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Review

First Choice for Total Parenteral Nutrition: The Peripheral Route

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ABSTRACT. Historically, total parenteral nutrition (TPN) has been administered by the central venous route because of the rapid development of thrombophlebitis when TPN solutions are administered into peripheral veins. The insertion and placement of central venous catheters is, however, associated with morbidity and mortality and is the main cause of TPN-related complications. By avoiding central venous catheterization, TPN can be made safer. Current awareness about the pathophysiology of peripheral vein thrombophlebitis and the use of a number of techniques that prevent or delay onset of peripheral vein thrombophlebitis mean it is now possible to administer TPN via the peripheral route. These techniques and changes in the practice of TPN in recent years (eg, reduction of caloric loads and use of lipid emulsions) mean peripheral parenteral nutrition is a technique that is now applicable to the majority of hospitalized, nutritionally compromised patients for whom intravenous feeding is anticipated for less than 10 to 14 days (*Journal of Parenteral and Enteral Nutrition* 17:468–478, 1993).

The adverse influences of malnutrition on the morbidity and mortality of patients is now well recognized. Great progress has been made in detecting, assessing, and correcting nutritional deficiencies in patients. For malnourished (or potentially malnourished) patients and those unable to take in adequate nutrients by the mouth, the safest and most physiologic means of delivering nutrients is via the enteral route. However, total parenteral nutrition (TPN) is accepted as the primary route of delivery for the patient with intestinal failure (eg, after massive small-bowel resection) or in whom enteral nutrition is contraindicated (eg, ileus or bowel obstruction).

TPN administration was pioneered by Dudrick et al,[1,2] who first reported the success of TPN in supporting growth and restoring weight loss. The use of hypertonic dextrose as the main energy source caused severe thrombophlebitis in peripheral veins within a few hours of intravenous (IV) administration. It is perhaps important to identify why the development of peripheral vein thrombophlebitis (PVT) necessitated the introduction of the central venous route for TPN administration.

Once PVT has developed, IV line failure will occur, which necessitates removal of the peripheral cannula and replacement in an alternative site. The patient may suffer pain. Persistent pain from an IV site is distressing for the hospitalized individual. Replacement of cannulas is stressful for the patient (who fears more pain) and also for the individual placing the cannula, who may believe that he or she is causing the patient more discomfort. Once a vein develops PVT, it ultimately occludes and extravasation of infusion solution or drugs into the perivenous tissues may take place, often retrogradely via the point of entrance of the cannula into the vein. This has two effects: reduction in the effective amount of drug or infusion solution delivered, and local bruising, swelling, and inflammation depending on the substance being infused. These events are what, in the early days of TPN, prevented routine peripheral IV delivery of hyperosmolar infusions and necessitated central venous access. The percutaneous method of subclavian vein cannulation was originally introduced by the French surgeon Aubaniac.[3]

Although use of the central venous route is standard practice for TPN administration throughout the world, it has a number of serious complications. Most of these are central venous catheter-related and may, in rare instances, be fatal. A complication rate of 5.7% (including arterial hemorrhage and pneumothoraces) for catheter placement has been observed.[4] The same review showed that "mechanical" (or late) catheter complications occurred with 9% of central venous catheters, and included inadvertent catheter removal and central venous thrombosis. The central venous catheter-associated sepsis rate was 6.5%. These figures are representative of complication rates quoted from other centers.[5,6] Thus, loss of peripheral venous access and the subsequent need for central venous catheterization may expose the patient to the risk of well-defined complications. Peripheral venous cannulation is not completely without septic complications. Peripheral vein cannulas may become colonized with bacteria, resulting in suppurative thrombophlebitis and septicemia.[8,10] Indeed, the presence of peripheral IV devices

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CHAPTER 36

Tonicity, Osmoticity, Osmolality and Osmolarity

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Basic Definitions

If a solution is placed in contact with a membrane that is permeable to molecules of the solvent, but not to molecules of the solute, the movement of solvent through the membrane is called osmosis. Such a membrane often is called *semipermeable*. As the several types of membranes of the body vary in their permeability, it is well to note that they are *selectively* permeable. Most normal living-cell membranes maintain various solute concentration gradients. A selectively permeable membrane may be defined either as one that does not permit free, unhampered diffusion of all the solutes present, or as one that maintains at least one solute concentration gradient across itself. Osmosis, then, is the diffusion of water through a membrane that maintains at least one solute concentration gradient across itself.

Assume Solution A is on one side of the membrane, and Solution B of the same solute but of a higher concentration is on the other side; the solvent will tend to pass into the more concentrated solution until equilibrium has been established. The pressure required to prevent this movement is the osmotic pressure. It is defined as the excess pressure, or pressure greater than that above the pure solvent, which must be applied to Solution B to prevent passage of solvent through a perfect semipermeable membrane from A to B. The concentration of a solution with respect to effect on osmotic pressure is related to the number of particles (unionized molecules, ions, macromolecules, aggregates) of solute(s) in solution and thus is affected by the degree of ionization or aggregation of the solute. See Chapter 16 for review of colligative properties of solutions.

Body fluids, including blood and lacrimal fluid, normally have an osmotic pressure which often is described as corresponding to that of a 0.9% solution of sodium chloride. The body also attempts to keep the osmotic pressure of the contents of the gastrointestinal tract at about this level, but there the normal range is much wider than that of most body fluids. The 0.9% sodium chloride solution is said to be *iso-osmotic* with physiological fluids. The term *isotonic*, meaning equal tone, is in medical usage commonly used interchangeably with isoosmotic. However, terms such as isotonic and tonicity should be used only with reference to a physiologic fluid. Isoosmotic actually is a physical term which compares the osmotic pressure (or another colligative property, such as freezing-point depression) of two liquids, neither of which may be a physiological fluid, or which may be a physiological fluid only under certain circumstances. For example, a solution of boric acid that is isoosmotic with both blood and lacrimal fluid is isotonic only with the lacrimal fluid. This solution causes hemolysis of red blood cells because molecules of boric acid pass freely through the erythrocyte membrane regardless of concentration. Thus, isotonicity infers a sense of physiological compatibility where isoosmoticity need not. As another example, a "chemically defined elemental diet" or enteral nutritional fluid can be iso-osmotic with the contents of the gastrointestinal tract, but would not be considered a physiological fluid, or suitable for parenteral use.

A solution is isotonic with a living cell if there is no net gain or loss of water by the cell, or other change in the cell when it is in contact with that solution. Physiological solutions with an osmotic pressure lower than that of body fluids, or of 0.9% sodium chloride solution, are referred to commonly as being *hypotonic*. Physiological solutions having a greater osmotic pressure are termed *hypertonic*.

Such qualitative terms are of limited value, and it has become necessary to state osmotic properties in quantitative terms. To do so, a term must be used that will represent all the particles which may be present in a given system. The term used is *osmol*. An osmol is defined as the weight, in grams, of a solute, existing in a solution as molecules (and/or ions, macromolecules, aggregates, etc), which is osmotically equivalent to a mole of an ideally behaving nonelectrolyte. Thus, the osmol-weight of a nonelectrolyte, in a dilute solution, generally is equal to its gram-molecular-weight. A milliosmol, abbreviated mOsm, is the weight stated in milligrams.

If one extrapolates this concept of relating an osmol and a mole of a nonelectrolyte as being equivalent, then one also may define an osmol in the following ways. It is the amount of solute which will provide one Avogadro's number (6.02×10^{23}) of particles in solution and it is the amount of solute which, on dissolution in 1 kg of water, will result in an osmotic pressure increase of 17,000 torr at 0° or 19,300 torr at 37°. One mOsmol is one-thousandth of an osmol. For example, 1 mole of anhydrous dextrose is equal to 180 g. One osmol of this nonelectrolyte is also 180 g. One mOsmol would be 180 mg. Thus 180 mg of this solute dissolved in 1 kg of water will produce an increase in osmotic pressure of 19.3 torr at body temperature.

For a solution of an electrolyte such as sodium chloride, one molecule of sodium chloride represents one sodium and one chloride ion. Hence, one mol will represent 2 osmols of sodium chloride theoretically. Accordingly, 1 osmol NaCl = 58.5 g/2 or 29.25 g. This quantity represents the sum total of 6.02×10^{23} ions as the total number of particles. Ideal solutions infer very dilute solutions or infinite dilution. However, as the concentration is increased, other factors enter. With strong electrolytes, interionic attraction causes a decrease in their effect on colligative properties. In addition, and in opposition, for all solutes, including nonelectrolytes, solvation and possibly other factors operate to intensify their colligative effect. Therefore, it is very difficult and often impossible to predict accurately the osmoticity of a solution. It may be possible to do so for a dilute solution of a single, pure and well-characterized solute, but not for most parenteral and enteral medicinal and/or nutritional fluids; experimental determination likely is required.

Attachment 7

Dextrose Pediatric Labeling Support Information

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DEPARTMENT OF HEALTH & HUMAN SERVICES

ANDA 16-673/S-122 (5%)
16-694/S-098 (10%)
20-179/S-003 (5%)

MAR 30 1999

Baxter Healthcare Corporation
Attn: Marcia Marconi
Route 120 and Wilson Road
Round Lake, IL 60073

Dear Madam:

This is in reference to your supplemental new drug applications dated June 7, 1996, submitted pursuant to 21 CFR 314.70 regarding your abbreviated new drug applications for Dextrose Injection.

The supplemental applications provide for response to the Final Rule published in the Code of the Federal Register on December 13, 1994 titled Specific Requirements on Content and Format of Labeling for Human Prescription Drugs; Revision of "Pediatric use" Subsection in the Labeling.

We have completed the review of these supplemental applications and they are approvable. However, before the supplemental applications may be approved, it is necessary that you revise your package insert as follows and submit 12 copies of final printed insert labeling:

1. PRECAUTIONS - Pediatric Use

   a. Beginning with the second sentence of paragraph one of this subsection, revise to read as follows:

      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.

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2. WARNINGS

a. Include the following:

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

The changes provided for in these supplemental applications may not be initiated until you have been notified in writing that the supplemental applications are approved.

Sincerely yours,

/S/

Robert L. West, M.S., R.Ph.
Director
Division of Labeling and Program Support
Office of Generic Drugs
Center for Drug Evaluation and Research

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WITHHOLD 2 PAGE (S)

Draft

Labeling

I. Format and Content

A. Labeling

1. Draft revised labeling

Attachment 1 to this correspondence contains draft revised labeling. This labeling reflects incorporation of new commentary in the Pediatric subsection of the Precautions section regarding considerations for use in the neonate and infant portions of the pediatric population. Additionally, we have made minor editorial changes (i.e., moving chemistry information previously appearing in the How Supplied section to the Description section).

2. Marked-up, annotated copy of current labeling

Attachment 2 contains a mark-up copy of the current labeling, clearly showing all deletions and additions, with annotations of where the supporting data are located in the submission. The annotation for the inclusion of the pediatric precaution statement identifies the reference literature article numbers and location in the correspondence.

B. Regulatory basis for labeling change

We are revising the labeling for these products in accordance with 21 CFR §201.57(f)(9)(iii). Our search of the medical literature found articles where dextrose was used as indicated by the current labeling, in adequate and well controlled studies, and in the pediatric population, with results indicating there are specific statements that can be made regarding use of these products in the pediatric population.

21 CFR 201.57(f)(9)(ii) does not apply since our search of the medical literature does not provide any information supporting an indication for the pediatric population different from those approved for the adult population.

21 CFR 201.57(f)(9)(iv), (v) and (vi) do not apply. Dextrose solutions have been in clinical use for many years. In fact, these products have been used in the adult population for over 60 years. As is the case with use of these products in the adult population, the efficacy of dextrose solutions in the pediatric population has been established through extensive clinical use.

21 CFR 201.57(f)(9)(vii) does not apply as we have selected sub-paragraph (iii) as the basis for our proposed labeling change.

21 CFR 201.57(f)(9)(viii) does not apply as the product does not contain one or more inactive ingredients that present an increased risk of toxic effect.

C. 21 CFR 201.57(f)(9)(iv) as regulatory basis for labeling change

Not Applicable.

D. The age categories for which pediatric data are being submitted.

The literature articles submitted with this correspondence pertain to the age categories of neonates, infants and children. The proposed labeling statement is specific to the neonate and infant populations.

E. Identification of data submitted for each age category.

Table 1

Safety/Adverse Reaction from Clinical Studies

Type of Data	Neonate (Birth up to 1 month)	Infant (1 month up to 2 years	Children (2 years up to 12 years)	Adolescent (12 years up to 16 years)
Pharmacokinetic/Pharmacodynamic				
- Raw Data				
- Literature				
Clinical Efficacy				
- Raw Data				
- Literature				
Safety/Adverse Reaction From Clinical Studies				
- Raw Data				
- Literature	√	√	√	
From Anecdotal Reports				
- Medwatch/3500's				
- Literature				
- Literature Reference/ Raw Data				

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F. Summary of information submitted to support the pediatric labeling statements

Development of the proposed labeling statement is the result of an evaluation process of existing clinical literature that involves the use of this product in pediatric patients.

A total of 109 articles were found from the literature searches. The method of search is described in the section titled Presentation of Data below. Eighty-one articles were evaluated for content and placed into an information database created by an outside consulting firm, [redacted] A bibliography of these articles is provided in Attachment 3. Twenty-eight studies were not evaluated because they only examined adult patients or were review articles.

The data base was reviewed by Medical Affairs and Regulatory Affairs for:

1. Interactions and Warnings Concerning Administration of Dextrose
2. Serious Adverse Reactions
3. Nonserious Adverse Reactions
4. Labeled Dosage and Administration Instructions Relative to Studies with Serious and Nonserious Adverse Reactions

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All articles with such information were thoroughly reviewed for information that might affect the product labeling. The following is a summary of each article meeting the criteria described above. The study # is a Baxter assigned identification number specific to the article and can be cross-referenced to the bibliography in Attachment 3. Actual copies of literature articles reviewed below are in Attachment 4.

1. Evaluation of Studies Identifying an Interaction and Warning Concerning the Administration of Dextrose:

Study # 40--Studied Jamaican term infants, randomized controlled study, n=101 controls, 87 dextrose/water group, 90 in oxytocin group. The authors concluded that "jaundice occurs more frequently in neonates born following oxytocin infusion during labor (60%) as compared to control neonates (8%), but no more when compared to neonates born following maternal dextrose/water infusion". Their data suggested that "the increased incidence of jaundice is probably causatively linked to transplacental hyponatremia caused by maternal oxytocin and dextrose or water infusion during labor." The percent dextrose was not identified in the study.

Study #18--The authors suggested that "the administration of 5% glucose with oxytocin significantly aggravated the tendency of plasma levels to decline, as demonstrated by the statistically significant drop in the postpartum sodium levels relative to the corresponding antepartum values in this group". The authors concluded that "the use of 5% glucose as a vehicle for oxytocin administration to parturient Nigerian women predisposes to the development of maternal and neonatal hyponatremia, especially when large volumes of fluid are used. The use of normal saline as an alternative to 5% glucose can prevent this problem and such a practice should be encouraged." There was also a significant correlation between the sodium levels in maternal postpartum and cord plasma samples, suggesting that these changes were transmitted to the fetus transplacentally.

According to the label copy for oxytocin, the drug should be diluted with 0.9% Normal Saline, Lactated Ringer's, or a nonhydrating solution. These studies appear to be an off-label use and therefore would not apply to labeling of dextrose products.

2. **Evaluation of Studies Identifying a Serious Adverse Drug Reaction:**

Congenital Metabolic Anomaly

Study #60--One patient case study, full term infant with an enlarged firm liver admitted to a regional hospital one hour after birth, 5% glucose given twice and formula started q 3 hours; 26 hours after birth respiratory depression and extreme metabolic acidosis occurred, 10% Dextrose infusion started; generalized edema, petechiae, apathy, Kussmaul respiration, and muscular hypotonia. Deep tendon, grasping, and sucking reflexes were absent. Chest x-rays revealed cardiomegaly and normal lungs. Bacteriological examination of blood and cerebrospinal fluid were normal. The patient's condition deteriorated, and he died 2 hours later after cardiac arrest. Necropsy was not allowed. The authors surmised "the extreme exacerbation of lactic acidemia was most probably caused by the parenteral administration of 10% glucose and suggested that in nonhypoxemic and normoglycemic patients with nonrenal severe metabolic acidosis, parenteral carbohydrate should not be given until the organic acid produced is analyzed by gas chromatography." A diagnosis was not confirmed in the body of the article, prenatal history was not discussed, and no reason given for the enlarged liver at birth.

Consequence of Prematurity-not attributed to Dextrose

Study #50--The study compared efficacy of glucose alone and glucose plus amino acids in premature neonates unable to receive oral feedings for 5 or more days. Eleven neonates presented with respiratory distress syndrome and 3 neonates developed necrotizing enterocolitis. "The results of the study indicated that infusions of amino acids along with glucose can reverse the negative nitrogen balance seen with conventional management of delivering glucose alone, and that his technique does not carry major biochemical risks." In a graph summary of study groups, it was noted one infant died with intraventricular hemorrhage at 12 days. The authors did not relate the hemorrhage to the glucose infusion and was not discussed in the body of the article.

Accidental Overdose of Dextrose

Study #67--A 6 1/2 year old child sustained irreversible, severe brain damage secondary to acute serum hyperosmolarity resulting from the inadvertent IV administration of 380 mL of a 50% glucose solution. Five weeks after admission, the child remained unresponsive except to painful stimuli and had severe spasticity with decorticate posturing.

Study #14--Case report, one 6-year-old child with Down's syndrome who developed hyperosmolar hyperglycemic non-ketotic coma following the infusion of 50% dextrose inexplicably administered during general anesthesia for a surgical procedure for cryptorchidism. Child recovered and was discharged.

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Consequences of Severe Prematurity

Study #11--Retrospective review of case records of all 27 week infants or less who survived for more than 24 hours over a 3 year period; infants were started on glucose infusions of 5 mg/kg/min (0.3g/kg/hr). Of the 99 infants, 12 infants were treated with a hypertonic dextrose/insulin infusions(varied concentrations) when serum potassium concentration reached 7.4 mmol/l. Two infants died as a result of hyperkalemia related complications. This was an off-label use of insulin infused by the intravenous route with the dextrose.

3. Evaluation of Studies Identifying Nonserious Adverse Drug Reactions:

Hyperglycemia

Study #38--1975-1981 examined 1157 newborns to evaluate the rates and risk factors associated with the administration of 10% dextrose during the first week of life and the development of hyperglycemia. Sixty-four (5.5%) had hyperglycemia documented during or one day following dextrose infusion, 24 of these incidents were not attributed to dextrose infusions by ward personnel. The authors identified three independent risk factors for hyperglycemia in this study: decreasing body weight, increasing dextrose dosage, and measure of the severity of illness. As a result of this study the authors believed that the risk of hyperglycemia is greatest in infants with very low birth weights, although hyperglycemia may occur in larger babies when other risk factors are present.

Hyperbilirubinemia

Study #40--278 (term) deliveries were studied prospectively to determine the association between the use of oxytocin during labor and the incidence of neonatal jaundice. "Jaundice was seen significantly more often in neonates following maternal infusion of oxytocin in dextrose water or dextrose water alone as compared to those whose mother did not receive either". The authors concluded that "increased jaundice is probably causatively linked to transplacental hyponatremia caused by maternal oxytocin and dextrose or water infusion during labor." As indicated in #1. Interactions and Warnings, label copy recommends diluting oxytocin with a nonhydrating solution.

Hyperglycemia and Glucosuria

Study #51--Tolerance of glucose was studied in 35 low birth weight infants. infants given a graded dose of glucose at 8.1, 11.2, or 14 mg/kg/min. In group 1 (8.1 mg/kg/min) there was no significant increase in plasma glucose concentrations. In groups 2 and 3 (11.2 and 14 mg/kg/min) the plasma glucose concentrations increased significantly over baseline values. Of the infants receiving 11.2 mg/kg/min, 8 of the 16 became hyperglycemic and 7 evidenced glucosuria. All infants receiving 14 developed hyperglycemia and glucosuria. The authors concluded that glucose infusion of 8.1 mg/kg/min is

suitable for clinically stable infants and does not pose a risk for hyperglycemia or glucosuria. The dose of 11.2 mg/kg/min was less predictable and 14 mg/kg/min was too large a dose for these infants, irrespective of prior clinical condition or postnatal age and the data demonstrate a lack of correlation between the presence of hyperglycemia and glucosuria and postnatal age. The authors recommended providing glucose as a substrate at the lowest possible concentration for the shortest period of time.

Study #48--Examined the degree of glucose tolerance and the renal handling of glucose, solute, and water during IV glucose infusions in low birthweight infants. At similar glucose infusion rates of 10 mg/kg/min or greater, 12 of 20 infants of lower gestational ages had higher plasma glucose concentrations and developed glucosuria while the remaining eight of 20 infant of higher gestational age did not. The authors concluded that "exogenous glucose infusions in low birthweight infants resulted in a greater degree of hyperglycemia in the less mature infants and produced significant changes in the renal handling of glucose and sodium associated with significant, although slight, increments in solute excretion".

Hypoglycemia

Study #80--Assessed the influence of pre-and perioperative infusion with and without glucose on pre- and postoperative blood glucose concentrations in neonates undergoing surgery during the first week of life. Thirty neonates with major congenital defects were divided into 4 groups: (1) had IV glucose before and Ringer's-acetate during anesthesia, (2) had no preoperative fluid and Ringer's-acetate during anesthesia, (3) had IV glucose before and IV glucose plus Ringer's-acetate during anesthesia and (4) had no preoperative fluid and IV glucose plus Ringer's-acetate during anesthesia. 3/10 infants experienced hypoglycemia occurring in the early phase of anesthesia when a preoperative infusion of glucose was changed to one of Ringer's-acetate; 1/11 infants experienced hypoglycemia occurring during preoperative infusion of glucose. The authors concluded that a certain proportion of neonates are at risk of hyperglycemia during surgery. Monitoring blood glucose and continuous adjustment of glucose supply appear to be necessary in order to avoid extensive fluctuations in blood concentrations of glucose.

Study #8--Described the contribution of fat mobilization and gluconeogenesis to energy homeostasis before, during, and after surgery in neonates with or without perioperative glucose infusions. One sixth of infants who received glucose preoperatively and Lactated Ringer's intraoperatively experienced hypoglycemia. The authors concluded that the starved neonates adapted to and could cope with a glucose-free preoperative fluid therapy and that the neonates given perioperative glucose could handle the amount of glucose given in this study.

Hyperglycemia/hypoglycemia

Study #52--12 premature infants (30-37 weeks gestational age) and 12 malnourished premature infants. Six premature and 6 malnourished premature infants received 5% glucose infusion and 6 premature and 6 malnourished premature infants receive 10% glucose infusion. Although the glucose infusion rate was not higher than 6 mg/kg/min, hyperglycemia occurred during glucose infusions in both of the treated groups; hypoglycemia was observed in the group receiving 5% glucose infusion, there were no cases with hypoglycemia in the 10% glucose infusion group; of the 4 infant groups, the mean blood sugar levels in the premature infants who received 5% glucose infusion revealed fewer fluctuations than the other three groups. Most fluctuations in the blood sugar levels were observed in the malnourished premature infants who received 10% glucose infusion. It seems that 5% glucose infusion was more appropriate for premature infants during the first few days of life. During the first few days of life a careful monitoring of blood sugar levels is necessary for not only the occurrence of hypoglycemia but also for the occurrence of hyperglycemia during glucose infusion.

Study #49--Evaluated the efficacy of treating symptomatic and asymptomatic hypoglycemic infants with a glucose minibolus of 200 mg/kg D10W followed immediately with continuous glucose infusion of 8 mg/kg/min in 23 premature infants. The minibolus led to correction of hypoglycemia within one minute in all infants and to hyperglycemia (150 mg/dl) at one minute in only one infant. The glucose level in this infant dropped to the euglycemic range 4 minutes later. The authors concluded that the minibolus is useful whenever correction of hypoglycemia is necessary; a minibolus and continuous infusion satisfies the requirement for ideal therapy--rapid correction of hypoglycemia without development of hyperglycemia. The authors still recommended close monitoring of blood glucose levels until stable.

Not Identified as Related to Glucose Infusion

Ketonuria

Study #24--Evaluated the effect of surgical stress on gluco-regulatory response to IV glucose and on insulin sensitivity at the receptor level in children. Twenty children received a continuous glucose infusion at 6.6 mg/kg/min during anesthesia, and then glucose 3.3 mg/kg/min thereafter until the next morning. 8 of 20 children had positive Ketostix. Blood glucose and plasma immunoreactive insulin, C-peptide, pancreatic glucagon, and enteroglucagon concentrations were not significantly different pre and post operatively when comparing children with and without ketonuria. The authors concluded that parenteral glucose administration is safe in young individuals during surgery, since physiological changes in the release of pancreatic hormones aim at maintaining normoglycemia.

Mechanical Ventilation

Study #50--The results of the study indicated that infusions of amino acids along with glucose can reverse the negative nitrogen balance seen with conventional management of delivering glucose alone, and that this technique does not carry major biochemical risks. In a graph summary of study groups two infants from each group--glucose only and glucose with amino acids required mechanical ventilation. The requirement of mechanical ventilation was not attributed to the glucose infusion and was not identified in the body of the article.

Anaphylactic Reaction--Insulin Dependent Diabetic

#47--An eight year old girl with a 7 year history of extrinsic asthma, allergic rhinitis and eczema and a 4 year history of diabetes had been treated until the age of 6 years for hypoglycemic episodes with IM administrations of glucagon, but for the last two years was treated with 50% Dextrose. On the 4 occasions when dextrose had been administered, the patient developed rhinorrhea, perinasal and periorbital edema as well as asthma within 2-3 minutes after the IV administration of 50% solution of dextrose. Investigations suggested that the dextrose, rather than any additives were responsible for the reaction. The authors suggested that the treatment of hypoglycemia with a 50% solution of dextrose is associated with a significant risk factor in those diabetic individuals who are either allergic or are receiving beta-adrenoreceptor blocking drugs. This precaution is covered in the package insert.

4. **Evaluation of Studies Identifying Serious and Nonserious Adverse Reactions in Relation to Dosage and Administration of Dextrose**

Study # 8--10% glucose/Ringer's acetate 20 mL/kg/hr first hour, 10 mL/kg/hr after first hour; control Ringer's acetate same schedule; IV active group--3 hours preoperatively glucose, during and 8 hours after surgery. One sixth of infants who received glucose preoperatively and Lactated Ringer's intraoperatively experienced hypoglycemia.

Study # 11--Glucose intake 5 mg/kg/min for 6-12 hours, two infants died as a result of hyperkalemia related complications and some infants had also been treated with a hypertonic dextrose/insulin infusion.

Study #14--Accidental overdose of 50% glucose administered intravenously.

Study #24--Glucose 6.6 mg/kg/min during anesthesia and 3.3 mg/kg/min thereafter until the next morning, continuous IV; 8/20 children had positive Ketostix.

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Study #38--10% dextrose x 1 week--< 5 mg/kg/min; 5-8.3 mg/kg/min; 121 mL/kg/day 5.5% (64) of 1157 newborns experienced hyperglycemia during or one day following dextrose infusions, 24 of the events were not attributed to the dextrose infusion by ward personnel.

Study #40--Off-label use of oxytocin diluted with dextrose--effect of jaundice in term infants.

Study #47--Anaphylactic reaction to 50% IV Dextrose in 10-50 mL dosages.

Study #48--The continuous glucose infusions were increased by graduated doses in each infant from 10-12 to 14 to 16 mg/kg/min over a six hour period. 12/ 20 infants experienced glucosuria and hyperglycemia .

Study #49--23 infants received 10% glucose in water as a bolus of one minute, 200 mg/kg; followed by a continuous infusion of 8 mg/kg/min (no % given). 4/9 AGA infants experienced hyperglycemia; 1/8 SGA infants experienced hypoglycemia; and 1 SGA infant experienced a drop in glucose to 24 mg/dl at 30 minutes and recovered by 40 and 60 minutes.

Study #50--14 infant received continuous infusion by Holter pump of glucose at 15.8g/kg/day plus water, electrolytes, and minerals x 5 days. Two infants required mechanical ventilation and one infant died of an intraventricular hemorrhage--the glucose infusion was not cited as the cause of this deterioration.

Study #51--35 infants received continuous infusions of either 8.1 mg/kg/min or 11.2 mg/kg/min or 14 mg/kg/min over a 3 hour period. Supports 8.1 mg/kg/min as a safe and adequate dose and 11.2 mg/kg/min is less predictable.

Study #52--24 infants received either 5% glucose solution at 3 mg/kg/min and 10% glucose solution at 6 mg/kg/min. 11/12 infants who received 10% glucose experienced hyperglycemia; 8/12 infants who received 5% glucose experienced hyperglycemia; and 3/12 infants who received 5% glucose experienced hypoglycemia.

Study #60--Infant diagnosed with lactic acidemia--no cause identified. Glucose feeding was started 3 hours after birth, 5% glucose was given twice, and subsequently formula every 3 hours.

Study #67--Accidental overdose of 50% glucose administered intravenously.

Study #80--Ringer's acetate with 10% glucose to give glucose 0.25-0.30 g/kg/hr; 15-20 mL/kg(-1) during 1st hour followed by 10 mL/kg/hr pre and post op IV. 3/10 infants experienced hypoglycemia in the early phase of anesthesia when the glucose was changed to Ringer's acetate solution and 1/11 infants experienced hyperglycemia when receiving glucose perioperatively.

II. Presentation of Data

A. The source of the data.

Data supporting the proposed labeling revision was derived from literature articles pertaining to the use of this product in the Pediatric population. A bibliography of the reviewed articles is provided in Attachment 3. Actual copies of the reviewed articles are in Attachment 4.

The search strategy for articles regarding of this product in pediatric patients included ———————————— performing a literature search to locate published studies, case reports, and other documentation pertaining to the use of dextrose in the pediatric population. The search was conducted in July, 1995. MEDLINE was searched from 1966 to July 1995 and International Pharmaceutical Abstracts was searched from 1970 to July 1995. The starting dates for the searches are the earliest years the databases are available in electronic form. Earlier references would need to be searched in the hard/print copy or culled from the bibliographies of the later articles. The search strategies for each database are described below.

The format of the searches is that used for the ——— on-line service. When editing the results of these two searches, references of glucose administered in total parenteral nutrition (TPN) solutions or those discussing the effects of glucose on infants/fetuses administered to mothers were edited out.

MEDLINE
The word glucose was exploded and using the subheading for administration, dosage, infusions, parenteral, injections, intravenous or infusion pumps. The search statement was ended with the term child which included infant, child, and adolescence.

International Pharmaceutical Abstracts
Glucose or dextrose was searched in the descriptor fields along with infusion pumps, syringe pumps, infusion syringe, intravenous, infusion, iv, parenteral, inject, injection, or adminis. The search statement was ended with the term child, neonate, newborn, infant, pediatric, or adoles. These terms could be found anywhere in the title or abstract.

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A total of 109 articles were found from the literature searches. Eighty-one articles were evaluated. Twenty-eight studies were not evaluated because they only examined adult patients or were review articles.

Each of the 81 articles were analyzed and the information organized into a searchable database. Information was organized into categories that characterized each article based on study objective, study design, patient information, dosage and administration, interactions and warnings, nonserious adverse drug reactions, and serious adverse drug reactions. Organization of literature information was performed by an outside consulting firm, ———

The information database was reviewed for identification of articles that have citation to either interactions, warnings, serious or nonserious adverse events, and any dosage and administration instructions associated with the adverse events related to use in the pediatric population. Any article meeting this criteria was reviewed for development of the proposed labeling revisions.

Attachment 5 contains a copy of the information performed by ———

Copies of articles listed in the bibliography not provided in this supplement are available upon request.

B. Summary Table

A summary of the articles reviewed in support of the proposed labeling statement is in Table 2.

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Table 2

Types of Studies and Design Features

ID	Investigator	Publication	Purpose of Study	Date Study Published	Age of Subjects	Number of Patients	Formulation/ IV Dosage	Dosage and Administration	Duration
8	Sandstrom K, et al.	Acta-Anaesthesiol -Scand	Describe the contribution of fat mobilization and gluconeogenesis to energy homeostasis before, during, and after surgery in neonates with or without preoperative glucose infusions	1993	Neonates	14	10% Glucose/ Ringer's Acetate	Test Group: total intraoperative infusion rate 20 mL/kg/hr of 10% glucose/Ringer's acetate first hour, 10 mL/kg/hr of 10% glucose Ringer's acetate after 1st hour, Control Group: Ringer's acetate same schedule	Test Group: 3 hrs prop glucose, during and 8 hrs after surgery
11	Lui, K, et al	Acta-Paediatr	Retrospective study of preterm infants with serum potassium concentrations > 7.4 mmol/L and were treated with dextrose/insulin	1992	Neonates	117	12.5% glucose, 10% glucose, 5% glucose	'dry' group - 50, 60, 70, 80, 90 100, 120 mL/kg/day during the first week, 200 mL/kg/day afterwards; 'control' group- 80, 100, 120, 150 mL/kg/day first week, 200 mL/kg/day afterwards	6-12 hours (mean=6)
14	Maioli M, et al.	Diabetes-Res	Case report of nondiabetic 6-year old boy with Down's syndrome who developed hyperosmolar hyperglycemic, non-ketotic coma due to an infusion of hypertonic dextrose during anesthesia for surgery of cryptorchidism.	1991	Children	1	50% Dextrose	100cc/hour continuous infusion	9 days
18	Omigbodun AO, et al.	East-Afr-Med J	Investigate effects of saline or glucose as vehicle for admin. of oxytocin on sodium plasma concentrations in the mother and in the umbilical cord	1991	Intrauterine	140	5% glucose as vehicle for oxytocin	Glucose volume 710 +/- 640mL, saline, 695 +/- 489 mL	During Labor

Table 2 (continued)

ID	Investigator	Publication	Purpose of Study	Date of Study	Age of Subjects	Number of Patients	Formulation/ IV Dosage	Dosage and Administration	Duration
24	Ryhanen P, et al.	Anesthesiology	Evaluate the effect of surgical stress on gluco-regulatory response to IV glucose and on insulin sensitivity at the receptor level in children	1988	Children	20	Ringer's solution [28 mmol acetate per liter] and 5% dextrose during anesthesia/0.3 % saline and 5% dextrose thereafter until next morning	Glucose, 6.6mg/kg/min during anesthesia; glucose, 3.3mg/kg/min thereafter until next morning	during anesthesia to first postoperative morning
38	Louik C, et al.	Am J Dis Child	Two patients from neonatal intensive care units studied in order to evaluate the rates and risk factors associated with 10% dextrose and the development of hyperglycemia	1985	Neonates	1157	10% dextrose	<72 mL/kg/day (<3mg/kg/min); 73-120 mL/kg/day (3-8.3mg/kg/min); 121 mL/kg/day (84.mL/kg/min)	One Week
40	Singhi SC, et al.	West Indian Med J	Study deliveries prospectively to determine the association between the use of oxytocin during labor and the incidence of neonatal jaundice	1984	Intrauterine, Neonates	278	unknown	unknown	During Labor

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Table 2 (continued)

ID	Investigator	Publication	Purpose of Study	Date of Study	Age of Subjects	Number of Patients	Formulation/IV Dosage	Dosage and Administration	Duration
47	Czarny D, et al.	Med J Aust	Analyze anaphylactoid reaction to 50% dextrose in an 8-year old girl with extrinsic asthma and insulin-dependent diabetes mellitus	1980	Children	1	50% dextrose in 10 mL to 50 mL concentrations	single dose	4 separate occasions
48	Stonestreet Bs, et al.	Pediatrics	Examine the degree of glucose tolerance and the renal handling of glucose, solute, and water during intravenous glucose infusions in low birth weight infants	1980	Neonates	20	Graduated doses in each infant from 10 to 12, to 14 and to 16 mg/kg/min	continuous	6 hours
49	Lilien LD, et al.	J-Pediatr	Study the efficacy of treating symptomatic and asymptomatic hypoglycemic infants with a glucose minibolus of 200 mg/kg, followed immediately by continuous glucose infusion of 8 mg/kg/minute.	1980	Neonates	23	10% glucose in water	bolus of one minute, 200 mg/kg; followed by continuous infusion 8 mg/kg/min (no glucose concentration given)	60 minutes
50	Anderson TL, et al.	J-Pediatr	Compare the efficacy of glucose alone and glucose plus amino acids in premature neonates unable to receive oral feedings for 5 or days	1979	Neonates	18	glucose(15.8.mg /kg/day) plus water, electrolytes, and minerals	continuous	5 days

Table 2 (continued)

ID	Investigator	Publication	Purpose of Study	Date of Study	Age of Subjects	Number of Patients	Formulation/ IV Dosage	Dosage and Administration	Duration
51	Cowett RM, et al.	Pediatrics	Evaluate glucose retention in healthy, low birth weight (mean=1216 g) neonates and infants following a graded increase of glucose infusion	1979	Neonates, Infants	35	Mean doses were: Group 1=8.1 mg/kg/min; Group 2a & 2b=11.2 mg/kg/min; Group 3=14 mg/kg/min	continuous infusion of 6 mL/kg/hr in Groups 1&2 and 7mL/kg/hr in Group 3	3 hours
52	Tuncer M	Turk J Pediatr	Study occurrence of hyperglycemia and hypoglycemia in premature and malnutrished infants during the first 48 hours of life	1978	Neonates	24	5% and 10% glucose solutions	5% glucose solution at 3mg/kg/min and 10% glucose solution at 6mg/kg/min. 80 mL/kg/24 hrs to 2 groups of infants	48 hours
60	Van Biervliet JP, et al.	Lancet	Use of parenteral glucose in a patient with severe lactic acidemia	1976	Neonates	1	5% glucose	twice 3 hrs after birth and subsequently a humanised-milk formula every 3 hr	Not Specified
67	Stanley CA and Baker L	J-Pediatr	Assessment of an accidental poisoning with 50% stock glucose solution	1974	Children	1	190 g glucose, or 380 mL 50% glucose solution	380 mL 50% glucose in one hour continuous	5 weeks
80	Larsson LE, et al.	British J Anaesthesia	Study the influence or pre- and perioperative infusion with and without glucose on pre- and postoperative blood glucose concentrations in neonates undergoing surgery during the first week of life	1990	Neonates	30	Ringer's acetate with 10% glucose to give glucose 0.25-0.30 g (14-17 mmol)/kg/hr	15-20 mL kg(-1) during 1st hour, followed by 10 mL/kg/hr	pre- and post-operative

C. Analysis of Data

See Section I.F.

D. Extent of exposure, duration of exposure, and adverse events.

See Table 2 for extent and duration of exposure. See Section I.F. for adverse events.

E. Description of formulation, route of administration, and acceptability for pediatric use.

See Table 2 for formulation and route of administration.

Dextrose solutions have been in clinical use for many years. In fact, these products have been used in the adult population for over 60 years. As is the case with use of these products in the adult population, the efficacy of dextrose solutions in the pediatric population has been established through extensive clinical use. The medical literature does not provide any information supporting an indication for the pediatric population different from those approved for the adult population.

F. The drug product does not contain any excipients that present an increased risk of toxic effect in the pediatric population.

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Attachment 1

Draft Revised Labeling

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Labeling

Attachment 2

Mark-Up Copy of Current Labeling

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Labeling

Attachment 3

Bibliography of Literature Articles

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Section J Original References and Study Reports

Study Identifier	Reference Citation
1	Sunehag A, Gustafsson J, et al. (1994). Very immature infants (< or = 30 Wk) respond to glucose infusion with incomplete suppression of glucose production. Pediatr-Res 36(4): 550-555
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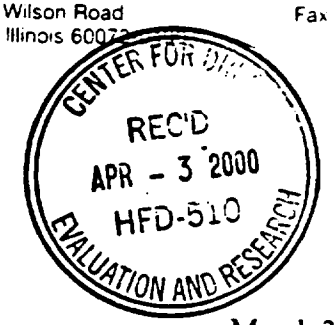

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March 31, 2000

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation II
Division of Metabolism and Endocrine Drug Products, HFD-510
Document Control Room 14B-19
5600 Fishers Lane
Rockville, MD 20857-1706

Re: NDA 19-520/S-018: Travasol® -sulfite-free (Amino Acid) in Dextrose Injection in Quick-Mix® Dual Chamber PL 146 Plastic Container

NDA 20-147/S-006: Travasol® -sulfite-free (Amino Acid) with Electrolytes in Dextrose Injection in Quick-Mix® Dual Chamber PL 146 Plastic Container

NDA 20-678/S-003: Clinimix E™ sulfite-free (Amino Acid with Electrolytes in Dextrose with Calcium) Injections in Clarity™ Dual Chamber Container

NDA 20-734/S-003: Clinimix E sulfite-free (Amino Acid in Dextrose) Injections

Minor Amendment - Pediatric Labeling Statements

Dear Colleague:

Baxter Healthcare Corporation is submitting this minor amendment to each of the above referenced pediatric labeling supplements in response to a request by the Agency for additional administrative requirements to complete the review package. The following four Attachments should provide sufficient information to complete the review of the Pediatric Labeling Supplements:

Attachment 1. Environment Assessment - Request for categorical exclusion.

Attachment 2. Patent Certification.

Attachment 3 Debarment Certification.

Attachment 4 Financial Disclosure – Justification for not certifying or disclosing financial information on investigators.

MAR 3 1 2000

Baxter

A completed 356h application form and a User Fee form are attached to this cover letter.

If you have any questions, please contact me or Lisa Skeens, PhD at (847) 270-2577.

Sincerely,

Marcia Marconi
Vice President, Regulatory Affairs
phone: (847) 270-4637
fax: (847) 270-4668

cc: Steve McCort

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MAR 3 1 2000

DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION

Form Approved: OMB No. 0910-0338
Expiration Date April 30, 2000
See OMB Statement on last page.

APPLICATION TO MARKET A NEW DRUG, BIOLOGIC, OR AN ANTIBIOTIC DRUG FOR HUMAN USE
(Title 21, Code of Federal Regulations, 314 & 601)

FOR FDA USE ONLY
APPLICATION NUMBER

APPLICANT INFORMATION

NAME OF APPLICANT
Baxter Healthcare Corporation

DATE OF SUBMISSION
March 31, 2000

TELEPHONE NUMBER *(Include Area Code)*
(847) 270-4637

FACSIMILE (FAX) Number *(Include Area Code)*
(847) 270-4668

APPLICANT ADDRESS *(Number, Street, City, State, Country, ZIP Code or Mail Code, and U.S. License Number if previously issued)*:
Route 120 and Wilson Road; RLT-10
Round Lake, IL 60073
Baxter Owner/Operator Number: 1417572

AUTHORIZED U.S. AGENT NAME & ADDRESS *(Number, Street, City, State, ZIP Code, telephone & FAX number)* IF APPLICABLE
N/A

PRODUCT DESCRIPTION

NEW DRUG OR ANTIBIOTIC APPLICATION NUMBER, OR BIOLOGICS LICENSE APPLICATION NUMBER (If previously issued) **NDA 20-678**

ESTABLISHED NAME (e.g., Proper name, USP/USAN name)
N/A

PROPRIETARY NAME (trade name) IF ANY
Clinimix E™ sulfite-free (Amino Acid with Electrolytes in Dextrose with Calcium) Injections in Clarity™ Dual Chamber Container

CHEMICAL/BIOCHEMICAL/BLOOD PRODUCT NAME (If any)
Amino Acids, Electrolytes, Dextrose Hydrous, USP

CODE NAME (If any)
N/A

DOSAGE FORM
Injection

STRENGTHS:
2.75% and 4.25% Amino Acids
5% and 10% Dextrose

ROUTE OF ADMINISTRATION:
Intravenous

(PROPOSED) INDICATION(S) FOR USE:
As a caloric component in a parenteral nutrition regimen and as a protein source for offsetting nitrogen loss

APPLICATION INFORMATION

APPLICATION TYPE
(check one) ☑ NEW DRUG APPLICATION (21 CFR 314.50) ☐ ABBREVIATED APPLICATION (ANDA, AADA, 21 CFR 314.94)
☐ BIOLOGICS LICENSE APPLICATION (21 CFR part 601)

IF AN NDA, IDENTIFY THE APPROPRIATE TYPE ☐ 505 (b) (1) ☑ 505 (b) (2) ☐ 507

IF AN ANDA, OR AADA, IDENTIFY THE REFERENCE LISTED DRUG PRODUCT THAT IS THE BASIS FOR THE SUBMISSION
Name of Drug Holder of Approved Application

TYPE OF SUBMISSION
(check one) ☐ ORIGINAL APPLICATION ☐ AMENDMENT TO A PENDING APPLICATION ☐ RESUBMISSION
☐ PRESUBMISSION ☐ ANNUAL REPORT ☐ ESTABLISHMENT DESCRIPTION SUPPLEMENT ☐ SUPAC SUPPLEMENT
☐ EFFICACY SUPPLEMENT ☑ LABELING SUPPLEMENT ☐ CHEMISTRY MANUFACTURING AND CONTROLS SUPPLEMENT ☐ OTHER

REASON FOR SUBMISSION
Pediatric Labeling Supplement

PROPOSED MARKETING STATUS (check one) ☑ PRESCRIPTION PRODUCT (Rx) ☐ OVER THE COUNTER PRODUCT (OTC)

NUMBER OF VOLUMES SUBMITTED 1 THIS APPLICATION IS ☑ PAPER ☐ PAPER AND ELECTRONIC ☐ ELECTRONIC

ESTABLISHMENT INFORMATION

Provide locations of all manufacturing, packaging and control sites for drug substance and drug product (continuation sheets may be used if necessary). Include name, address, contact, telephone number, registration number (CFN), DMF number, and manufacturing steps and/or type of testing (e.g. Final dosage form, Stability testing) conducted at the site. Please indicate whether the site is ready for inspection or, if not, when it will be ready.

LABELING SUPPLEMENT - **Not applicable**

Cross References (list related License Applications, INDs, NDAs, PMAs, 510(k)s, IDEs, BMFs, and DMFs referenced in the current application)

LABELING SUPPLEMENT - **Not applicable**

MAR 31 2000

This application contains the following items: *(Check all that apply)*	
	1. Index
X	2. Labeling (check one) ☑ Draft Labeling ☐ Final Printed Labeling
	3. Summary (21 CFR 314.50 (c))
	4. Chemistry section
	A. Chemistry, manufacturing, and controls information (e.g. 21 CFR 314.50 (d) (1), 21 CFR 601.2)
	B. Samples (21 CFR 314.50 (e) (1), 21 CFR 601.2 (a)) (Submit only upon FDA's request)
	C. Methods Validation Package (e.g. 21 CFR 314.50 (e) (2) (i), 21 CFR 601.2)
	5. Nonclinical pharmacology and toxicology section (e.g. 21 CFR 314.50 (d) (2), 21 CFR 601.2)
	6. Human pharmacokinetics and bioavailability section (e.g. 21 CFR 314.50 (d) (3), 21 CFR 601.2)
	7. Clinical Microbiology (e.g. 21 CFR 314.50 (d) (4))
	8. Clinical data section (e.g. 21 CFR 314.50 (d) (5), 21 CFR 601.2)
	9. Safety update report (e.g. 21 CFR 314.50 (d) (5) (vi) (b), 21 CFR 601.2)
	10. Statistical section (e.g. 21 CFR 314.50 (d) (6), 21 CFR 601.2)
	11. Case report tabulations (e.g. 21 CFR 314.50 (f) (1), 21 CFR 601.2)
	12. Case reports forms (e.g. 21 CFR 314.50 (f) (2), 21 CFR 601.2)
	13. Patent information on any patent which claims the drug (21 U.S.C. 355 (b) or (c)
	14. A patent certification with respect to any patent which claims the drug (21 U.S.C. 355 (b) (2) or (j) (2) (A))
	15. Establishment description (21 CFR Part 600, if applicable)
	16. Debarment certification (FD&C Act 306 (k) (1))
	17. Field copy certification (21 CFR 314.5 (k) (3))
X	18. User Fee Cover Sheet (Form FDA 3397)
	19. OTHER (Specify)

CERTIFICATION

I agree to update this application with new safety information about the product that may reasonably affect the statement of contraindications, warnings, precautions, or adverse reactions in the draft labeling. I agree to submit safety update reports as provided for by regulation or as requested by the FDA. If this application is approved, I agree to comply with all applicable laws and regulations that apply to approved applications, including, but not limited to the following:

1. Good manufacturing practice regulations in 21 CFR 210 and 211, 606, and/or 820.
2. Biological establishment standards in 21 CFR Part 600.
3. Labeling regulations in 21 CFR 201, 606, 610, 660 and/or 809.
4. In the case of a prescription drug product or biological product, prescription drug advertising regulations in 21 CFR 202.
5. Regulations on making changes in application in 21 CFR 314.70, 314.71, 314.72, 314.97, 314.99, and 601.12.
6. Regulations on reports in 21 CFR 314.80, 314.81, 600.80, and 600.81.
7. Local, state and Federal environmental impact laws.

If this application applies to a drug product that FDA has proposed for scheduling under the Controlled Substances Act I agree not to market the product until the Drug Enforcement Administration makes a final scheduling decision.

The data and information in this submission have been reviewed and, to the best of my knowledge are certified to be true and accurate.

Warning: a willfully false statement is a criminal offense, U.S. Code, title 18, Section 1001.

SIGNATURE OF RESPONSIBLE OFFICIAL OR AGENT	TYPED NAME AND TITLE	DATE
P Rodriguez for Marcia Marconi	**Marcia Marconi, V.P. Regulatory Affairs I.V. Systems Division**	**March 31, 2000**

ADDRESS *(Street, City, State, Zip Code)*	TELEPHONE Number
Baxter Healthcare Corporation Route 120 and Wilson Road Round Lake, IL 60073	**(847) 270-4637**

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION

Form Approved: OMB No. 0910-0297
Expiration Date: 04-30-01

USER FEE COVER SHEET

See Instructions on Reverse Side Before Completing This Form

1. APPLICANT'S NAME AND ADDRESS

Marcia Marconi
Vice President, Regulatory Affairs
I.V. Systems Division
Baxter Healthcare Corporation
Route 120 and Wilson Road
Round Lake, IL 60073

2. TELEPHONE NUMBER *(Include Area Code)*
(847) 270-4637

3. PRODUCT NAME
Clinimix E sulfite-free (Amino Acid with Electrolytes in Dextrose with Calcium) Injections

4. DOES THIS APPLICATION REQUIRE CLINICAL DATA FOR APPROVAL? IF YOUR RESPONSE IS "NO" AND THIS IS FOR A SUPPLEMENT, STOP HERE AND SIGN THIS FORM.

IF RESPONSE IS 'YES', CHECK THE APPROPRIATE RESPONSE BELOW

☐ THE REQUIRED CLINICAL DATA ARE CONTAINED IN THE APPLICATION

☐ THE REQUIRED CLINICAL DATA ARE SUBMITTED BY REFERENCE TO (APPLICATION NO. CONTAINING THE DATA)

5. USER FEE I.D. NUMBER

6. LICENSE NUMBER / NDA NUMBER
20-678

7. IS THIS APPLICATION COVERED BY ANY OF THE FOLLOWING USER FEE EXCLUSIONS? IF SO, CHECK THE APPLICABLE EXCLUSION

☐ A LARGE VOLUME PARENTERAL DRUG PRODUCT APPROVED UNDER SECTION 505 OF THE FEDERAL FOOD, DRUG, AND COSMETIC ACT BEFORE 9/1/92 *(Self Explanatory)*

☐ A 505(b)(2) APPLICATION THAT DOES NOT REQUIRE A FEE *(See item 7, reverse side before checking box.)*

☐ THE APPLICATION QUALIFIES FOR THE ORPHAN EXCEPTION UNDER SECTION 736(a)(1)(E) of the Federal Food, Drug, and Cosmetic Act. *(See item 7, reverse side before checking box.)*

☒ THE APPLICATION IS A PEDIATRIC SUPPLEMENT THAT QUALIFIES FOR THE EXCEPTION UNDER SECTION 736(a)(1)(F) of the Federal Food, Drug, and Cosmetic Act *(See item 7, reverse side before checking box.)*

☐ THE APPLICATION IS SUBMITTED BY A STATE OR FEDERAL GOVERNMENT ENTITY FOR A DRUG THAT IS NOT DISTRIBUTED COMMERCIALLY *(Self Explanatory)*

FOR BIOLOGICAL PRODUCTS ONLY

☐ WHOLE BLOOD OR BLOOD COMPONENT FOR TRANSFUSION

☐ A CRUDE ALLERGENIC EXTRACT PRODUCT

☐ AN APPLICATION FOR A BIOLOGICAL PRODUCT FOR FURTHER MANUFACTURING USE ONLY

☐ AN "IN VITRO" DIAGNOSTIC BIOLOGICAL PRODUCT LICENSED UNDER SECTION 351 OF THE PHS ACT

☐ BOVINE BLOOD PRODUCT FOR TOPICAL APPLICATION LICENSED BEFORE 9/1/92

8. HAS A WAIVER OF AN APPLICATION FEE BEEN GRANTED FOR THIS APPLICATION? ☐ YES ☐ NO *(See reverse side if answered YES)*

A completed form must be signed and accompany each new drug or biologic product application and each new supplement. If payment is sent by U.S. mail or courier, please include a copy of this completed form with payment.

SIGNATURE OF AUTHORIZED COMPANY REPRESENTATIVE	TITLE	DATE
D Schuyler for Marcia Marconi	Vice President, Regulatory Affairs	3-31-2000

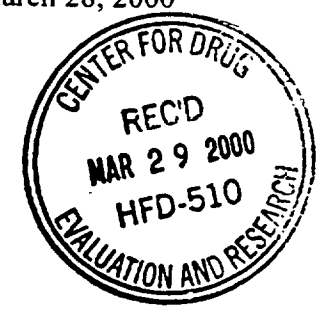
Regulatory Affairs

Route 120 & Wilson Road
Round Lake, Illinois 60073-0490

Fax: 847.270.4668

Baxter

March 28, 2000



Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation II
Division of Metabolism and Endocrine Drug Products, HFD-510
Document Control Room 14B-19
5600 Fishers Lane
Rockville, MD 20857-1706

Re: NDA 19-520/S-018: Travasol® -sulfite-free (Amino Acid) in Dextrose Injection in Quick-Mix® Dual Chamber PL 146 Plastic Container

NDA 20-147/S-006: Travasol® -sulfite-free (Amino Acid) with Electrolytes in Dextrose Injection in Quick-Mix® Dual Chamber PL 146 Plastic Container

NDA 20-678/S-003: Clinimix E™ sulfite-free (Amino Acid with Electrolytes in Dextrose with Calcium) Injections in Clarity™ Dual Chamber Container

NDA 20-734/S-003: Clinimix E sulfite-free (Amino Acid in Dextrose) Injections

Minor Amendment - Pediatric Labeling Statements

Dear Colleague:

Baxter Healthcare Corporation is submitting this minor amendment to each of the above referenced pediatric labeling supplements in response to a request by the Agency for minor modifications to the proposed labeling submitted in those supplements. A copy of the labeling submitted with the pediatric labeling supplement is provided in **Attachment 1**. Labeling revised in accordance with FDA's request in provided in **Attachment 2**.

A completed 356h application form and a User Fee form are attached to this cover letter.

APPEARS THIS WAY
ON ORIGINAL

MAR 28 2000

s:\nda\20-678\pedlbl\letter 2.doc

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Baxter

If you have any questions, please contact me or Lisa Skeens, PhD at (847) 270-2577.

Sincerely,

for

Marcia Marconi
Vice President, Regulatory Affairs
phone: (847) 270-4637
fax: (847) 270-4668

cc: Steve McCort

APPEARS THIS WAY
ON ORIGINAL

MAR 2 8 2000

s:\nda\20-678\pedlbl\letter 2.doc

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