CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:
17-521/S062, S063

Trade Name: Dextrose Injection in Plastic Container

Generic Name:

Sponsor: Baxter Healthcare Corporation

Approval Date: November 14, 2002

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

17-521/S062, S063

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APPLICATION NUMBER:
17-521/S062, S063

APPROVAL LETTER

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 17-521/S-062, S-063

Baxter Healthcare Corporation
Route 120 & Wilson Road
Round lake, IL 60073-0490

Attention: Marcia Marconi
Vice President, regulatory Affairs

Dear Ms. Marconi:

Please refer to your supplemental new drug applications dated January 26 and February 26, 2001, received January 29 and February 27, 2001, respectively, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Dextrose 10%, 20%, 30%, 40%, 50%, 60%, and 70% injection in plastic container.

Supplement S-062 is submitted to comply with the requirements of 21 CFR 201.323 regarding "Aluminum in Large and Small Volume Parenterals Used in Total Parenteral Nutrition." This supplement has been superseded by supplement S-063; therefore, it is being retained in our files.

Supplement S-063 is submitted in response to revisions of 21 CFR 201.57 and in accordance with the information provided in the Guidance for Industry on Content and Format for Geriatric labeling.

We have completed our review of supplement S-063, and it is approved, effective on the date of this letter.

The final printed labeling (FPL) must be identical to the submitted draft labeling dated February 26, 2001.

Please submit the FPL electronically according to the guidance for industry titled Providing Regulatory Submissions in Electronic Format – NDA. Alternatively, you may submit 20 paper 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 supplement NDA 17-521/S-063." Approval of this submission by FDA is not required before the labeling is used.

If a letter communicating important information about this drug product (i.e., a "Dear Health Care Professional" 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.

If you have any questions, call Ms. Lisa Marie Malandro, Regulatory Health Project Manager, at (301) 827-7410.

Sincerely,

{See appended electronic signature page}

Bob Rappaport, M.D.
Acting Director
Division of Anesthetic, Critical Care, and
Addiction Drug Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

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/s/

Bob Rappaport
11/14/02 04:49:59 PM

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:
17-521/S062, S063

LABELING

Baxter

10%, 20%, 30%, 40%, 50%, 60%, and 70% Dextrose Injection, USP

in Viaflex® Plastic Container

A Parenteral Nutrient

Description

Dextrose Injections, USP are sterile, nonpyrogenic, hypertonic solutions for fluid replenishment and caloric supply in single dose containers for intravenous administration after compounding. They contain no antimicrobial agents. Composition, osmolarity, pH, and caloric content are shown in Table 1.

The Viaflex® plastic container is fabricated from a specially formulated polyvinyl chloride (PL 146® Plastic). Exposure to temperatures above 25°C/77°F during transport and storage will lead to minor losses in moisture content. Higher temperatures lead to greater losses. It is unlikely that these minor losses will lead to clinically significant changes within the expiration period. The amount of water that can permeate from inside the container into the overwrap is insufficient to affect the solution significantly. Solutions in contact with the plastic container may leach out certain chemical components from the plastic in very small amounts; however, biological testing was supportive of the safety of the plastic container materials.

Clinical Pharmacology

Dextrose Injections, USP have value as a source of water and calories. They are capable of inducing diuresis depending on the clinical condition of the patient.

Indications and Usage

Dextrose Injections, USP are indicated as a caloric component in a parenteral nutrition regimen. They are used with an appropriate protein (nitrogen) source in the prevention of nitrogen loss or in the treatment of negative nitrogen balance in patients where: (1) the alimentary tract cannot or should not be used, (2) gastrointestinal absorption of protein is impaired, or (3) metabolic requirements for protein are substantially increased, as with extensive burns.

Contraindications

The infusion of hypertonic dextrose injections is contraindicated in patients having intracranial or intraspinal hemorrhage, in patients who are severely dehydrated, in patients who are anuric, and in patients in hepatic coma.

Solutions containing dextrose may be contraindicated in patients with known allergy to corn or corn products.

Warnings

Dilute before use to a concentration which will, when administered with an amino acid (nitrogen) source, result in an appropriate calorie to gram of nitrogen ratio and which has an osmolarity consistent with the route of administration.

Unless appropriately diluted, the infusion of hypertonic dextrose injection into a peripheral vein may result in vein irritation, vein damage, and thrombosis. Strongly hypertonic nutrient solutions should only be administered through an indwelling intravenous catheter with the tip located in a large central vein such as the superior vena cava.

In very low birth weight infants, excessive or rapid administration of dextrose injection may result in increased serum osmolality and possible intracerebral hemorrhage.

WARNING: This product contains aluminum that may be toxic. Aluminum may reach toxic levels with prolonged parenteral administration if kidney function is impaired. Premature neonates are particularly at risk because their kidneys are immature, and they require large amounts of calcium and phosphate solutions, which contain aluminum.

Research indicates that patients with impaired kidney function, including premature neonates, who receive parenteral levels of aluminum at greater than 4 to 5 µg/kg/day accumulate aluminum at levels associated with central nervous system and bone toxicity. Tissue loading may occur at even lower rates of administration.

Precautions

Administration of hypertonic dextrose and amino acid solutions via central venous catheter may be associated with complications which can be prevented or minimized by careful attention to all aspects of the procedure. This includes attention to solution preparation, administration and patient monitoring.

It is essential that a carefully prepared protocol, based upon current medical practice, be followed, preferably by an experienced team. The package insert of the protein (nitrogen) source should be consulted for dosage and all precautionary information.

Clinical evaluation and periodic laboratory determinations are necessary to monitor changes in fluid balance, electrolyte concentrations, and acid base balance during prolonged parenteral therapy or whenever the condition of the patient warrants such evaluation.

The administration of these solutions can cause fluid and/or solute overloading resulting in dilution of serum electrolyte concentrations, overhydration, congested states, or pulmonary edema. The risk of dilutive states is inversely proportional to the electrolyte concentration of the injections. The risk of solute overload causing congested states with peripheral pulmonary edema is directly proportional to the electrolyte concentrations of the injections.

Caution must be exercised in the administration of these injections to patients receiving corticosteroids or corticotropin.

These injections should be used with caution in patients with overt or subclinical diabetes mellitus.

Drug product contains no more than 25 µg/L of aluminum.

Carcinogenesis, mutagenesis, impairment of fertility. Studies with Dextrose Injection, USP have not been performed to evaluate carcinogenic potential, mutagenic potential, or effects on fertility.

Pregnancy: Teratogenic Effects
Pregnancy Category C. Animal reproduction studies have not been conducted with Dextrose Injections, USP. It is also not known whether Dextrose Injections, USP can cause fetal harm when administered to a pregnant woman or can affect reproduction capacity. Dextrose Injections, USP should be given to a pregnant woman only if clearly needed.

Nursing Mothers: Caution should be exercised when Dextrose Injection, USP is administered to a nursing woman.

Pediatric Use: Dextrose is safe and effective for the stated indications in pediatric patients (see **Indications and Usage**). As reported in the literature, the dosage selection and constant infusion rate of intravenous dextrose must be selected with caution in pediatric patients, particularly neonates and low birth weight infants, because of the increased risk of hyperglycemia/hypoglycemia. Frequent monitoring of serum glucose concentrations is required when dextrose is prescribed to pediatric patients, particularly neonates and low birth weight infants.

Geriatric Use: Clinical studies of Dextrose Injection, USP did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects. Other reported clinical experience has not identified differences in responses between the elderly and younger patients. In general, dose selection for an elderly patient should be cautious, usually starting at the low end of the dosing range, reflecting the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy.

Adverse Reactions

Too rapid infusion of a hypertonic dextrose solution may result in diuresis, hyperglycemia, glycosuria, and hyperosmolar coma. Continual clinical monitoring of the patient is necessary in order to identify and initiate measures for these clinical conditions.

Reactions which may occur because of the solution or the technique of administration include febrile response, infection at the site of injection, venous thrombosis or phlebitis extending from the site of injection, extravasation and hypervolemia.

If an adverse reaction does occur, discontinue the infusion, evaluate the patient, institute appropriate therapeutic countermeasures, and save the remainder of the fluid for examination if deemed necessary.

Dosage and Administration

Following suitable admixture of prescribed drugs, the dosage is usually dependent upon the age, weight and clinical condition of the patient as well as laboratory determinations. See directions accompanying drugs.

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

Do not administer unless solution is clear and seal is intact.

These admixed injections in Viaflex® plastic containers are intended for intravenous administration using sterile equipment.

Additives may be incompatible. Complete information is not available. Those additives known to be incompatible should not be used. Consult with pharmacist, if available. If, in the informed judgement of the physician, it is deemed advisable to introduce additives, use aseptic technique. Mix thoroughly when additives have been introduced. Do not store solutions containing additives.

How Supplied

See Table 1.

Exposure of pharmaceutical products to heat should be minimized. Avoid excessive heat. Protect from freezing. It is recommended the product be stored at room temperature (25°C/77°F).

Directions for use of Viaflex® plastic container

Warning: Do not use plastic containers in series connections. Such use could result in air embolism due to residual air being drawn from the primary container before administration of the fluid from the secondary container is completed.

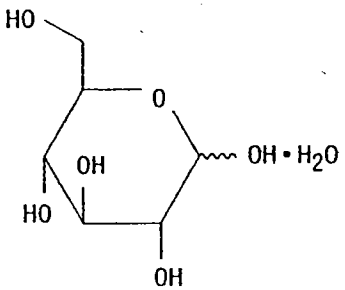
Preparation for Administration

1. Tear overwrap down side at slit and remove solution container. Some opacity of the plastic due to moisture absorption during the sterilization process may be observed. This is normal and does not affect the solution quality or safety. The opacity will diminish gradually. Check for minute leaks by squeezing inner bag firmly. If leaks are found, discard solution as sterility may be impaired.
2. Insert transfer set into prepared solution container to be transferred. Follow directions accompanying transfer set.
3. Remove protector from extended middle port of dextrose solution conta and insert connector of transfer set.
4. Transfer solution by gravity or by using a Viavac® unit.
5. After desired solution has been transferred, mix thoroughly and seal extension tubing of extended middle port. Cut between seal and connector of transfer set.
6. Check for leaks.
7. **Warning:** Additives may be incompatible. Supplemental medication ma be added with a 19 to 22 gauge needle through the medication injection on the dextrose solution container. Mix solution and medication thorou For high density medications, such as potassium chloride, squeeze port while ports are upright and mix thoroughly.
8. Suspend container from eyelet support.
9. Remove plastic protector from outlet port at bottom of container.
10. Attach administration set. Refer to complete directions accompanying s

Table 1

	Composition	Osmolarity (mOsmol/L) (calc.)	pH	Caloric Content (kcal/L)	How Supplied	
	Dextrose Hydrous, USP (g/L)				Size	
					500 mL in 1000 mL unit	1000 mL in 2000 mL unit
					Code and NDC	
10% Dextrose Injection, USP	100	505	4.0 (3.2 to 6.5)	340	2B0174 NDC 0338-0023-13	2B0176 NDC 0338-0023-34
20% Dextrose Injection, USP	200	1010	4.0 (3.2 to 6.5)	684	2B0124 NDC 0338-0711-13	2B0126 NDC 0338-0711-34
30% Dextrose Injection, USP	300	1510	4.0 (3.2 to 6.5)	1030	2B0134 NDC 0338-0713-13	2B0136 NDC 0338-0713-34
40% Dextrose Injection, USP	400	2020	4.0 (3.2 to 6.5)	1370	2B0154 NDC 0338-0715-13	2B0156 NDC 0338-0715-34
50% Dextrose Injection, USP	500	2520	4.0 (3.2 to 6.5)	1710	2B0264 NDC 0338-0031-13	2B0266 NDC 0338-0031-34
60% Dextrose Injection, USP	600	3030	4.0 (3.2 to 6.5)	2050	2B0104 NDC 0338-0717-13	
70% Dextrose Injection, USP	700	3530	4.0 (3.2 to 6.5)	2390	2B0114 NDC 0338-0719-13	

The structural formula of Dextrose Hydrous, USP is:



Dextrose Hydrous, USP
(D-Glucose monohydrate)

BAR CODE PLACEMENT

071917237

Baxter Healthcare Corporation
Clintec Nutrition Division
Deerfield, IL 60015 USA

Printed in USA

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07-19-17-237
Rev. February 2001

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:
17-521/S062, S063

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

Division of Anesthetics, Critical Care, and Addiction Drug Products

REGULATORY PROJECT MANAGER REVIEW

Application Number: NDA 17-521/S-062, S-063
Name of Drug: Dextrose 10%, 20%, 30%, 40%, 50%, 60%, 70% Injection in Plastic Container
Sponsor: Baxter Healthcare

Material Reviewed

Submission date(s): January 26, 2001 (S-062)
February 26, 2001 (S-063)
Receipt Date(s): January 29, 2001 (S-062)
February 27, 2001 (S-063)

Background and Summary description:
Supplement S-062 provides for a statement for the aluminum content in accordance with 21 CFR 201.323.

Supplement S-063 provides for a revised PRECAUTIONS section. A "Geriatric use" subsection is added in accordance with the requirements of 21 CFR 201.57(f)(10).

Status Report

Reviews Completed: Parinda Jani, CPMS, November 4, 2002.

Reviews Pending: None.

RPM REVIEW

Please note that a strikethrough indicates deletion and an underline indicates addition to the approved label.

HEADER: There wee no changed made to the header.

BOX WARNING: Not applicable.

DESCRIPTION: There were no changed made to this section.

CLINICAL PHARMACOLOGY: There were no changed made to this section.

INDICATION AND USAGE: There were no changed made to this section.

CONTRAINDICATIONS: The statement "Solutions containing dextrose may be contraindicated in patients with known allergy to corn or corn products." is relocated from WARNINGS section to this section.

WARNINGS: The following information is added as second paragraph.

"In very low birth weight infants, excessive or rapid administration of dextrose injection may result in increased serum osmolality and possible intracerebral hemorrhage.

The following information regarding aluminum toxicity is added.

"This product contains aluminum that may be toxic. Aluminum may reach toxic levels with prolonged parenteral administration if kidney function is impaired. Premature neonates are particularly at risk because their kidneys are immature, and they require large amounts of calcium and phosphorous solutions, which contain aluminum.

Research indicates that patients with impaired kidney function, including premature neonates, who receive parenteral levels of aluminum at greater than 4 to 5mcg/kg/day accumulate aluminum at levels associated with central nervous system and bone toxicity. Tissue loading may occur at even lower rates of administration."

PRECAUTIONS:

The following statement is revised.

The administration of these solutions can cause fluid and/or solute overloading resulting in dilution of serum electrolyte concentrations, overhydration, congested states, or pulmonary edema. The risk of dilutive states is inversely proportional to the electrolyte concentration of the injections. The risk of solute overload causing congested states with peripheral pulmonary edema is directly proportional to the electrolyte concentrations of the injections.

The following statement is added.

Drug product contains no more than 25 µg/L of aluminum.

The following "Geriatric use" subsection is provided in supplement S-063.

Clinical studies of Dextrose Injection, USP did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects. Other reported clinical experience has not identified differences in responses between the elderly and younger patients. In general, dose selection for an elderly patient should be cautious, usually starting at the low end of the dosing range, reflecting the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy.

ADVERSE REACTIONS: There are no changes made to this section.

DRUG ABUSE AND DEPENDENCE: Not Applicable.

OVERDOSAGE: There are no changes made to this section.

DOSAGE AND ADMINISTRATION: There were no changed made to this section.

HOW SUPPLIED: There were no changed made to this section.

RECOMMENDATIONS

The changes provided in supplement S-062 are incorporated in supplement S-063; therefore, S-062 should be acknowledged and retained in our files. Dr. McCormick's review of S-063 recommends approval of this supplement.

Parinda Jani, Chief, project Management Staff

Bob Rappaport, M.D.
Acting Division Director
Division of Anesthetics, Critical care, and Addiction Drug products

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/s/

Parinda Jani
11/12/02 02:42:59 PM
CSO

FDA CENTER FOR DRUG EVALUATION AND RESEARCH
DIVISION OF ANESTHETIC, CRITICAL CARE, AND ADDICTION DRUG PRODUCTS
HFD-170, Room 9B-45, 5600 Fishers Lane, Rockville MD 20857
Tel: (301) 827-7410

Division Director's Review and Basis for Action

DATE: August 19, 2001

FROM: Cynthia G. McCormick, MD, Director
Division of Anesthetic, Critical Care and Addiction Drug Products
Office of Drug Evaluation II, CDER, FDA

TO: File, NDA # 17-521 SLR-063

RE: Labeling Supplement for Geriatric Use

DRUG: Dextrose Injection, USP, 10%, 20%, 30%, 40%, 50%, 60% and 70%

SPONSOR; Baxter Healthcare Corporation

I have reviewed the supporting documentation for the addition of the Geriatric Use subsection of the labeling in accordance with 21 CFR §201.57(f)(10)(ii)(A). The proposed labeling reflects the lack of clinical data in patients >65 years of age on the use of Dextrose for injection to determine if their response differs from younger patients. Caution is indicated. This is accurate.

Action: Approval of SLR-063

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/s/

Cynthia McCormick
8/19/01 06:37:25 PM
MEDICAL OFFICER