENCLOSURE
(November 19, 1998, approved draft labeling text)

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CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: : 019445/S04/S06

MEDICAL REVIEW(S)

MEDICAL REVIEW

of

NDA 19-445/s-004 & 006

SPONSOR: Abbott Laboratories

DRUG: 25% dextrose injection in 10-ml plastic syringe

INDICATION: Treatment of acute hypoglycemia in the neonate or older infant/source of carbohydrate calories

DATE SUBMITTED: 11/21/97

DATE OF REVIEW: 11/16/98

BACKGROUND

Abbott currently markets a 25% dextrose injection in a 10-ml glass syringe for..... "the treatment of acute symptomatic episodes of hypoglycemia in the neonate or older infantand also as a source of carbohydrate calories." This product is not approved per se - that is, it is a pre-1938 or a grandfathered drug.

Abbott also markets an approved 50% dextrose injection in a 50 ml plastic syringe under NDA 19-455. This product is indicated for use in adults for the treatment of insulin hypoglycemia to restore blood glucose levelsThe solution is also indicated for intravenous infusion as a source carbohydrate calories.....

In a letter of September 3, 1996 (attached), Dr Roger Williams, Deputy Center Director for Pharmaceutical Science, laid out a submission approach for Abbott to pursue for their 25% dextrose injection in a 10-ml plastic syringe (with an indication for the treatment of hypoglycemia in the neonate/older infant and as a source of carbohydrate calories). In his letter, Dr Williams states, ".....Therefore, dextrose injection, USP, 25% in the new syringe may be submitted as a supplement to NDA 19-455.If the 25% product bears a different indication (for example, use for a different condition or population with different recommendations pertaining to dose or dosage regimen), a separate efficacy supplement that requires clinical data as defined in the PDUFA would normally be subject to an application fee....."

Thereafter, Abbott did submit the application under review as a 505(b)(2)-efficacy supplement to NDA 19-455. To support the safety and efficacy of this product the company submitted clinical data in the form of published literature. Given the grandfathered status of 25% dextrose injection in glass, it is not

surprising that there are, to best of my and the sponsor's knowledge, no published adequate and well controlled studies examining the safety and effectiveness of 25% dextrose injection in the treatment of hypoglycemia or as a source of carbohydrate calories in neonates and infants.

The relevant literature on dextrose injection is found in standard pediatric textbooks. It is appropriate here to refer to a November 6, 1998 letter (attached) from Dr. Murray Lumpkin, Deputy Center Director (Review Management), to Dr. Thomas Willer of Abbott Laboratories. In his letter, Dr. Lumpkin states, ".....Based on your description of the products, including the apparent substantial marketing history, you should consider whether an application under section 505(b)(2), which may sometimes consist of simple literature/medical textbook information to support safety and efficacy, may be feasible for each of these drug products."

Hence, the safety and effectiveness of 25% dextrose injection in plastic syringe, as submitted, will be based on literature from standard pediatric textbooks.

Indication #1 – Treatment of Acute Symptomatic Episodes of Hypoglycemia in the Neonate and Older Infant

Pathophysiology of Hypoglycemia in Neonates and Infants

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In general, blood glucose levels below 40 mg/dl, with or without symptoms (i.e., irritability, lethargy, tachycardia, sweating, seizure, coma) warrant immediate attention.

The pathophysiology of hypoglycemia in the neonate may differ from that of the older infant; consequently, a brief discussion of the causes of low blood glucose will be provided below for these two populations.

Neonates (< 72 hours)

**APPEARS THIS WAY
ON ORIGINAL**

Two populations of neonates are at increased risk for hypoglycemia. One group is the small for gestational age infants - due to impaired gluconeogenesis. The second group is newborns of gestational diabetic mothers. Here, transient hyperinsulinemia leads to suppressed levels of blood glucose in the neonate.

Infants (> 72 hours)

**APPEARS THIS WAY
ON ORIGINAL**

In infants and older children there are numerous causes of hypoglycemia. The following table provides many of the conditions associated with hypoglycemia in this population.

-
1. **Abnormalities in hormone secretion**
 - Hyperinsulinemia
 - Glucagon deficiency
 - Growth hormone, thyroid, and adrenal insufficiency
 2. **Abnormalities in fuel substrate metabolism**
 - Inborn error of carbohydrate, amino acid, or fatty acid metabolism
 - Reyes syndrome
 - Ethyl alcohol
 - ASA
 3. **Abnormalities of substrate availability**
 - Ketotic hypoglycemia
 - Hypoglycemia associated with surgery
-

**APPEARS THIS WAY
ON ORIGINAL**

Treatment of Acute Hypoglycemia

The obvious goal of treatment of acute hypoglycemia with symptoms is restoration of normal blood glucose levels with amelioration of symptoms. This can usually be achieved by the immediate administration of an intravenous injection of concentrated dextrose. According to standard pediatric textbooks, intravenous doses ranging from 2ml/kg of 10% dextrose up to 0.5-1.0 ml/kg of 50% dextrose can be used initially to treat acute symptomatic hypoglycemia in the neonate and older infant.¹⁻⁴ In general, more severe cases of hypoglycemia require higher initial doses of dextrose. In cases where there is an inadequate response to the first injection of dextrose, higher concentrations can be used, or other drugs such as glucagon and epinephrine may be administered.

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Indication #2 – A Minimal Source of Carbohydrate Calories

It is standard practice to use a glucose solution as the source of carbohydrate in newborns and infants on total parenteral nutrition (TPN). In fact, glucose is the most commonly used carbohydrate in TPN solutions.³ Intravenous glucose should be provided at a rate of approximately 6 to 7 mg/kg/min. Pediatric textbooks commonly advocate using a 10 % to 20% glucose solution in TPN for infants and lower concentrations (i.e., < 10%) for neonates and premature infants.⁴⁻⁶ Dextrose concentrations of greater than 12% should be administered by a central venous line rather than peripherally due to hypertonicity and risk for phlebitis.

APPEARS THIS WAY
ON ORIGINAL

Labeling Review

1. Description – acceptable
2. Clinical Pharmacology – recommend changing the definition of hypoglycemia from < 30mg/dl in the neonate and < 50mg/dl in older infants to < 40mg/dl.
3. Indications and Usage – acceptable
4. Contraindications – acceptable
5. Warnings – acceptable
6. Precautions – I recommend that the following be inserted as the first paragraph: “frequent monitoring of serum glucose concentrations is required when intravenous dextrose is given to pediatric patients, particularly neonates and low birth weight infants.”
7. Carcinogenesis, Mutagenesis, Impairment of Fertility – defer to pharmacology
8. Adverse Reactions – acceptable
9. Overdose – acceptable
10. Dosage and Administration – recommend inserting the following after the first sentence: “ When possible, glucose concentration of greater than 12% should be administered by central vein to reduce the risk for phlebitis and thrombosis.” I also recommend that the following statement be included as a second paragraph: “The dosage and constant infusion rate of intravenous dextrose must be selected with caution, particularly in neonates and low birth weight infants, because of the increased risk of hyperglycemia/hypoglycemia.”

APPEARS THIS WAY
ON ORIGINAL

APPEARS THIS WAY
ON ORIGINAL

RECOMMENDATION

Twenty-five percent dextrose injection in a 10-ml glass syringe has been on the market for over 60 years. According to company statistics, over 45,000 units/year of this product were distributed in the past three years. Remarkably, Abbott has not received a single adverse event report for 25% dextrose injection during its entire marketing history.⁷ This, coupled with wide-spread textbook reference to the use of dextrose injection in the treatment of acute hypoglycemia in neonates, infants, and older children and its use as a source of carbohydrate calories, lead this Reviewer to conclude that 25% dextrose injection in a 10-ml plastic syringe is safe and effective. This product should be approved.

13/ - 11/19/8
Eric Colman, MD
15/ 11/19/98
cc: NDA file
McCortS/TroendleG

APPEARS THIS WAY
ON ORIGINAL

References

1. Current Pediatric Diagnosis and Treatment. Hay WW, et al. Editors. 13th edition 1997.
2. Pediatrics. Ziai M. 4th edition. 1990.
3. Rosen's Emergency Medicine: Concepts and Clinical Practice. 4th edition. 1998.
4. Nelson's Textbook of Pediatrics. Behrman Editor. 14th edition. 1992.
5. Parenteral Nutrition. Rombeau and Caldwell Editors. 2nd edition. 1993
6. Modern Nutrition in Health and Disease. Shils, Olson, and Shike Editors. 8th edition. 1994
7. Fax from Dr. Thomas Willer, Abbott Laboratories, dated 11/18/98.

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CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: : 019445/S04/S06

CHEMISTRY REVIEW(S)

McCart

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| | | |
|--|------------------------|---|
| CHEMIST'S REVIEW | 1. ORGANIZATION | 2. NDA NUMBER |
| | DMEDP, HFD-510 | 19-445 |
| 3. NAME AND ADDRESS OF APPLICANT | | 4. SUPPLEMENT NUMBER, DATE |
| Abbott Laboratories Hospital Products Division D-389, Bldg. AP30 200 Abbott Park Road Abbott Park, Illinois 60064-3537 | | 19-445/SCP-005 Dated 11-21-97 |
| 5. NAME OF THE DRUG | 6. NONPROPRIETARY NAME | User Fee Date: 11-25-98 |
| 50% Dextrose Injection in PET Abboject® Vials | | |
| 7. SUPPLEMENT PROVIDES FOR: | | 8. AMENDMENTS/REPORT, DATE |
| a new strength (25% dextrose concentration), a new fill volume (10 mL), and a new container/closure system (polypropylene plastic syringe). | | Amendment dated 5-11-98 Amendment dated 6-12-98 Amendment dated 7-27-98 |
| 9. PHARMACOLOGICAL CATEGORY | 10. HOW DISPENSED | 11. RELATED IND/NDA/DMF NDA 19-445/S-002 |
| Provides a source of carbohydrate calories in a form more suitable for administration to infants and neonates | By Rx only | |
| 12. DOSAGE FORM | 13. POTENCY | |
| Prefilled syringe | 25% | |
| 14. CHEMICAL NAME AND STRUCTURE. | | |
| Dextrose C ₆ H ₁₂ O ₆ | | |
| 15. COMMENTS | | |
| <p>This submission, originally designated as a manufacturing supplement, was split into two efficacy supplements (SE-004 and SE-006) and one Chemistry Supplement (SCF-005), due to the addition of two new indications. This review only deals with new formulations and the chemistry of the plastic container. This supplemental application (NDA 19-445/S-005) provides for: 1) a new drug product strength (25% Dextrose) and 2) a new container (10 mL polypropylene Ansy® plastic syringe). The new strength (25%) is being added to NDA 19-445 (see letter from R. Williams, Deputy Center Director, dated 9-3-96 "Products for which there is no approved reference drug", in which the addition of the 25% strength to NDA 19-445 [Dextrose 50% Injection] was approved). The drug product is manufactured/formulated in an identical fashion to that used for the 50% injection. The proposed container/closure system is identical in composition to that approved for NDA 19-445/S-002, consisting of the following components</p> | | |

(Continued on the next Page)

The issues associated with the Ansy® syringe, including the suitability of syringe components, and monitoring of additional extractables have been reviewed previously for NDA 19-445/S-002

The amendment dated 5-11-98 provides information regarding the labeling materials (inks, adhesives, etc.). This communication verified that these materials are identical to those submitted previously to Supplement S-002 of this NDA. The amendment dated 6-12-98 provides for NA-11 and DBF monitoring for NDA 19-445 (50% dextrose injection in Ansy® syringes) and NDA 18-801 (WFI in Ansy® syringes); these data will serve to "bracket" NDA 19-445/S-005 (25% dextrose injection in Ansy® syringes). The amendment dated 7-27-98 provides for a reversion back to the originally approved stability testing schedule for lots of drug product manufactured after the first three post-approval lots. Letters of authorization allowing reference to

16. CONCLUSION AND RECOMMENDATION

Adequate information has been supplied. The supplement is approvable. Issue approval letter.

| 17. NAME | REVIEWER SIGNATURE | DATE COMPLETED |
|-----------------------|--------------------|---------------------------------|
| David B. Lewis, Ph.D. | /S/ | October 29 th , 1998 |
| DISTRIBUTION: | ORIGINAL JACKET | CSO |
| | REVIEWER | DIVISION FILE |

/S/

10/29/98

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CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: : 019445/S04/S06

MICROBIOLOGY REVIEW(S)

HFD-510
MCCCR

MAR 30 1998

REVIEW FOR HFD-510

OFFICE OF NEW DRUG CHEMISTRY
MICROBIOLOGY STAFF HFD-805
Microbiologist's Review #1 of NDA 19-445/SCF-005/SE5-004
March 25, 1998

- A. 1. APPLICATION NUMBER: 19-445/SCF-005 and SE5-004
 APPLICANT: Abbott Laboratories
 200 Abbott Park Road, D-389 AP30
 Abbott Park IL, 60064-3537
2. PRODUCT NAME: 50% Dextrose Injection, USP
3. DOSAGE FORM AND ROUTE OF ADMINISTRATION: Sterile 50% dextrose (10 mL fill volume) in 10 mL PET Abobject vials. For intravenous (single-dose) administration.
4. METHODS OF STERILIZATION:
5. PHARMALOGICAL CATAGORY and/or PRINCIPLE INDICATION: Treatment of hypoglycemia. The 25% formulation will be indicated for neonates and older infants.
- B. 1. DATE OF SUBMISSION: November 21, 1997
 2. DATE OF CONSULT: December 1, 1997
 3. RELATED DOCUMENTS:
 4. ASSIGNED FOR REVIEW: December 22, 1997
 5. SUPPLEMENT PROVIDES FOR: The supplement provides for a 25% dextrose concentration (25% Dextrose Injection, USP) in a 10 mL polyethylene plastic syringe.

C. REMARKS:

Two supplements were filed in support of the 25% Dextrose concentration:

- SCF-005: Manufacturing supplement for a new formulation.
- SE5-004: Efficacy supplement for an indication and dose regimen for the 25% dextrose

Microbiology consult reviews were requested for both SCF-005 and SE5-004. However, the microbiology contents of both supplements are identical.

A description of the ~~supplement~~ ~~microbiology~~ ~~contents~~ ~~of~~ ~~both~~ ~~supplements~~ ~~are~~ ~~identical~~, was duplicated and included in the NDA ~~application~~. Therefore, the DMF review was performed.

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D. CONCLUSIONS:

The submission is recommended for approval for microbiology issues concerning, sterility assurance.

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/S/

3/25/98

Neal Sweeney, Ph.D.

APPEARS THIS WAY
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/S/

3/30/98

cc: NDA 19-445/SCF-005
NDA 19-445/SE5-004
HFD-510/Division File
HFD-510/S. McCort
HFD-805/Consult File/N. Sweeney

APPEARS THIS WAY
ON ORIGINAL

Drafted by: N. Sweeney, March 25, 1998
R/D Initialed by P. Cooney, March 25, 1998

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: : 019445/S04/S06

**CLINICAL PHARMACOLOGY AND
BIOPHARMACEUTICS REVIEW(S)**

CLINICAL PHARMACOLOGY & BIOPHARMACEUTICS REVIEW

NDA 19-445
SE5-004; SCF-005; SE1-006

SUBMISSION DATE: 21-NOV-97, 03-APR-98 (BZ)

GENERIC NAME: 25% dextrose in 10 mL polypropylene syringe

REVIEWER: Robert M. Shore, Pharm.D.

SPONSOR: Abbott Laboratories,
Abbott Park, IL

TYPE OF SUBMISSION: New concentration; new indication

SUBMISSION:

Currently, the sponsor markets 25% dextrose in-glass and 50% dextrose in plastic. The 25% dextrose is specifically labeled for use in neonates/infants while the 50% dextrose has no age restrictions in the labeling. However, the 25% dextrose in glass is 'grandfathered' - it does not have an NDA because it was marketed before the law required an NDA. Therefore, when the sponsor decided to make changes to the 25% dextrose product (glass to plastic container), the Agency decided it should be done through supplements to the approved 50% dextrose product (NDA 19-445). It is noteworthy that the same plastic is already used in the marketed 50% dextrose product. All products are indicated for intravenous administration only. All products contain only dextrose (no preservatives or buffers) in solution and are for single-dose injection only.

SCF-005 pertains to the change in concentration from 50% to 25% dextrose. SE5-004 and SE1-006 pertain to the change in labeling which specify use in infants/neonates. As per Steve McCort (CSO) the labeling proposed for the 25% dextrose in plastic product is identical to that of the marketed 25% dextrose in glass product.

21 CFR 320.21 (c) indicates that a supplemental application shall include either (1) evidence demonstrating the *in vivo* bioavailability of the drug product, or (2) information to permit FDA to waive the submission of evidence demonstrating *in vivo* bioavailability. 21 CFR 320.22 (b) - (e) outlines the criteria for waiver of evidence of *in vivo* bioavailability or bioequivalence. Paragraph (b), as it pertains to this product, states that the FDA shall waive the requirement for evidence of *in vivo* bioequivalence if the drug product is both a parenteral solution and contains the same active and inactive ingredients in the same concentration as an approved product. Although the proposed product does not strictly meet this criteria since the concentrations differ, the Office of Clinical Pharmacology and Biopharmaceutics believes that there will be no differences in systemic availability of dextrose since the product will be administered intravenously and the same concentration of dextrose is already marketed in a glass container.

RECOMMENDATION:

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The Office of Clinical Pharmacology and Biopharmaceutics has reviewed the supplements submitted to NDA 19-445 on 21-NOV-97 and 03-APR-98 and finds that it is reasonable to grant a waiver of the requirement to submit evidence of *in vivo* bioavailability for 25% dextrose in plastic under 21 CFR 320.22.

Robert M. Shore, Pharm.D.
Division of Pharmaceutical Evaluation II
Office of Clinical Pharmacology and Biopharmaceutics

/S/

12-NOV-98

RD initialed by Hae-Young Ahn, Ph.D., Team Leader 12-NOV-98

FT initialed by Hae-Young Ahn, Ph.D., Team Leader /S/ 11/21 98

CC: NDA 19-644/S-004,S-005,S-006 (orig.,1 copy), HFD-510(McCort, ColmanE), HFD-870(Ahn, ChenME), HFD-850(Lesko), CDR (Barbara Murphy).

Code: AP

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CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ADMINISTRATIVE DOCUMENTS/CORRESPONDENCE

**Division of Metabolic and Endocrine Drug Products
REVIEW OF DRAFT LABELING**

Application Number: 19-445/S-004 & S-006

Name of Drug: 25% Dextrose Injection, USP

Sponsor: Abbott Laboratories

Material Reviewed

Submission Date(s): November 19, 1998

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Receipt Date(s): November 19, 1998

Background and Summary Description:

Based upon comments conveyed to the Sponsor by Dr. Eric Colman, Medical Reviewer on November 19, 1998, and communicated by Dr. Duu-Gong Wu, Chemistry Supervisor, in a telephone conversation dated November 19, 1998, the labeling was revised to reflect those changes.

Review

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The revised labeling dated November 19, 1998, was compared with the labeling dated November 17, 1997. All the changes requested by the Division are included in the November 19, 1998. In addition the following additional revision was included as follows::

The "Rx only" statement on the container and carton labels has been added and deleted from the package insert, as required per FDAMA 1997, section 126.

**APPEARS THIS WAY
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Page 3

cc:

NDA 19-445/S-004 & S-006

HFD-510/Div. Files

HFD-510/SMcCort

HFD-510/Solomon Sobel, M.D.

draft: smm/November 20, 1998/n19445.lab

r/d Initials:

final:

LABEL REVIEW

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Hospital Products Division

Abbott Laboratories
D-389 Bldg AP30
200 Abbott Park Road
Abbott Park, Illinois 60064-3537

November 19, 1998

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CENTER FOR DRUG EVALUATION AND RESEARCH
DIVISION OF METABOLISM AND ENDOCRINE
DRUG PRODUCTS, HFD #510
Attn. DOCUMENT CONTROL ROOM #14B-19
5600 Fishers Lane
Rockville, Maryland 20857

ATTENTION: Solomon Sobel, M.D.
Director

FAX 301-443-9282
(Paper Copy Via Mail)

Re: NDA 19-445 50% Dextrose Injection in PET Abboject Vials, S-004, S-005, S-006
Telephone Amendment

Abbott Laboratories hereby amends the above-referenced supplements to provide for the 25% Dextrose Injection, USP, to be packaged in a plastic syringe. In response to a telephone request from Dr. Duu-Gong Wu and Mr. Steve McCort, FDA, to Dr. Jessie Lee, Abbott Laboratories, we have deleted List 7898, Abboject Glass Unit (Grandfathered Drug), from the package insert for the above-referenced supplement. We will submit a "Changes Being Effected" Supplement for the Abboject Glass Unit with additional information in order to comply with the regulatory requirements for this product in the near future. In addition, we have added the "Rx only" statement on the container and carton labels and deleted it from the insert labeling for the 25% Dextrose plastic syringe as required per FDAMA 1997, Section 126. We provide annotated labeling per the Agency's request in Exhibit I.

We trust that this submission is complete. We will make the changes and submit twenty copies of the final printed labeling prior to marketing this product.

Sincerely,

ABBOTT LABORATORIES

Jessie Y. Lee, Ph.D.
Manager, Regulatory Affairs
Hospital Products Division
Phone: (847) 937-5513
Fax: (847) 938-7867
e-Mail: LEEJ@hpd.abbott.com

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16 Page(s) Redacted

DRAFT
LABELING



PATENT AND EXCLUSIVITY INFORMATION

1. Active Ingredient(s): Dextrose
2. Strength(s): 250 mg / mL
3. Trade Name: 25% Dextrose Injection, USP
in Plastic Syringe
4. Dosage Form: Injectable solution
5. Route of Administration: Intravascular administration
6. Applicant Firm Name: Abbott Laboratories
7. NDA Number: NDA 19-445
8. Approval Date: To be determined
9. Exclusivity - Date first ANDA could be approved and length of exclusivity period:
None
10. Applicable patent numbers and expiration date of each:
None

Per 21 CFR 314.94 (a) (12), this is a "Paragraph II Certification" stating that the patent has expired.

Thomas F. Willer

Nov. 17, 1998

Thomas F. Willer, Ph.D.
Associate Director, Regulatory Affairs
Hospital Products Division
D-389, AP30
Abbott Laboratories
200 Abbott Park Road
Abbott Park, Illinois 60064-3537

Date

EXCLUSIVITY SUMMARY FOR NDA # 19-445 SUPPL # 004

Trade Name 25% Dextrose Injection In Plastic Vial Generic Name Dextrose

Applicant Name Abbott Laboratories HFD # 510

Approval Date If Known 11-23-98

PART I IS AN EXCLUSIVITY DETERMINATION NEEDED?

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

a) Is it an original NDA?

YES / / NO / /

b) Is it an effectiveness supplement?

YES / / NO / /

If yes, what type? (SE1, SE2, etc.) SE5

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

YES / / NO / /

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

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

cc: Original NDA Division File HFD-93 Mary Ann Holovac

d) Did the applicant request exclusivity?

YES /___/ NO /_x_/

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

e) Has pediatric exclusivity been granted for this Active Moiety? No

IF YOU HAVE ANSWERED "NO" TO ALL OF THE ABOVE QUESTIONS, GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

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

YES /___/ NO /_x_/

If yes, NDA # _____ Drug Name _____

IF THE ANSWER TO QUESTION 2 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

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

YES /___/ NO /_x_/

IF THE ANSWER TO QUESTION 3 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8 (even if a study was required for the upgrade).

PART II FIVE-YEAR EXCLUSIVITY FOR NEW CHEMICAL ENTITIES

(Answer either #1 or #2 as appropriate)

1. Single active ingredient product.

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

YES /_x_/ NO /___/

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

NDA# 19-445 50% Dextrose Injection in Plastic Container

NDA# _____

NDA# _____

2. Combination product.

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

Not Applicable

YES /___/ NO /___/

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

NDA# _____

NDA# _____

NDA# _____

IF THE ANSWER TO QUESTION 1 OR 2 UNDER PART II IS "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8. IF "YES" GO TO PART III.

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

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

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

YES / / NO / /

IF "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

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

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

YES / / NO / /

If "no," state the basis for your conclusion that a clinical trial is not necessary for approval AND GO DIRECTLY TO SIGNATURE BLOCK ON PAGE 8:

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

YES / / NO / /

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

YES /___/ NO /___/

If yes, explain: _____

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

YES /___/ NO /___/

If yes, explain: _____

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

Studies comparing two products with the same ingredient(s) are considered to be bioavailability studies for the purpose of this section.

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

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

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

Investigation #1 !

IND # ____ YES / __ / ! NO / __ / Explain: _____
 !
 _____ ! _____

Investigation #2 !

IND # ____ YES / __ / ! NO / __ / Explain: _____

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

Investigation #1 !

YES / __ / Explain _____ ! NO / __ / Explain _____
 !

_____ ! _____
 !
 _____ ! _____

Investigation #2 !

YES / __ / Explain _____ ! NO / __ / Explain _____
 !

_____ ! _____
 !
 _____ ! _____

EXCLUSIVITY SUMMARY FOR NDA # 19-445 SUPPL # 006

Trade Name 25% Dextrose Injection In Plastic Vial Generic Name _____

Applicant Name Abbott Laboratories HFD # 510

Approval Date If Known 11-23-98

PART I IS AN EXCLUSIVITY DETERMINATION NEEDED?

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

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

b) Is it an effectiveness supplement?

YES / / NO / /

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

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

YES / / NO / /

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

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

cc: Original NDA Division File HFD-93 Mary Ann Holovac

d) Did the applicant request exclusivity?

YES /___/ NO /_x_/

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

e) Has pediatric exclusivity been granted for this Active Moiety? No

IF YOU HAVE ANSWERED "NO" TO ALL OF THE ABOVE QUESTIONS, GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

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

YES /___/ NO /_x_/

If yes, NDA # _____ Drug Name _____

IF THE ANSWER TO QUESTION 2 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

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

YES /___/ NO /_x_/

IF THE ANSWER TO QUESTION 3 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8 (even if a study was required for the upgrade).

PART II FIVE-YEAR EXCLUSIVITY FOR NEW CHEMICAL ENTITIES

(Answer either #1 or #2 as appropriate)

1. Single active ingredient product.

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

YES /_x_/ NO /___/

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

NDA# 19-445 50% Dextrose Injection in Plastic Container

NDA# _____

NDA# _____

2. Combination product.

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

Not Applicable

YES / / NO / /

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

NDA# _____

NDA# _____

NDA# _____

IF THE ANSWER TO QUESTION 1 OR 2 UNDER PART II IS "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8. IF "YES" GO TO PART III.

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

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

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

YES /___/ NO /x/

IF "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

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

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

YES /___/ NO /___/

If "no," state the basis for your conclusion that a clinical trial is not necessary for approval AND GO DIRECTLY TO SIGNATURE BLOCK ON PAGE 8:

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

YES /___/ NO /___/

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

YES /___/ NO /___/

If yes, explain: _____

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

YES /___/ NO /___/

If yes, explain: _____

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

Studies comparing two products with the same ingredient(s) are considered to be bioavailability studies for the purpose of this section.

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

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

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

Investigation #1 !
 IND # ____ YES / __ / ! NO / __ / Explain: _____
 !
 ! _____

Investigation #2 !
 IND # ____ YES / __ / ! NO / __ / Explain: _____

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

Investigation #1 !
 YES / __ / Explain _____ ! NO / __ / Explain _____
 !
 ! _____
 ! _____
 !
 Investigation #2 !
 YES / __ / Explain _____ ! NO / __ / Explain _____
 !
 ! _____
 ! _____
 ! _____

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

YES /__/

NO /__/

If yes, explain: _____

 /S/ 11-20-98
Signature Date
Title: CSO

APPEARS THIS WAY
ON ORIGINAL

 /S/ 11-23-98
Signature of Office/ Date
Division Director

cc: Original NDA

Division File

HFD-93 Mary Ann Holovac

APPEARS THIS WAY
ON ORIGINAL