CENTER FOR DRUG EVALUATION AND RESEARCH

APPROVAL PACKAGE for:

APPLICATION NUMBER: 020678

TRADE NAME: Clinimix E sulfite-free Injections in Clarity Dual Chamber Container

GENERIC NAME: Amino Acid with Electrolytes in Dextrose with Calcium

SPONSOR: Baxter Healthcare Corporation

APPROVAL DATE: 03/26/97

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

NDA 20-678

MAR 26 1997

Baxter Healthcare Corporation
Attention: Ms. Marcia Marconi
Vice President, Regulatory Affairs
Route 120 & Wilson Road
ROUND LAKE, ILLINOIS 60073-0490

Dear Ms. Marconi:

Please refer to your new drug application dated March 21, 1996, received March 27, 1996, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Clinimix™ E sulfite-free (Amino Acid with Electrolytes in Dextrose with Calcium) Injections in Clarity™ Dual Chamber Container for the following 12 strengths:

Clinimix™ E 2.75/5 sulfite-free (2.75% Amino acid with Electrolytes in 5% Dextrose with Calcium) Injection
Clinimix™ E 2.75/10 sulfite-free (2.75% Amino acid with Electrolytes in 10% Dextrose with Calcium) Injection
Clinimix™ E 2.75/25 sulfite-free (2.75% Amino acid with Electrolytes in 25% Dextrose with Calcium) Injection
Clinimix™ E 4.25/5 sulfite-free (4.25% Amino acid with Electrolytes in 5% Dextrose with Calcium) Injection
Clinimix™ E 4.25/10 sulfite-free (4.25% Amino acid with Electrolytes in 10% Dextrose with Calcium) Injection
Clinimix™ E 4.25/20 sulfite-free (4.25% Amino acid with Electrolytes in 20% Dextrose with Calcium) Injection
Clinimix™ E 4.25/25 sulfite-free (4.25% Amino acid with Electrolytes in 25% Dextrose with Calcium) Injection
Clinimix™ E 5/10 sulfite-free (5% Amino acid with Electrolytes in 10% Dextrose with Calcium) Injection
Clinimix™ E 5/15 sulfite-free (5% Amino acid with Electrolytes in 15% Dextrose with Calcium) Injection
Clinimix™ E 5/20 sulfite-free (5% Amino acid with Electrolytes in 15% Dextrose with Calcium) Injection
Clinimix™ E 5/25 sulfite-free (5% Amino acid with Electrolytes in 25% Dextrose with Calcium) Injection
Clinimix™ E 5/35 sulfite-free (5% Amino acid with Electrolytes in 35% Dextrose with Calcium) Injection

We acknowledge receipt of your submissions dated June 5 1996, and February 7 and 13, and March 18 and 25, 1997. The user fee goal date for this application is March 27, 1997.

This 505(b)(2) application provides for new parenteral nutrition combination products to be used as a source of calories and protein in patients where: (1) the alimentary tract cannot or should not be used, (2) gastrointestinal absorption is impaired, or (3) metabolic requirements for protein are substantially increased.

We have completed the review of this application, including the submitted draft labeling, 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 draft labeling in the submission dated March 18, 1997. Accordingly, the application is approved effective on the date of this letter.

The final printed labeling (FPL) must be identical to the draft labeling submitted on March 18, 1997. Marketing the product with FPL that is not identical to this draft labeling 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 "FINAL PRINTED LABELING" for approved NDA 20-678. Approval of this submission by FDA is not required before the labeling is used.

Should additional information relating to the safety and effectiveness of the drug become available, revision of that labeling may be required.

In addition, please submit three copies of the introductory promotional material 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 material and the package insert directly to:

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

Validation of the regulatory methods has not been completed. At the present time, it is the policy of the Center not to withhold approval because the methods are being validated. Nevertheless, we expect your continued cooperation to resolve any problems that may be identified.

Please submit one market package of the drug product when it is available.

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

If you have any questions, please contact Steve McCort, Consumer Safety Officer, at (301) 443-3510.

Sincerely yours,

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

Baxter

Clinimix™ E

lfite-free (Amino Acid with Electrolytes in Dextrose with Calcium) Injections

MAR 18 1997

E

in Clarity™ Dual Chamber Container

Description

Clinimix™ E sulfite-free (Amino Acid with Electrolytes in Dextrose with Calcium) Injections are sterile, nonpyrogenic, hypertonic solutions in a Clarity™ Dual Chamber Container.

The sulfite-free Amino Acid Injections with Electrolytes in the lower chamber are solutions of essential and nonessential amino acids provided with electrolytes.

The Dextrose Injections with Calcium in the upper chamber are solutions for fluid replenishment and caloric supply.

After opening the seal between the chambers and mixing thoroughly, the admixed product is intended for intravenous use. See Table 1 for composition, pH, osmolarity, ionic concentration and caloric content of the admixed product.

The Clarity™ Dual Chamber Container is a lipid-compatible plastic container (PL 2401 Plastic). 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

Clinimix™ E sulfite-free (Amino Acid with Electrolytes in Dextrose with Calcium) Injections administered intravenously provide biologically utilizable source material for protein synthesis and have value as a source of calories, electrolytes, and water.

Indications and Usage

Clinimix™ E sulfite-free (Amino Acid with Electrolytes in Dextrose with Calcium) Injections are indicated as a caloric component in a parenteral nutrition regimen and as the protein (nitrogen) source for offsetting nitrogen loss or for 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.

Central Vein Administration: Central vein infusion should be used when amino acid solutions are admixed with hypertonic dextrose to promote protein synthesis such as for hypercatabolic depleted patients or those requiring long term parenteral nutrition.

Ipheral Vein Administration: For patients in whom the central vein route is not indicated, .ino acid solutions diluted with low dextrose concentrations may be infused by peripheral vein.

Contraindications

Clinimix™ E sulfite-free (Amino Acid with Electrolytes in Dextrose with Calcium) Injections are contraindicated in patients having intracranial or intraspinal hemorrhage, in patients who are severely dehydrated, in patients hypersensitive to one or more amino acids and in patients with severe liver disease or hepatic coma.

Warnings

Additives may be incompatible. Consult with pharmacist, if available. When introducing additives, use aseptic techniques. Mix thoroughly. Do not store.

Because of the potential for life-threatening events, caution should be taken to ensure that precipitates have not formed in any parenteral nutrient admixture.

These Clinimix™ E sulfite-free (Amino Acid with Electrolytes in Dextrose with Calcium) Injections, **must be** admixed prior to infusion. For admixing instructions **see Directions for Use of Plastic Container.**

The infusion of hypertonic nutrient injections into a peripheral vein may result in vein irritation, vein damage, and thrombosis. After mixing, strongly hypertonic nutrient injections should only be administered through an indwelling intravenous catheter with the tip located in a large central vein, such as the superior vena cava.

Proper administration of these admixed amino acid with electrolytes/dextrose with calcium injections requires a knowledge of fluid and electrolyte balance and nutrition as well as clinical expertise in recognition and treatment of the complications which may occur.

Laboratory Tests

Frequent clinical evaluation and laboratory determinations are necessary for proper monitoring during administration. Studies should include blood sugar, serum proteins, kidney and liver function tests, electrolytes, complete blood count with differential, carbon dioxide combining power or content, serum osmolarities, blood cultures, and blood ammonia levels.

Administration of amino acid solutions to a patient with hepatic insufficiency may result in serum amino acid imbalances, hyperammonemia, stupor, and coma.

Hyperammonemia is of **special significance in infants.** This reaction appears to be related to a deficiency of the urea cycle amino acids of genetic or product origin. It is essential that blood ammonia be measured frequently in infants.

Conservative doses of these admixed amino acid with electrolytes/dextrose with calcium injections should be given to patients with known or suspected hepatic dysfunction. Should symptoms of hyperammonemia develop, administration should be discontinued and the patient's clinical status be reevaluated.

Administration of amino acid solutions in the presence of impaired renal function presents ecial issues associated with retention of electrolytes.

se admixed injections should not be administered simultaneously with blood through the me infusion set because of the possibility of pseudoagglutination.

Precautions

With the administration of these Clinimix™ E sulfite-free (Amino Acid with Electrolytes in Dextrose with Calcium) Injections, hyperglycemia, glycosuria, and hyperosmolar syndrome may result. Blood and urine glucose should be monitored on a routine basis in patients.

Use with caution when administering to patients with anuria or renal failure.

These injections contain sufficient electrolytes to provide for most parenteral nutritional needs with the possible exception of potassium, where supplementation may be required. However, replacement of exceptional electrolyte loss due to nasogastric suction, fistula drainage, or unusual tissue exudation may be necessary. Particular attention should be given to monitoring serum potassium levels.

The metabolizable acetate anion and amino acid profiles in these admixed injections were designed to minimize or prevent occurrences of hyperchloremic metabolic acidosis and hyperammonemia. However, the physician should be aware of appropriate countermeasures if they become necessary.

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.

Because of its anti-anabolic activity, concurrent administration of tetracycline may reduce the protein-sparing effect of infused amino acids.

Care should be taken to avoid excess fluid accumulation, particularly in patients with renal disease, pulmonary insufficiency, and heart disease.

Administration of admixed amino acid with electrolytes/dextrose with calcium injections and other nutrients via central or peripheral 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 on current medical practices be followed, preferably by an experienced team.**

Although a detailed discussion of the complications is beyond the scope of this insert, the following summary lists those based on current literature:

Technical: The placement of a central venous catheter should be regarded as a surgical procedure. The physician should be fully acquainted with various techniques of catheter insertion as well as recognition and treatment of complications. For details of techniques and placement sites, consult the medical literature. X-ray is the best means of verifying catheter placement. Complications known to occur from the placement of central venous catheters are pneumothorax, hemothorax, hydrothorax, artery puncture and transection, injury to the brachial plexus, malposition of the catheter, formation of arteriovenous fistula, phlebitis, thrombosis, cardiac arrhythmia, and catheter embolus.

Septic: The constant risk of sepsis is present during total parenteral nutrition. Since contaminated solutions and infusion catheters are potential sources of infection, it is imperative that the preparation of solution and the placement and care of catheters be accomplished under controlled aseptic conditions. If fever develops, the solution, its delivery system, and the site of the indwelling catheter should be changed.

Metabolic: The following metabolic complications have been reported: metabolic acidosis, hypophosphatemia, alkalosis, hyperglycemia and glycosuria, osmotic diuresis and dehydration, rebound hypoglycemia, elevated liver enzymes, hypo- and hypervitaminosis, electrolyte imbalances, and hyperammonemia. Frequent clinical evaluation and laboratory determinations are necessary, especially during the first few days of therapy to prevent or minimize these complications.

Caution must be exercised in the administration of these admixed amino acid with electrolytes/dextrose with calcium injections to patients receiving corticosteroids or corticotropin.

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

Carcinogenesis, Mutagenesis, Impairment of Fertility: Studies with Clinimix™ E sulfite-free (Amino Acid with Electrolytes in Dextrose with Calcium) Injections 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 Clinimix™ E sulfite-free (Amino Acid with Electrolytes in Dextrose with Calcium) Injections. It is also not known whether Clinimix™ E sulfite-free (Amino Acid with Electrolytes in Dextrose with Calcium) Injections can cause fetal harm when administered to a pregnant woman or can affect reproduction capacity. Clinimix™ E sulfite-free (Amino Acid with Electrolytes in Dextrose with Calcium) Injections should be given to a pregnant woman only if clearly needed.

Nursing mothers: Caution should be exercised when Clinimix™ E sulfite-free (Amino Acid with Electrolytes in Dextrose with Calcium) Injections are administered to a nursing woman.

Pediatric use: See Dosage and Administration.

Adverse Reactions

See **Warnings** and **Precautions**

Too rapid infusion of these Clinimix™ E sulfite-free (Amino Acid with Electrolytes in Dextrose with Calcium) Injections 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 that 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. Policies and procedures should be established for the recognition and management of such reactions.

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.

Table 1 **Cont**

	After mixing the product represents 2000 mL of: 2.75% Amino Acid with Electrolytes in	Dextrose Hydrous, USP[1] (g/100 mL)	Amino Acids (g/100 mL)	Total Nitrogen (mg/100 mL)	Essential Amino Acids (mg/100 mL)									Ne
					Leucine - $(CH_3)_2CHCH_2CH(NH_2)COOH$	Isoleucine - $CH_3CH_2CH(CH_3)CH(NH_2)COOH$	Valine - $(CH_3)_2CHCH(NH_2)COOH$	Lysine (added as the hydrochloride salt) - $H_2N(CH_2)_4CH(NH_2)COOH$	Phenylalanine - $(C_6H_5)CH_2CH(NH_2)COOH$	Histidine - $(C_3H_3N_2)CH_2CH(NH_2)COOH$	Threonine - $CH_3CH(OH)CH(NH_2)COOH$	Methionine - $CH_3S(CH_2)_2CH(NH_2)COOH$	Tryptophan - $(C_8H_6N)CH_2CH(NH_2)COOH$	Alanine - $CH_3CH(NH_2)COOH$	
Clinimix™ E 2.75/5 sulfite-free Injection	5% Dextrose with Calcium Injection	5	2.75	454	201	165	160	159	154	132	116	110	50	570	
Clinimix™ E 2.75/10 sulfite-free Injection	10% Dextrose with Calcium Injection	10	2.75	454	201	165	160	159	154	132	116	110	50	570	
Clinimix™ E 2.75/25 sulfite-free Injection	25% Dextrose with Calcium Injection	25	2.75	454	201	165	160	159	154	132	116	110	50	570	
	4.25% Amino Acid with Electrolytes in														
Clinimix™ E 4.25/5 sulfite-free Injection	5% Dextrose with Calcium Injection	5	4.25	702	311	255	247	247	238	204	179	170	77	880	
Clinimix™ E 4.25/10 sulfite-free Injection	10% Dextrose with Calcium Injection	10	4.25	702	311	255	247	247	238	204	179	170	77	880	
Clinimix™ E 4.25/20 sulfite-free Injection	20% Dextrose with Calcium Injection	20	4.25	702	311	255	247	247	238	204	179	170	77	880	
Clinimix™ E 4.25/25 sulfite-free Injection	25% Dextrose with Calcium Injection	25	4.25	702	311	255	247	247	238	204	179	170	77	880	
	5% Amino Acid with Electrolytes in														
Clinimix™ E 5/10 sulfite-free Injection	10% Dextrose with Calcium Injection	10	5	826	365	300	290	290	280	240	210	200	90	1035	
Clinimix™ E 5/15 sulfite-free Injection	15% Dextrose with Calcium Injection	15	5	826	365	300	290	290	280	240	210	200	90	1035	
Clinimix™ E 5/20 sulfite-free Injection	20% Dextrose with Calcium Injection	20	5	826	365	300	290	290	280	240	210	200	90	1035	
Clinimix™ E 5/25 sulfite-free Injection	25% Dextrose with Calcium Injection	25	5	826	365	300	290	290	280	240	210	200	90	1035	
Clinimix™ E 5/35 sulfite-free Injection	35% Dextrose with Calcium Injection	35	5	826	365	300	290	290	280	240	210	200	90	1035	

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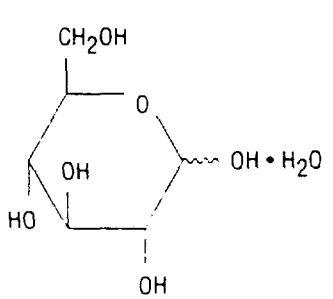

Dextrose Hydrous, USP
(β-Glucopyranose monohydrate)

2. Balanced by ions from amino acids.
3. Derived from glacial acetic acid (for pH adjustment) and sodium acetate
4. Contributed by calcium chloride, lysine hydrochloride, magnesium chloride and sodium chloride
5. pH of sulfite-free Amino Acid Injection with Electrolytes in the lower chamber was adjusted with glacial acetic acid and may have been adjusted with sodium hydroxide

of Admixed Product

Composition																		
al Amino Acids (mg/100 mL)				Electrolytes (mg/100 mL)					Electrolyte Profile (mEq/L)[2]									
Glycine - H_2NCH_2COOH	Proline - $[(CH_2)_3 NH CH] COOH$	Serine - $HOCH_2CH (NH_2) COOH$	Tyrosine - $[C_6H_4 (OH)] CH_2CH (NH_2) COOH$	Sodium Acetate Trihydrate, USP - $C_2H_3NaO_2 \cdot 3H_2O$	Dibasic Potassium Phosphate, USP - K_2HPO_4	Sodium Chloride, USP - NaCl	Magnesium Chloride, USP - $MgCl_2 \cdot 6H_2O$	Calcium Chloride Dihydrate, USP - $CaCl_2 \cdot 2H_2O$	Sodium	Potassium	Magnesium	Calcium	Acetate[3]	Chloride[4]	Phosphate (as $HPO_4^{=}$)	pH[5] (range)	Osmolarity (mOsmol/L) (calc)	Caloric Content kcal/L
283	187	138	11	217	261	112	51	33	35	30	5	4.5 (2.2 mmol/L)	51	39	30 (15 mmol/L)	6.0 (4.5 to 7.0)	665	170
283	187	138	11	217	261	112	51	33	35	30	5	4.5 (2.2 mmol/L)	51	39	30 (15 mmol/L)	6.0 (4.5 to 7.0)	920	340
283	187	138	11	217	261	112	51	33	35	30	5	4.5 (2.2 mmol/L)	51	39	30 (15 mmol/L)	6.0 (4.5 to 7.0)	1675	850
438	289	213	17	297	261	77	51	33	35	30	5	4.5 (2.2 mmol/L)	70	39	30 (15 mmol/L)	6.0 (4.5 to 7.0)	815	170
438	289	213	17	297	261	77	51	33	35	30	5	4.5 (2.2 mmol/L)	70	39	30 (15 mmol/L)	6.0 (4.5 to 7.0)	1070	340
[illegible]	289	213	17	297	261	77	51	33	35	30	5	4.5 (2.2 mmol/L)	70	39	30 (15 mmol/L)	6.0 (4.5 to 7.0)	1575	680
438	289	213	17	297	261	77	51	33	35	30	5	4.5 (2.2 mmol/L)	70	39	30 (15 mmol/L)	6.0 (4.5 to 7.0)	1825	850
515	340	250	20	340	261	59	51	33	35	30	5	4.5 (2.2 mmol/L)	80	39	30 (15 mmol/L)	6.0 (4.5 to 7.0)	1145	340
515	340	250	20	340	261	59	51	33	35	30	5	4.5 (2.2 mmol/L)	80	39	30 (15 mmol/L)	6.0 (4.5 to 7.0)	1395	510
515	340	250	20	340	261	59	51	33	35	30	5	4.5 (2.2 mmol/L)	80	39	30 (15 mmol/L)	6.0 (4.5 to 7.0)	1650	680
515	340	250	20	340	261	59	51	33	35	30	5	4.5 (2.2 mmol/L)	80	39	30 (15 mmol/L)	6.0 (4.5 to 7.0)	1900	850
515	340	250	20	340	261	59	51	33	35	30	5	4.5 (2.2 mmol/L)	80	39	30 (15 mmol/L)	6.0 (4.5 to 7.0)	2405	1190

Dosage and Administration

If a patient is unable to take oral nourishment for a prolonged period of time, institution of total parenteral nutrition should be considered.

The total daily dose of Clinimix™ E sulfite-free (Amino Acid with Electrolytes in Dextrose with Calcium) Injections depends on the patient's metabolic requirement and clinical response. The determination of nitrogen balance and accurate daily body weights, corrected for fluid balance, are probably the best means of assessing individual nitrogen requirements.

Recommended Dietary Allowances* of protein range from approximately 0.75 g/kg of body weight for adults to 1.68 g/kg for infants up to three months of age. It must be recognized, however, that protein as well as caloric requirements in traumatized or malnourished patients may be increased substantially. Daily amino acid doses of approximately 1.0 to 1.5 g/kg of body weight for adults and 2 to 3 g/kg of body weight for infants with adequate calories are generally sufficient to satisfy protein needs and promote positive nitrogen balance.

For the initial treatment of trauma or protein calorie malnutrition, higher doses of protein with corresponding quantities of carbohydrates will be necessary to promote adequate patient response to therapy. The severity of the illness being treated is the primary consideration in determining proper dose level. Such higher doses, especially in infants, must be accompanied by more frequent laboratory evaluation.

Care should be exercised to insure the maintenance of proper levels of serum potassium. Quantities of 60 to 180 mEq of potassium per day have been used with adequate clinical effect. It may be necessary to add quantities of this electrolyte to these admixed injections, depending primarily on the amount of carbohydrate administered to and metabolized by the patient.

Total daily fluid requirements can be met beyond the volume of amino acids solution by supplementing with noncarbohydrate or carbohydrate-containing electrolyte solutions.

Maintenance vitamins, additional electrolytes, and trace elements should be administered as required.

In many patients, provision of adequate calories in the form of hypertonic dextrose may require the administration of exogenous insulin to prevent hyperglycemia and glycosuria.

Fat emulsion administration should be considered when prolonged (more than 5 days) parenteral nutrition is required in order to prevent essential fatty acid deficiency (EFAD). Serum lipids should be monitored for evidence of EFAD in patients maintained on fat-free TPN.

Intravenous fat emulsions provide approximately 1.1 kcal per mL (10%), 2.0 kcal per mL (20%), or 3.0 kcal per mL (30%) and may be admixed along with amino acid with electrolytes/dextrose with calcium injections in the Clarity™ Container to supplement caloric intake.

Depending upon the clinical condition of the patient, approximately 3 liters of solution may be administered per 24 hour period. When used postoperatively, the therapy should begin with 1000 mL on the first postoperative day. Thereafter, the dose may be increased to 3000 mL per day.

Do not administer unless seal between chambers is opened, other seals are intact, and solution is clear and thoroughly mixed.

Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration whenever solution and container permit. Use of a final filter is recommended during administration of all parenteral solutions, where possible.

A slight yellow color does not alter the quality and efficacy of this product.

Additives may be incompatible. Complete information is not available. Those additives known to be incompatible should not be used. Consult with pharmacist, if available. When 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.

These amino acid with electrolytes/dextrose with calcium injections should be used promptly after mixing. Any storage should be under refrigeration and limited to a brief period of time, less than 24 hours.

Central Vein Administration: Hypertonic mixtures of amino acid with electrolytes/dextrose with calcium injections may be administered safely by continuous infusion through a central vein catheter with the tip located in the vena cava. In addition to meeting nitrogen needs, the administration rate is governed, especially during the first few days of therapy, by the patient's tolerance to dextrose, as indicated by frequent determinations of urine and blood sugar levels. Daily intake of amino acid with electrolytes/dextrose with calcium injections should be increased gradually to the maximum required dose.

Sudden cessation in administration of these admixed injections may result in insulin reaction due to continued endogenous insulin production. Parenteral nutrition mixtures should be withdrawn slowly.

Peripheral Vein Administration: For patients requiring parenteral nutrition in whom the central vein route is not indicated, low concentration amino acid with electrolytes/dextrose with calcium injections may be administered by peripheral vein.

Directions for Use of 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.

BE SURE THE CONTENTS ARE MIXED. If not, the full contents of this product can not be completely injected.

To Open

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 to ensure seal between chambers is intact, i.e., solutions are contained in separate chambers. Check for minute leaks by separately squeezing each chamber. If external leaks or leakage between the top and bottom chambers are found, discard solution as sterility or stability may be impaired.

*Food and Nutrition Board, National Academy of Sciences-National Research Council (Revised 1989)

BAR CODE PLACEMENT

071901794

To Mix Solutions

Grasp the container firmly above the seal as shown in Figure 1. Squeeze to open seal between chambers as shown in Figure 2. Mix solutions thoroughly. Check for leaks.

Storage: Storage of the admixture must be under refrigeration and limited to a brief period of time, no longer than 24 hours.

To add Fat Emulsion for 3-in-1 admixture:

A. Prior to adding fat emulsion, mix amino acid and dextrose injection as shown in Figure 2.
B. Prepare fat emulsion transfer set following instructions provided.
C. Attach transfer set to fat emulsion bottle using aseptic technique.
D. Remove plastic protector on the additive port of the Clarity™ container.
E. Attach the transfer set to the exposed additive port.
F. Open clamp on transfer set.
G. After completing transfer, use appropriate plastic clamp or metal ferrule to seal off additive port tube.
H. Remove transfer set.
I. Mix contents of Clarity™ container thoroughly. Check for leaks.

Figure 1

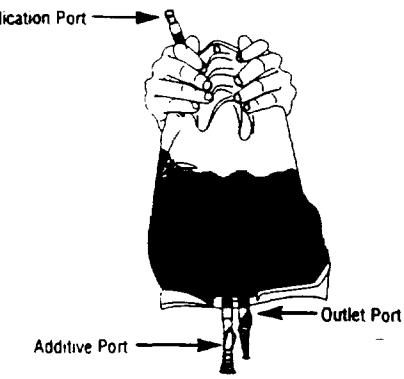

Figure 2

Storage: Storage of the 3-in-1 admixture must be under refrigeration and limited to a brief period of time, no longer than 24 hours.

To Add Medication

WARNING: Additives may be incompatible.

Supplemental medication may be added with a 19 to 22 gauge needle through the medication port.

A. Prepare medication port.
B. Using syringe with 19 to 22 gauge needle, puncture resealable medication port and inject.
C. Mix solution and medication thoroughly. For high density medication, such as potassium chloride, squeeze ports while ports are upright and mix thoroughly.
D. Check for leaks.

Preparation for Administration

A. Suspend container from eyelet support.
B. Remove plastic protector from outlet port at bottom of container.
C. Attach administration set. Refer to complete directions accompanying set.

How Supplied

Clinimix™ E sulfite-free (Amino Acid with Electrolytes in Dextrose with Calcium) Injections in a Clarity™ Dual Chamber Container are supplied in the following concentrations:

2B7713	NDC 0338-1107-04	**Clinimix™ E 2.75/5 sulfite-free (2.75% Amino Acid with Electrolytes in 5% Dextrose with Calcium) Injection**
2B7714	NDC 0338-1109-04	**Clinimix™ E 2.75/10 sulfite-free (2.75% Amino Acid with Electrolytes in 10% Dextrose with Calcium) Injection**
2B7715	NDC 0338-1111-04	**Clinimix™ E 2.75/25 sulfite-free (2.75% Amino Acid with Electrolytes in 25% Dextrose with Calcium) Injection**
2B7716	NDC 0338-1113-04	**Clinimix™ E 4.25/5 sulfite-free (4.25% Amino Acid with Electrolytes in 5% Dextrose with Calcium) Injection**
2B7717	NDC 0338-1115-04	**Clinimix™ E 4.25/10 sulfite-free (4.25% Amino Acid with Electrolytes in 10% Dextrose with Calcium) Injection**
2B7718	NDC 0338-1117-04	**Clinimix™ E 4.25/20 sulfite-free (4.25% Amino Acid with Electrolytes in 20% Dextrose with Calcium) Injection**
2B7719	NDC 0338-1119-04	**Clinimix™ E 4.25/25 sulfite-free (4.25% Amino Acid with Electrolytes in 25% Dextrose with Calcium) Injection**
2B7720	NDC 0338-1121-04	**Clinimix™ E 5/10 sulfite-free (5% Amino Acid with Electrolytes in 10% Dextrose with Calcium) Injection**
2B7721	NDC 0338-1123-04	**Clinimix™ E 5/15 sulfite-free (5% Amino Acid with Electrolytes in 15% Dextrose with Calcium) Injection**
2B7722	NDC 0338-1125-04	**Clinimix™ E 5/20 sulfite-free (5% Amino Acid with Electrolytes in 20% Dextrose with Calcium) Injection**
2B7723	NDC 0338-1127-04	**Clinimix™ E 5/25 sulfite-free (5% Amino Acid with Electrolytes in 25% Dextrose with Calcium) Injection**
2B7724	NDC 0338-1129-04	**Clinimix™ E 5/35 sulfite-free (5% Amino Acid with Electrolytes in 35% Dextrose with Calcium) Injection**

Exposure of pharmaceutical products to heat should be minimized. Avoid excessive heat. Protect from freezing. It is recommended that the product be stored at room temperature (25°C/77°F); brief exposure up to 40°C/104°F does not adversely affect the product.

Do not remove container from overpouch until ready to use.

Do not use if overpouch has been previously opened or damaged.

Baxter Healthcare Corporation
Clintec Nutrition Division
Deerfield, IL 60015 USA

Printed in USA

7-19-1-794
Rev. March 1997

LABEL REVIEW

Application Number: 20-678

Name of Drug: Travasol II® - sulfite free (Amino acids) with Electrolytes in Dextrose with Calcium Injections in Clinimix (PL 2401) Dual Chamaber Container.

Sponsor: Baxter Healthcare

Material Reviewed: February 7, 1997 draft labeling

Submission Date(s): February 7, 1997 Draft Labeling

Receipt Date(s): February 10, 1997 draft labeling

Background and Summary Description: This submission included revised draft labeling in response to a February 4, 1997 FAX communication regarding the trade product "Travasol II" product name. The division expressed a preference to some other name other than numbers to distinguish the other trade names other than "Travasol II"

Review

The revised draft labeling dated February 7, 1997, was compared with the draft labeling dated March 21, 1996. The following changes were noted:

1. The name *"TRAVASOL® II - sulfite free (Amino Acid) with Electrolytes in Dextrose with Calcium) Injections in Clinimix™ Dual Chamber Container*

   Has been revised to read,

   "Clinimix™ E (sulfite free Amino Acid) with Electrolytes in Clarity™ Dual Chamber Container"

2. Under Table 1 left top caption that reads,

"2.75% Travasol® II sulfite-free (Amino Acid) with Electrolytes in . . ."

"5% Dextrose Injection with Calcium Injection. . ."

has been revised to read,

"2.5% sulfite-free Amino Acid with Electrolytes in . . ."

Clinimix™ 2.5/5E Injection . . . . 5% Dextrose with Calcium Injection . . ."

3. In the **HOW SUPPLIED** section, line 1 paragraph 1 which reads,

"Travasol® II -sulfite free (Amino Acid) with Electrolytes in Dextrose with Calcium Injection in a Clinimix™ Dual Chamber are supplied ....."

has been revised to read,

"Clinimix™ E (sulfite-free Amino Acid with Electrolytes in Dextrose with Calcium) Injections in a Clarity™ Dual Chamber Container are supplied ....."

3. In the **HOW SUPPLIED** section each of the concentrations that read,

"2.75% Travasol II - sulfite free (Amino Acid) with Electrolytes in 5% Dextrose with Calcium Injection.... (etc.)"

have been revised to read,

"Clinimix™ 2.75% E (2.75% sulfite-free Amino Acid with Electrolytes in 5% Dextrose with Calcium Injection . . . (etc.)"

CONCLUSIONS:

The following recommendations have been made to the labeling as follows:

1. The "E" in the proprietary name "CLINIMIX E" should be dropped from the name of the product The new name should read,

   "Clinimix™ (sulfite-free Amino Acid with Electrolytes in Dextrose with Calcium) Injections" **(Nomenclature Committee)**

2. The numbers after the name "Clinmix™ 2.75/5E Injection" in both table 1 and the HOW SUPPLIED section should be dropped. A different presentation such as "Clinimix 5% with Electrolytes/Calcium in 25% Dextrose " was suggested **(Nomenclature Committee)**

RECOMMENDATIONS:

Based upon the information recommended by the nomenclature committee, this reviewer has the following recommendations:

1. The "E" in the proprietary name "CLINIMIX E" should be dropped from the name of the product. The new name should read,

   "Clinimix™ (sulfite-free Amino Acid with Electrolytes in Dextrose with Calcium) Injections" **(Nomenclature Committee)**

2. The format presented in Table 1 should be revised as follows:

   a. The columns in the left side of the table which read,

      "Clinimix™ 2.75% E Injection . . . (etc . . "

      should be deleted.

   b. The second row headings which begin

      "2.75% sulfite-free Amino Acid with Electrolytes in . . . "

      should be revised to read,

      "2.75% Clinimix™ sulfite-free Amino Acid with Electrolytes in..."

3. In the **HOW SUPPLIED** section, line 1 paragraph 1 which reads,

"Clinimix™ E (sulfite-free Amino Acid with Electrolytes in Dextrose with Calcium) Injections in a Clarity™ Dual Chamber Container are supplied ....."

Should be revised to read,

"Clinimix™ (sulfite-free Amino Acid with Electrolytes in Dextrose with Calcium) Injections in a Clarity™ Dual Chamber Container are supplied ....."

4. In the **HOW SUPPLIED** section each of the concentrations that read,

"Clinimix™ 2.75% E (2.75% sulfite-free Amino Acid with Electrolytes in 5% Dextrose with Calcium Injection . . . (etc.)"

should be revised to read,

"Clinimix™ 2.75% (sulfite-free Amino Acid with Electrolytes in 5% Dextrose with Calcium Injection . . . (etc.)"

Steve McCort, CSO
Project Manager

Pharmacology Supervisor

3/6/97
Medical Officer

Chemistry Reviewer

Gloria Troendle
Deputy Director

Chemistry Team Leader

cc:
NDA 20-678
HFD-510/Div. Files
HFD-510/SMcCortDWu/EColman/GTroendle/RSteigerwalt
HFD-510/Solomon Sobel, M.D.

CSO REVIEW

LABEL REVIEW - ADDENDUM

Application Number: 20-678

Name of Drug: Travasol II® - sulfite free (Amino acids) with Electrolytes in Dextrose with Calcium Injections in Clinimix (PL 2401) Dual Chamber Container.

Sponsor: Baxter Healthcare

Material Reviewed: February 7, 1997 draft labeling

Submission Date(s): February 7, 1997 Draft Labeling

Receipt Date(s): February 10, 1997 draft labeling

Background and Summary Description: This submission included revised draft labeling in response to a February 4, 1997, FAX communication regarding the trade product "Travasol II" product name. The Division expressed a preference for some name other than numbers to distinguish the other trade name "Travasol II" from other amino acid solutions. On March 12, 1997, in a teleconference with the firm, the Division agreed to the February 7, 1997 draft labeling submitted by the sponsor which included the following revisions to the March 21, 1996 draft labeling:

1. The name change for the product "Clinimix™ E (sulfite free Amino Acid with Electrolytes in Dextrose with Calcium) Injections" to replace "Travasol® II -sulfite free (Amino Acid) with Electrolytes in Dextrose with Calcium Injection.

2. The revision of Table 1 left top caption that reads,

   "2.75% Travasol® II sulfite-free (Amino Acid) with Electrolytes in . . ."

   "5% Dextrose Injection with Calcium Injection.

   Has been revised to read:

   "2.75% sulfite-free Amino Acid with Electrolytes in . . ."

   Clinimix™ 2.75/5E Injection . . . . 5% Dextrose with Calcium Injection . . ."

3. The **HOW SUPPLIED** section, line 1 paragraph 1 which reads,

"Travasol® II -sulfite free (Amino Acid) with Electrolytes in Dextrose with Calcium Injection in a Clinimix™ Dual Chamber are supplied ....."

to read,

"Clinimix™ E (sulfite-free Amino Acid with Electrolytes in Dextrose with Calcium) Injections in a Clarity™ Dual Chamber Container are supplied ....."

4. In the **HOW SUPPLIED** section each of the concentrations that read,

"2.75% Travasol II - sulfite free (Amino Acid) with Electrolytes in 5% Dextrose with

revised to read,

"Clinimix™ E (sulfite-free Amino Acid with Electrolytes in Dextrose with Calcium) Injections in a Clarity™ Dual Chamber Container are supplied ....."

POST REVIEW OF LABELING:

In a follow up conversation after the meeting with Mr. Stan Koch, Reviewing Chemist it was agreed that the following labeling comments be conveyed to the Sponsor:

1. Point out to the Sponsor that the proprietary name "Clinimix™ E" as stated in the February 7, 1997 draft labeling may restrict the firm from marketing other products for Clinimix™ E or for Clinimix ™ that do not include Dextrose or Calcium. The Division suggests another option:

   "Clinimix E ® sulfite-free (Amino Acids with Electrolytes) in Dextrose with Calcium Injections"

2. In Table 1, change the position of the E to read,

   "Clinimix™ E 2.75/5. . . "

3. Remove "sulfite free" from the established name in these drug products. This statement can be used in association with the proprietary name in a manner similar to Baxter's Novamine Injection.

4. In the HOW SUPPLIED section of the package insert, sentence 1, paragraph 1 will now read,

"Clinimix E sulfite-free (Amino acid with Electrolytes) in Dextrose with Calcium Injections in . . ."

In the HOW SUPPLIED section the concentration of each of the products will now read,

e.g., "Clinimix™ E 2.75/5 sulfite- free (2.75% Amino Acids with Electrolytes) in 5% Dextrose with Calcium Injection.

CONCLUSIONS:

The recommendations and comments stated above will be conveyed to the Sponsor.

Steve McCort, Project Manager

Ron Steigerwalt, Ph.D.
Pharmacology Team Leader

Eric Colman, M.D., Medical Officer

Stan Koch, Chemistry Reviewer

Gloria Troendle, M.D., Deputy Director

Duu-Gong Wu, Ph.D., Chemistry Team Leader

Solomon Sobel, M.D.,Division Director

cc:
NDA 20-678
HFD-510/Div. Files
HFD-510/SMcCortDWu/EColman/GTroendle/RSteigerwalt
HFD-510/Solomon Sobel, M.D.

LABEL REVIEW 3

Application Number: 20-678

Name of Drug: Clinimix™ E sulfite free (Amino Acid with Electrolytes in Dextrose with Calcium) Injections in Clarity™ Dual Chamber Container

Sponsor: Baxter Healthcare

Material Reviewed: March 18, 1997, draft labeling

Submission Date(s): March 18, 1997, draft labeling

Receipt Date(s): March 18, 1997, draft labeling

Background and Summary Description: The submission of the March 18, 1997, draft labeling included revised labeling per agreement between Baxter and the Division in a March 17, 1997, teleconference.

Review

The March 18, 1997 labeling included the following labeling revisions:

1. The words "sulfite free" have been removed from the association with the established name such that they are now associated with proprietary name of the product. The proprietary and established names now read as follows:

   "Clinimix™ E sulfite free (Amino Acid with Electrolytes in Dextrose with Calcium) Injections".

2. For all product configurations, the potency designation for the amino acid and dextrose solutions will be placed after the suffix "E" such that there is no separation between the suffix and the product trademark [e.g. Clinimix™ E 5/25 sulfite free (5% Amino acid with Electrolytes in 25% Dextrose with Calcium) Injection].

RECOMMENDATION:

All changes requested by this Division have been made for the revised March 18, 1997 draft labeling. With the concurrence of the reviewing staff, I recommend that the March 18, 1997, draft labeling be approved.

Steve McCort
Project Manager

Ronald W. Steigerwalt
Pharmacology Leader

Medical Officer

for O.H. Roggeman (retired)
Chemistry Reviewer

Gloria Troendle
Deputy Director

Chemistry Team Leader

cc:

NDA 20-678
HFD-510/Div. Files
HFD-510/SMcCortDWu/EColman/GTroendle/RSteigerwalt
HFD-510/Solomon Sobel, M.D.

CSO REVIEW

EXCLUSIVITY SUMMARY for NDA #20-678 SUPPL #_____

Trade Name Clinimix™ E **Generic Name** (AMINO ACID W/TH ELECTROLYTES IN DEXTROSE W/TH CALCIUM) INJECTION
Applicant Name BAXTER **HFD-**510

Approval Date 3-26-97

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 questions about the submission.

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

   b) Is it an effectiveness supplement?

   YES /__/ NO /X/

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

   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 /X/

   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:

_____

_____

Form OGD-011347 Revised 8/7/95; edited 8/8/95
cc: Original NDA Division File HFD-85 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?

_____

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?

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 /___/ NO /___/

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

NDA # _____ _____

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.)

YES /X/ 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.

   For the purposes of this section, studies comparing two products with the same ingredient(s) are considered to be bioavailability studies.

   (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:

Investigation #1, Study # _____

Investigation #2, Study # _____

Investigation #3, Study # _____

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.

a) For each investigation identified as "essential to the approval," has the investigation been relied on by the agency to demonstrate the effectiveness of a previously approved drug product? (If the investigation was relied on only to support the safety of a previously approved drug, answer "no.")

Investigation #1	YES /___/	NO /___/
Investigation #2	YES /___/	NO /___/
Investigation #3	YES /___/	NO /___/

If you have answered "yes" for one or more investigations, identify each such investigation and the NDA in which each was relied upon:

NDA # _____ Study #_____
NDA # _____ Study #_____
NDA # _____ Study #_____

b) For each investigation identified as "essential to the approval," does the investigation duplicate the results of another investigation that was relied on by the agency to support the effectiveness of a previously approved drug product?

Investigation #1	YES /___/	NO /___/
Investigation #2	YES /___/	NO /___/
Investigation #3	YES /___/	NO /___/

If you have answered "yes" for one or more investigations, identify the NDA in which a similar investigation was relied on:

NDA # _____ Study #_____
NDA # _____ Study #_____
NDA # _____ Study #_____

c) If the answers to 3(a) and 3(b) are no, identify each "new" investigation in the application or supplement that is essential to the approval (i.e., the investigations listed in #2(c), less any that are not "new"):

Investigation #_, Study # _____

Investigation #_, Study # _____

Investigation #_, Study # _____

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: _____

_____

_____

_____

[signature] 3/1/97

Signature Date

Title: Consumer Safety Officer

[signature] 3/25/97

Signature of Division Director Date

cc: Original NDA Division File HFD-85 Mary Ann Holovac

DRUG STUDIES IN PEDIATRIC PATIENTS
(To be completed for all NME's recommended for approval)

NDA # 20-678 Trade (generic) names Clinimix™ E Sulfite-Free (Amino Acid with Electrolytes in Dextrose with Calcium) Inj.

Check any of the following that apply and explain, as necessary, on the next page:

____ 1. A proposed claim in the draft labeling is directed toward a specific pediatric illness. The application contains adequate and well-controlled studies in pediatric patients to support that claim.

____ 2. The draft labeling includes pediatric dosing information that is not based on adequate and well-controlled studies in children. The application contains a request under 21 CFR 210.58 or 314.126(c) for waiver of the requirement at 21 CFR 201.57(f) for A&WC studies in children.

____ a. The application contains data showing that the course of the disease and the effects of the drug are sufficiently similar in adults and children to permit extrapolation of the data from adults to children. The waiver request should be granted and a statement to that effect is included in the action letter.

____ b. The information included in the application does not adequately support the waiver request. The request should not be granted and a statement to that effect is included in the action letter. (Complete #3 or #4 below as appropriate.)

____ 3. Pediatric studies (e.g., dose-finding, pharmacokinetic, adverse reaction, adequate and well-controlled for safety and efficacy) should be done after approval. The drug product has some potential for use in children, but there is no reason to expect early widespread pediatric use (because, for example, alternative drugs are available or the condition is uncommon in children).

____ a. The applicant has committed to doing such studies as will be required.

____ (1) Studies are ongoing.
____ (2) Protocols have been submitted and approved.
____ (3) Protocols have been submitted and are under review.
____ (4) If no protocol has been submitted, on the next page explain the status of discussions.

____ b. If the sponsor is not willing to do pediatric studies, attach copies of FDA's written request that such studies be done and of the sponsor's written response to that request.

____ 4. Pediatric studies do not need to be encouraged because the drug product has little potential for use in children.

X 5. If none of the above apply, explain.

Explain, as necessary, the foregoing items:

Dosing information includes range of doses per kg body weight. Sponsor should search literature for information relating to safety of this class of drug in children.

Signature of Preparer

3-14-97
Date

cc: Orig NDA
HFD-510 /Div File
NDA Action Package

2.75%, 4.25%, and 5% Travasol® II - sulfite-free (Amino Acid) with Electrolytes
in Dextrose with Calcium Injections
in Clinimix™ Dual Chamber Container
NDA 20-678

CERTIFICATION PER THE GENERIC DRUG ENFORCEMENT ACT OF 1992

In accordance with section 306(k) of the act (21 U.S.C. 335a(k)(1)), Baxter Healthcare Corporation wishes to certify that Baxter Healthcare Corporation did not and will not use in any capacity the services of any person debarred under subsections (a) or (b) [section 306(a) or (b)], in connection with this application.

In addition, in accordance with section 306(k) of the act (21 U.S.C. 335a(k) (2)), Baxter Healthcare Corporation wishes to certify that there are no convictions that occurred within 5 years of today's date, for which a person can be debarred, of the applicant and affiliated persons responsible for the development or submission of the application.

Marcia Marconi
Vice President
Regulatory Affairs

3/21/96
Date

MAR 2 1 1996

M E M O R A N D U M

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

DATE: March 10, 1997

FROM: Steve McCort, Project Manager

SUBJECT: DSI Audit for NDA 20-678 Travasol II

TO: Division file for NDA 20-678

The Division of Scientific Investigations (DSI) audit is not needed. There were no clinical studies submitted for this application.

Steve McCort, Project Manager
HFD-510

Gloria Troendle 3-12-97
Gloria Troendle, M.D.
Deputy Division Director

cc: Original NDA
HFD-510/DivFile

There was no group leader's memo for this application.

JUN 17 1996

MEDICAL REVIEW

NDA #: 20-678

SPONSOR: Baxter HealthCare Corporation

DRUG: Travasol II - sulfite-free (amino acid) with electrolytes in dextrose with calcium injection in a plastic dual-chamber container.

INDICATION: Source of calories and protein to be used in a total parenteral nutrition admixture

SUBMITTED: 3/21/96

DATE RECEIVED, CDER: 3/27/1996

DATE RECEIVED, M.O.: 4/1/1996

DATE OF REVIEW: 5/13/96

BACKGROUND: Baxter HealthCare currently markets Travasol with electrolytes under NDA 20-147. These products contain 5.5%, 8.5%, and 10% amino acid solutions. The 5.5% and 8.5% products do not contain the amino acid serine; the 10% product does contain serine. Dextrose is also included in these products in the following concentrations: 10%, 20%, 30% 40% and 50%. These products do not contain calcium. This NDA has no clinical data and therefore this review is limited to the labeling.

There are three changes proposed under NDA 20-678. First, the Sponsor is proposing to change the container to PL 2401, a multilayered plastic sheeting composed primarily of ethylene vinyl acetate. Second, the Sponsor is adding the amino acid serine to the 5.5% and 8.5% amino acid solutions. And third, the Company is adding 9 mEq/L of calcium chloride to the proposed products.

According to the Sponsor, the primary reason for the addition of calcium to the Travasol II solutions is to eliminate the need of the pharmacist to add the calcium to the parenteral admixture; thus reducing the chance of contamination and compounding errors.

Serine is synthesized endogenously from the amino acid glycine. Because of reports that serum glycine levels are elevated in some patient populations (neonates) after the infusion of currently marketed glycine-containing amino acid solutions the Sponsor is lowering the concentration of glycine in the proposed amino acid-containing products. Given these facts the Sponsor feels it is necessary to add serine to the proposed products.

LABELING REVIEW: The labels for these products are essentially identical to those of the approved products Travasol® - sulfite-free (amino acid) with electrolytes in dextrose injection. The changes made to these product do not merit making significant changes to the current labels.

I Package insert

A. Description: Acceptable.

B. Clinical Pharmacology: This section is concise and accurate. This section is acceptable.

C. Indications and Usage: It should be noted that the Sponsor has not changed the indications for the use of this product; this is appropriate. This section is acceptable.

D. Central Vein Administration: Acceptable.

E. Peripheral Vein Administration: Acceptable.

F. Contraindications: Acceptable.

G. Warnings: Acceptable.

H. Laboratory Tests: Acceptable.

I. Precautions: Acceptable.

J. Carcinogenesis, Mutagenesis, Impairment of Fertility: The Sponsor states that no studies have been conducted to evaluate the carcinogenic or mutagenic potential, or the effects on fertility of the proposed product.

J. Pregnancy: Acceptable.

K. Nursing Mothers: Acceptable.

L. Pediatric Use: Acceptable.

M. Adverse Reactions: Acceptable.

N. Dosage and Administration: Acceptable.

O. Central Vein Administration: Acceptable.

P. Peripheral Vein Administration: Acceptable.

II Immediate container label

Acceptable

III Over pouch labels

Acceptable

Recommendation: This Reviewer recommends approval of NDA 20-678.

6/14/02

Eric Colman, M.D.
Medical Officer

cc: NDA Arch
HFD-510 SMcCort/EColman/GTroendle

MEDICAL OFFICER'S ADDENDUM TO REVIEW OF NDA 20-678

DRUG: Clinimix E (amino acid) with electrolytes in dextrose with calcium injection in a plastic dual-chamber container.

DATE OF ADDENDUM: 3/24/97

The purpose of this addendum is to clarify the process by which the safety and efficacy of the products proposed in this NDA were evaluated. Baxter has various combinations of approved amino acid, dextrose, and electrolytes solutions (NDAs 18-931, 19-520, 20-147, and 20-173) that satisfy the efficacy and safety requirements for the amino acid, electrolyte, and dextrose components of NDA 20-678. The proposed products also contain 9 mEq/L of calcium. The Agency is relying on Abbott's approved NDAs 19-683 and 19-714 (amino acids with electrolytes and dextrose and 10 mEq/L of calcium) to support its safe and efficacy use. In addition, the Sponsor has submitted published literature which provide supplementary information on the safety and efficacy of calcium at concentrations of 9 mEq/L pre-admixture and 5 mEq/L post-admixture.

3/25/97

Eric Colman, M.D.

3/25/97

cc: NDA Arch
McCort/Colman/Troendle
HFD-510/div. file

There was no safety update review on this application since no clinical studies were submitted for this application.

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW

NDA: 20-678 SUBMISSION DATE: 03/21/96

BRAND NAME: TRAVASOL® II-sulfite-free (Amino Acid) with Electrolytes in Dextrose with Calcium Injections in Clinimix™ (PL 2401) Dual Chamber Container

GENERIC NAME: Amino Acids with Electrolytes in Dextrose with Calcium Injections in a single dose plastic container

REVIEWER: Carolyn D. Jones, Ph.D.

SPONSOR: Baxter Healthcare Corporation, IV Systems Division
Round Lake, IL

TYPE OF SUBMISSION: Submission of an Original NDA

I. SYNOPSIS:

The proposed drug product, Travasol® II sulfite-free (Amino Acid) with Electrolytes in Dextrose with Calcium Injections in Clinimix™ (PL 2401) Dual Chamber Container is a plastic container constructed of two (2) one-liter compartments separated by a peel seal for single dose administration. Prior to administration, the seal is opened and amino acid and dextrose solutions are mixed together.

The proposed product will provide many of the elements of total parenteral nutrition (i.e., amino acids, dextrose and electrolytes) and will allow for direct addition of fat emulsion. Various combinations of these components are available on the market. The combination of active components in the proposed Travasol® II sulfite-free (Amino Acids) with Electrolytes in Dextrose with Calcium Injections solution, is not the subject of an approved Baxter Healthcare Corporation NDA. More specifically, approved Baxter drug products do not contain the two active ingredients serine and calcium. Furthermore, the Dual Chamber PL 2401 Plastic Container has not been previously used as a container

for drug product solutions.

II. RECOMMENDATION:

The Office of Clinical Pharmacology and Biopharmaceutics has reviewed NDA 20-678 submitted on March 21, 1996 and it grants a waiver of the requirement to submit in vivo bioavailability data. The sponsor has formally requested a waiver of the requirement under 21 CFR 320.22 (b)(1), however the Office of Clinical Pharmacology and Biopharmaceutics will grant a waiver based on "...for good cause..." 21 CFR 320.22(e) which indicates a waiver can be granted if compatible with the protection of the public health.

note: The reviewing medical officer in the Division of Metabolism and Endocrine Products, indicates that 1) the addition of the compounds serine and calcium should have no effect on safety and efficacy and 2) no new clinical data will be required for submission.

Carolyn D Jones

5/7/96
Carolyn D. Jones, Ph.D.
Division of Pharmaceutical Evaluation II

RD initialed by Hae Young Ahn, Ph.D., Team leader 5/8/96

FT initialed by Hae Young Ahn, Ph.D., Team leader 5/09/96

cc: NDA 20-678, HFD-510 (Colman, McCort), HFD-340 (Viswanathan), HFD-860 (Malinowski), HFD-870 (Ahn, Jones and M. Chen), HFD-880 (Fleischer), HFD-870 (Chron, Drug, Reviewer), HFD-205 (FOI).

A statistical review was not needed for this application.

AUG 14 1996

NDA 20-678 August 14, 1996

Sponsor: Baxter Healthcare Corp.; Round Lake, IL 60073

Date Submitted: March 21, 1996 **Date Received:** March 27, 1996

PHARMACOLOGY AND TOXICOLOGY REVIEW

Original NDA Submission(March 27, 1996)

DRUG: Travasol® II-sulfite-free (Amino Acid) with Electrolytes in Dextrose with Calcium Injections in Clinimix™ (PL2401) Dual Chamber Container.
Dosage formulation: 2000mL for intravenous administration. Strengths: Amino acids: 2.75%, 4.25%, 5% Dextrose: 5%, 10%, 15%, 20%, 25%, 35%.

CATEGORY: Large Volume Parenteral

INDICATION: Caloric component in a parenteral nutrition regimen and as a protein source for off-setting nitrogen loss.

RELATED NDA'S: NDA 20-147, 18-931, 17-493, 17-521 Abbott NDA19-714

INTRODUCTION

The Clinimix™ Dual Chamber is a new plastic container constructed of two one-liter compartments separated by a peel seal. The seal is opened and amino acid and dextrose solutions are mixed together prior to administration. The proposed configurations include: 5.5, 8.5 or 10 % Travasol® II-sulfite-free (Amino Acid) with Electrolytes in the lower chamber and 10, 20, 30, 40, 50, 60 or 70% Dextrose with Calcium in the upper chamber. Mixing the two chambers provides 2L of the permutations of Amino acids at 2.75%, 4.25%, or 5% combined with Dextrose at 5%, 10%, 15%, 20%, 25%, or 35% final concentrations. This product represents an extension of current product lines. These formulations do not contain any new drug substances. Each component is covered under approved NDA's (NDA 20-147 18-931, 17-493, 17-521 Abbott NDA19-714). The PL2401 plastic film is compatible with lipid emulsions and is offered as a means to administer lipid simultaneously with the rest of the amino acid, dextrose and electrolyte components. Lipid emulsions can be added up to 1 L to the bag after seal activation.

The Dual Chamber PL2401 Plastic Container has not been used previously as a container for drug product submissions. It is the container/closure that is the subject of this submission. Specifically, the following components have been tested:

- PL2401 film
- PL2400 port tubes
- B5603AB hot stamp materials

USP<661>, PHYSICOCHEMICAL TESTS FOR CONTAINER COMPONENTS

Each of the test components were analyzed by the sponsor for compliance with USP<661>, Physicochemical Tests-Plastics. Aqueous extracts of the samples were prepared at 70°C for 24 h using a material surface to volume ratio of 6 cm^2/ml. Results of the tests are summarized in the following table. Acceptable limits are provided in the heading for each test. A GLP statement was provided.

Table 1: Summary of USP Physicochemical Testing

MATERIAL	BUFFERING CAPACITY (limit < 10 mL)	HEAVY METALS (limit < 1ppm)	NON-VOLATILE RESIDUE (limit < 15 mg)	RESIDUE ON IGNITION (limit < 5mg)
PL2401	0.14	<1	0.6	not conducted
PL2400 port tubes	0.039	<1	0.0001	not conducted
B5603AB hot stamp	0.03	<1	0.0000	not conducted

USP BIOLOGICAL TESTS

Test components were examined by the sponsor for compliance with USP biological tests for direct contact and agar diffusion *in vitro*, and systemic, implantation and intracutaneous toxicity *in vivo*. Test methods are briefly outlined below. Summary of results is presented in Table 2. A GLP statement was provided.

USP<87>, BIOLOGICAL REACTIVITY TEST, *IN VITRO* (CYTOTOXICITY):
Each of the test components were tested for compliance with USP<87>, Biological Reactivity Tests, *In Vitro* for cytotoxicity to mouse fibroblasts. Direct contact and agar diffusion cytotoxicity were determined. 1 cm^2 portions of materials were added to growing cell monolayers. Following 24 h incubation, cell morphology and size of the area of cellular damage relative to test article size were observed. Responses are rated from 0 (no adverse effect) to 4+ (severe toxicity).

USP<88>, BIOLOGICAL REACTIVITY TEST, *IN VIVO*:
Systemic and intracutaneous injection assays were used to evaluate the systemic and local toxicity potential of extractables able to diffuse from the test components. Materials were extracted in saline, saline-alcohol (5% solution), cottonseed oil and polyethylene glycol 400 (PEG) for one hour at 121°C. Systemic injection was performed in mice; intracutaneous assay was performed in rabbits. The implantation method measures the *in vivo* cellular response to material extractables when test materials are implanted in the intravertebral muscles of New Zealand rabbits. USP negative control strips are implanted in the contralateral muscle of each rabbit. After 7 days, the amount of tissue reaction around the imbedded implants was measured and graded.

Table 2: Summary of USP Biological Tests[a]

MATERIAL	DIRECT CONTACT	AGAR DIFFUSION	SYSTEMIC TOXICITY[b]	INTRACUTANEOUS[b]	IMPLANTATION
PL2401	P	P	P	P	NAR
PL2400 port tubes	P	P	P	P	NAR
B5000AB hot stamp	P	P	P	P	NAR

a: P indicates passed; NAR indicated no apparent reaction
b: passed for saline, saline-alcohol, cottonseed oil and PEG extracts

30-DAY IV TOXICITY STUDY OF PL2401 AND PL2400 EXTRACTS IN RATS

PURPOSE: To evaluate the potential toxicity of PBS extracts ("leachables") of containers made of PL2401 and PL2400 materials.

EXPERIMENTAL DESIGN: Daily intravenous infusion in 6 rats/sex/group for 30 days of Phosphate buffered saline (PBS) or 1X or 10X PBS extracts of Quick Mix™ containers. Volume of administration was 40 ml/kg at a rate of 1 ml/min. Extracts were prepared by autoclaving 1x5 cm strips of the containers in PBS for 1 h at 121°C such that extracts equivalent to one bag/liter (1X) or 10 bags/liter (10X) were prepared. Quality assurance and GLP statements were provided. Report dated 9/16/93. Study period 4-9/93. Study performed by sponsor.

RESULTS: No group differences were evident for survival, body weight, organ weight, ophthalmology, urinalysis, hematology, gross pathology or histopathology. Slight elevation of total bilirubin concentration was noted for high dose males, but did not correlate with any other findings, were within the range of historical controls and are not likely to be of biological significance.

CONCLUSION: Under the conditions of the study, no systemic toxicity was demonstrated for extracts of containers made of PL2401 and PL2400 materials.

IN VITRO HEMOLYSIS

In vitro hemolysis testing was performed by sponsor according to standard practice for assessment of hemolytic properties of materials (ASTM 756-93). No difference in hemolytic indices of the container film and the vehicle or reference controls were observed. These results indicate that PL2401 is blood compatible under the conditions of the test. GLP statement was provided.

BACTERIAL MUTAGENICITY STUDY ("AMES" TEST)

PURPOSE: To evaluate the potential for saline extracts of PL2401 to induce reverse mutations at the histidine locus of *S.typhimurium* tester strains in the absence and presence of metabolic activation (S9). GLP statement was provided. Study was performed by for the sponsor. Study dates: 7-8/93.

EXPERIMENTAL DESIGN: Standard plate incorporation assay with 48 h incubation at 37°C prior to scoring.
Tester Strains: TA98, TA100, TA1535, TA1537 and TA1538. Each phenotype (*rfa* and pKM101) was appropriately confirmed.
Metabolic Activation System: Standard microsomal preparation from Arochlor-induced rat liver (S9).
Test article: Saline extract of PL2401 tested at 10 and 200 µl/plate. A ratio of 6cm^2 test article surface area/ml of saline was autoclaved at 121°C for 1h.
Vehicle Control: 200 µl/plate. This represents the maximum volume of extract that can be tested without modification to the test protocol.
Positive Controls: 2-aminoanthracene at 2.5 µg/plate was used in the presence of S9 mix for all strains. In the absence of metabolic activation, the following positive controls were used:
TA98, TA1538: 2-nitrofluorene, 1.0 µg/plate
TA100, TA1535: sodium azide, 2.0 µg/plate
TA1537: ICR-191, 2.0 µg/plate

CONCLUSION: Under the conditions of this study, the saline extract of PL2401 did not cause an increase in the number of histidine revertants in any of the tester strains in either the presence or absence of metabolic activation system.

MAGNUSSON AND KLIGMAN DERMAL SENSITIZATION STUDY IN GUINEA PIGS

PURPOSE: To evaluate the potential for saline extracts of PL2401 to induce dermal sensitization in male guinea pigs using the Magnusson and Kligman procedure. GLP statement was provided. Study was performed by for the sponsor. Study dates: 7-8/93.

EXPERIMENTAL DESIGN: 10 animals were used in the saline extract group and the positive control (sulfathiazole) groups. 5 animals were used in the saline blank and naive positive control groups. Saline extract was prepared by autoclaving 120 cm^2 total surface area of test material in 20 ml of saline for 1 h at 121°C. The induction period consisted of a series of 6 intradermal injections of extract or saline blank on day 1 and a 48 h occlusive, topical application of saline blank or test extract on day 8. Induction sites were treated with 10% sodium lauryl sulfate in petrolatum 24 h prior to the topical application on day 8. A 24 h occlusive, topical challenge application was performed on day 22. Challenge reactions were evaluated at 24, 48 and 72 h after patch removal.

RESULTS: None of the test, saline blank or naive positive control animals exhibited dermal reactions to the challenge application. All 10 positive control animals exhibited sensitization responses when challenged with 10% w/w sulfathiazole in petrolatum.

CONCLUSION: The saline extract of PL2401 was not a skin sensitizer under the conditions of the guinea pig assay.

SUMMARY OF PRECLINICAL DATA

1. Test components of the PL2401 container system met the requirements of chemical tests in USP<661> for Physicochemical Testing.

2. Test components of the PL2401 container system met the requirements of biological tests in USP<87>, biological reactivity test *in vitro* (cytotoxicity) and USP<88>, biological reactivity test *in vivo*.

3. PL2401 was blood compatible under the conditions of the *in vitro* hemolysis test.

4. There was no indication of systemic toxicity for extracts made of PL2401 and PL2400 materials under the conditions of the 30-day toxicity study in rats.

5. Saline extracts of PL2401 material were not mutagenic in the bacterial mutagenicity study.

6. Saline extracts of PL2401 were not sensitizing in the Magnusson and Kligman dermal sensitization assay in guinea pigs.

7. A literature review of the toxicity of identified individual extractives indicated that concentrations and potential human exposure of each extractive is low and that toxic potential from each individual extractable is likely to be negligible.

CONCLUSION

The extractables of the components of the Clinimix™Dual Chamber did not exhibit any toxic potential in the studies provided by the sponsor. No changes in labeling were necessary. Pharmacology recommends approval of NDA 20-678.

Ronald W Steigerwalt 8/14/96

Ronald W. Steigerwalt, Ph.D.

cc: NDA Arch
HFD510
HFD510/Steigerwalt/McCort

Consult #729 (HFD-510)

TRAVASOL II amino acid (sulfite-free) in dextrose intravenous injection

The Committee did not evaluate the proprietary name TRAVASOL since it is already in use on marketed products. The Committee felt that using "II" was inappropriate for distinguishing this product from companion products that will remain on the market under the TRAVASOL name. Numbers are discouraged in proprietary names since the practice may lead to confusing the name of the product with the number of dosage units to be dispensed.

The Committee finds the name unacceptable.

D Uberuaga 3/5/97, Chair
CDER Labeling and Nomenclature Committee

FEB 12 1997

DIVISION OF METABOLISM & ENDOCRINE DRUG PRODUCTS HFD-510
Review of Chemistry, Manufacturing, & Controls

NDA: 20-678

CHEMISTRY REVIEW

REVIEW COMPLETED: 2/12/97

SUBMISSION TYPE	DOCUMENT DATE	CDER DATE	ASSIGNED DATE
ORIGINAL	21 Mar 96	29 Mar 96	12 Apr 96

NAME & ADDRESS OF APPLICANT: BAXTER HEALTHCARE CORP
Route 120 & Wilson Rd.
Round Lake, Il 60073-0490

DRUG PRODUCT NAME:

Nonproprietary: Travasol II - sulfite free (Amino Acid) with Electrolytes in Dextrose with Calcium Injections in Clinimix (PL 2401) Dual Chamber Container

PHARMACOLOGICAL CATEGORY/INDICATION: Caloric component in a parenteral nutrition regimen & as a protein source for off-setting nitrogen loss.

DOSAGE FORM: Sterile I. V. Injection.

STRENGTHS: 2.75%, 4.25%, 5% Amino Acids; 5%, 10%, 15%, 20%, 25%, 35% Dextrose (after mixing).

ROUTE OF ADMINISTRATION: Intravenous.

DISPENSED: Rx

CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:
N/A

SUPPORTING DOCUMENTS:

REMARKS/COMMENTS:

The Chemistry Review #1 completed on 1/14/97 indicates that from a chemistry standpoint, the NDA can be approved, pending (1) satisfactory consult reviews for microbiology and toxicology of the new plastics, (2) a satisfactory review for the Environmental Assessment section, and (3) an acceptable CGMP inspection on all facilities. Both microbiology and pharmacology consult reviews have now been completed. The response to microbiolgy deficiencies outlined in the Consult Review #1 dated 8/9/97 by Dr. Sweeney of HFD-160 has been provided by Baxter in the faxed copies (to be followed by a formal submission) on 2/7/97 and the NDA was recommended for approval based on sterility assurance (see Microbiology Consult Review #1 and #2 dated 2/10/97). In the Pharmacology Consult Review, Dr. Steigerwalt also found that the

toxicity studies for extractables performed by the applicant is satisfactory(see Pharmacology and Toxicology Review dated 8/14/97). The cGMP inspection has been completed by the Office of Completed and all facilities are found acceptable (see attached EER dated 1/9/97). However, due to missing information, the EA review is still pending. Baxter indicates that those missing information will be send to the agency shortly.

CONCLUSIONS AND/OR RECOMMENDATIONS:

From chemistry standpoint, the NDA can be approved, pending a satisfactory EA review and the concurrence of FONSI by the CDER EA Review Team.

Duu-Gong Wu, Ph.D
Team Leader II, ONDC II

cc:
Orig. NDA 20-678
HFD-510/Division File
HFD-510/DG Wu
HFD-510/CSO/McCort
Init. by:

File Name: 20678ND2

ENVIRONMENTAL ASSESSMENT

AND

FINDING OF NO SIGNIFICANT IMPACT

FOR

TRAVASOL II

AMINO ACID WITH ELECTROLYTES IN DEXTROSE WITH CALCIUM INJECTION IN CLINIMIX (PL 2401) DUAL CHAMBER CONTAINER

NDA 20-678

FOOD AND DRUG ADMINISTRATION

CENTER FOR DRUG EVALUATION AND RESEARCH

DIVISION OF METABOLISM & ENDOCRINE DRUG PRODUCTS
HFD-510

ENVIRONMENTAL ASSESSMENT

1. Date:

Review: #1
EA Date: 3/21/96; Amendments, 2/7/97 and 2/13/97
CSO: Steve McCort

The entire EA section submitted in the original NDA was stamped with "Baxter Confidential". Also, the environmental certification for the drug substances manufacturer, Ajinomoto Co., was not provided and the information for Baxter's drug product manufacturing facility, which is considered as non-confidential, was included in the confidential section. These deficiencies were communicated to Baxter prior to completion of this review. Firm has amended the EA section to correct these deficiencies in the amendments dated 2/7/97 and 2/13/97 (faxed copies to be followed by formal submissions). The amendment dated 2/7/97 contain revised EA section without "Baxter Confidential" footnote as also pointed out in the amendment dated 2/13/97.

Adequate.

2/3. Name/Address of applicant:

Baxter Healthcare Corp.
Route 120 & Wilson Rd.
Round Lake, IL 60073

Adequate.

4. Description of proposed action:

a. Requested Approval:

Baxter Healthcare Corporation is requesting approval of an NDA for the manufacture of Travasol II -sulfite-free (Amino Acid) with Electrolytes in Dextrose with Calcium Injections in Clinimix Dual Chamber Container PL 2401 including sterilization, testing, packaging, & marketing at Jayuya, Puerto Rico Facility in Jayuya, Puerto Rico. Travasol will be marketed by Baxter Healthcare Corp. worldwide.

Adequate.

b. Need for action:

Travasol II with Electrolytes is indicated as a caloric component in a parenteral nutrition regimen & as the protein (nitrogen) source for offsetting nitrogen loss or for treatment of negative nitrogen balance in patients where the alimentary tract cannot or should not be used.

Adequate.

c. Locations of Production:

The address of the Baxter facility where the manufacturing & packaging of the finished drug product will be performed was originally given in Confidential Addendum I of the original NDA submission. However, based on the comment from CDER Environmental Assessment Review Team that was communicated to the firm, the manufacturing site is now included in the non-confidential section of the revised EA section submitted as an amendment dated 2/7/97(faxed copies to be followed by a formal submission). **The manufacturing facility is located at Road 144, KM 20.6, Jayuya, Puerto Rico**

The amino acids are manufactured by numerous firms located in Japan (Ajinomoto, Kyowa Hakko). Ajinomoto also manufactures amino acids in the United States in Clinton, North Carolina. Ajinomoto acquires individual amino acids from numerous secondary manufacturers; Ajinomoto then purifies these amino acids at several different locations. Kyowa Hakko located in Tokyo, Japan also manufactures some of the amino acids, Kyowa Hakko also purchases individual amino acids from numerous secondary manufactures; Kyowa Hakko then purifies these amino acids at several different locations. Dextrose is manufactured in France by Roquette Freres, 62136 Lestrem, France & in the U.S. by Roquette America, 1003 South Fifth St. Keokuk, IA., & by Corn Products, 6400 Archer Rd. Summit-Argo, IL. The electrolytes are manufactured in the U.S., Canada, & Germany. **A certification dated 1/27/97 from Ajinomoto Co. indicating that their facilities in Japan are operated in accordance with Japanese environmental laws (see attached).**

Adequate.

d. Locations of product use & disposal:

The drug product will be used & disposed of primarily in hospitals & related institutions located in both urban & rural environments throughout the United States, Puerto Rico, & the rest of the world. The expected route of product disposal will be in accordance with the hospital's handling procedures for medical waste. The disposal sites used by the hospitals & clinics are located throughout the United States & the world. The plastic container is usually deposited in land-fills, but may be incinerated at the individual facility's incinerator.

The amino acid-electrolyte-dextrose solution will be discharged to the regional wastewater treatment plant. Amino acids, electrolytes, & dextrose pose no environmental hazard when discharged as above.

In the amendment dated 2/13/97, the information regarding liquid and solid wastes disposal sites are provided. The liquid wastes are discharged into the Jayuya Regional Wastewater Treatment Plant(Puerto Rico Aqueduct and Sewer Authority permit number PR 0020541). The solid wastes were sent to a landfill at Jayuya Municipal Lanfill(Permit numbar RSM-38) or the BFI pronce Landfill (Permit number PRD980594709). **Adequate.**

5. **Identification of chemical substances that are the subject of the proposed action:**

All the active and inactive ingredients are included in Table 1.

The proposed products are stable solutions of the same ingredients at the same concentration as those which have been available for many years packaged in glass & plastic containers. This submission is mainly for the use of a new plastic to serve as the container for the finished drug product. The drug substances consist of 15 amino acids; alanine, arginine, glycine, histidine, isoleucine, leucine, lysine HCl, methionine, phenylalanine, proline, serine, threonine, tryptophan, tyrosine, & valine. The four electrolytes are Sodium Acetate Trihydrate, USP, Dibasic Potassium Phosphate, USP, Magnesium Chloride Hexahydrate, USP & Calcium Chloride Dihydrate, USP. Dextrose is also one of the

drug products. Molecular formula, molecular weight, & chemical name are given for the drug substances. MSDSs are provided for the various chemicals which make up the plastic container/closure system, & for the container system itself.

MSDS for the drug product is provided in the amendment dated 2/7/97 (see attached Attachment I, pages 12-18).

Adequate.

6. **Introduction of substances into the environment:** For drug product manufacturing facilities.

The substances emitted into the atmosphere during the manufacture of the drug product in Puerto Rico are identified in Confidential Addendum # 2.

Exhaust air from manufacturing and packaging areas will be collected by HEPA filtration. Firm indicated that approval of this NDA will not impact the facility's ability to comply with applicable

Organic & inorganic liquid emissions discharged to the aquatic environment are identified in Confidential Addendum # 2. The wastewater is discharged in conformity with the applicable environmental limits. Off-specification liquid will be sent to the wastewater treatment plant.

Solid waste is collected in dust residues. These wastes will be recycled as appropriate. Non-hazardous waste will be land filled. Off-specification plastic material or material returned to the plant will be sent to landfill.

Adequate.

7. **Fate of emitted substances in the environment:**

Baxter states that the emission controls exercised during the drug product manufacturing limit the amounts of drug substance that escapes into the environment. Use of the product will not alter significantly its concentration or distribution since the plastic materials are sent to landfills. The amino acids & electrolytes are abundant in nature & are not toxic. They have been manufactured for many years with no

environmental hazard. They will not adversely effect wastewater, air, or soil.

Adequate.

8. **Environmental effects of released substances:**

Substances emitted consist of amino acids, electrolytes, & plastic material. Solutions of amino acids & electrolytes are non-toxic. Amino acids & electrolytes are abundant in nature. Amino acids and electrolytes are present in all plants & animals, therefore, the amounts that will be added are insignificant when compared to the amounts already present. The plastic materials are inert & pose no environmental hazard. Dextrose is present in many plants & poses no hazards.

Adequate.

9. **Use of resources and energy:**

The raw materials Baxter uses to produce the proposed product are plentiful. The energy committed to drug manufacture is not excessive & is minimal when compared to other energy uses. The firm predicts that energy used will be no greater than it now uses.

Adequate.

10. **Mitigation Measures:**

Measures which Baxter has taken to prevent adverse environmental effects are described. MSDSs for the plastics materials have been provided.

Adequate.

11. **Alternatives to the proposed action:**

Alternatives have not been developed due to a lack of adverse environmental effects.

Adequate.

12. **List of preparers:**

Baxter provides a list of the preparers of the environmental assessment documentation and their

qualifications in the confidential Addendum 3 portion of the EA.

Adequate.

13. **Certification:**

Baxter certifies this document is true, accurate, and complete to the best of the knowledge of Baxter Healthcare Corporation.

Adequate.

14. **References:**

References to environmental permits & regulations governing the manufacture of the drug product are described in the confidential portion of the EA.

Adequate.

15. **Appendices:**

Information cited in the environmental assessment are provided in the confidential attachments.

Reviewer's Conclusion & Recommendation:

The Environmental Assessment is satisfactory & a FONSI can be prepared for the NDA.

Signature for OH Riggleman (notin
O. H. Riggleman
Review Chemist 2/14/97

cc:
Orig. NDA 20-678
HFD-510/Division File
HFD-510/Riggleman/DG Wu
HFD-510/McCort
R/D Init. by: DG Wu, Ph.D.

Attachment: Revised EA section in the 2/7/97 amendment (Attachment 8), MSDS (Attachment I)

Material Safety Data Sheet

1. Chemical Product and Company Identification

Product name: Clinimix™ E (sulfite-free Amino Acid) with Electrolytes in Dextrose with Calcium) Injections in Clarity™ Dual Chamber Container

Product codes: 2B7713, 2B7714, 2B7715, 2B7716, 2B7717, 2B7718, 2B7719, 2B7720, 2B7721, 2B7722, 2B7723, 2B7724

Description: Sterile solution for intravenous infusion

Product use: Intravenous infusion solution for use as a supply of calories, electrolytes and source material for protein synthesis

User code/identification:

_____

_____

_____

Manufacturer:
Baxter Healthcare Corporation
One Baxter Parkway
Deerfield, IL 60015 USA

Telephone: 1-800-422-2751 (8-5 pm; M-F)

For emergency information contact:

1-800-228-5635 (USA)

612-221-3096 (outside USA)

2. Composition/Information on Ingredients

Component (synonym)	CAS No.	Percentage* (%, w/v)	Exposure Limit**
Water	7732-18-5	> 59	none
Dextrose Hydrous, USP	5996-10-1	5 - 35.0	none
alanine	56-41-7	0.57 - 1.04	none
arginine	74-79-3	0.32 - 0.58	none
sodium chloride, USP	7647-14-5	0.06 - 0.11	none
glycine	56-40-6	0.28 - 0.52	none
leucine	61-90-5	0.20 - 0.37	none
sodium acetate trihydrate, USP	6131-90-4	0.22 - 0.34	none
proline	147-85-3	0.19 - 0.34	none
isoleucine	73-32-5	0.17 - 0.30	none
valine	72-18-4	0.16 - 0.29	none
lysine	56-87-1	0.16 - 0.29	none
phenylalanine	63-91-2	0.15 - 0.28	none
dibasic potassium phosphate, USP	7758-11-4	0.26	none
serine	56-45-1	0.14 - 0.25	none
histidine	71-00-1	0.13 - 0.24	none
threonine	72-19-5	0.12 - 0.21	none
methionine	63-68-3	0.11 - 0.20	none
tryptophan	73-22-3	0.05 - 0.09	none
magnesium chloride hexahydrate, USP	7791-18-6	0.05	none
calcium chloride dihydrate, USP	10035-04-8	0.03	none
tyrosine	60-18-4	0.01 - 0.02	none

* Range of component concentrations. See package insert in shipping carton for component concentration for specific product configuration.

** Limit established by ACGIH and NIOSH.

3. Hazards Identification

Emergency Overview:

Nonvolatile, nonflammable mixture in water packaged in a dual-chambered container with one liter compartments (approximately 8 cups when chambers have been combined).

Potential Health Effects:

Allergic reactions: Not known to occur.
Eye contact: Nonirritant. No cumulative effects reported.
Ingestion: Not hazardous by ingestion in small quantities
Inhalation: Inhalation not likely under normal use conditions. Aspiration hazard like that of water.
Skin absorption: Skin absorption unlikely under normal conditions of use.
Skin contact: Nonirritant.
Carcinogen status:
OSHA: Not listed.
NTP: Not listed
IARC:Not listed
Medical conditions aggravated by exposure: Not applicable from accidental exposure.

4. First Aid Measures

Eye contact: Rinse with water or normal saline.
Ingestion: Not harmful if accidentally ingested in small quantities.
Inhalation: Nonvolatile liquid. Treat for aspiration of water.
Skin contact: Nonhazardous. Wash affected area with soap or mild detergent and water. Remove and launder or clean contaminated clothing and shoes.

5. Fire Fighting Measures

Nonflammable water solution.

6. Accidental Release Measures

This product is a nonhazardous waste when spilled or disposed of, as defined in Resource Conservation Recovery Act (RCRA) regulations (40 CFR 261).

7. Handling and Storage

Store under the following conditions:
Store at room temperature (25°C/77°F).
Avoid excessive heat; protect from freezing.
Use within the expiration date on package.

8. Exposure Controls/Personal Protection

NOTE: Pharmacy personnel should use aseptic technique to prevent contamination of sterile solution.
Clothing: No protective clothing is required under normal conditions of use.
Eye protection: No eye protection is required under normal conditions of use.
Gloves: No protective gloves are required under normal conditions of use.
Respiratory Protection: No respiratory protection needed under normal use conditions.
Skin Protection: No skin protection needed under normal use conditions.
Ventilation: No additional ventilation required under normal conditions of use.
Exposure guidelines or limits: No occupational exposure limits established by ACGIH or NIOSH.

9. Physical and Chemical Properties

Appearance:	Colorless to slightly yellow liquid
Unit Size	2000 mL (approximately 8 cups when chambers combined)
Boiling point:	Not established
Freezing point:	Not established
Vapor pressure:	Not established
Specific gravity:	Not established
Solubility in water:	soluble
pH:	6.0 (4.5 - 7.0)*
osmolarity**:	665 - 2405 mOsmol/L*

* after contents of chambers are combined
** see package insert in shipping carton for osmolarity data for specific product configurations

10. Stability and Reactivity

This product is stable through the expiration date listed on the package using recommended storage conditions (see Section 7).
Hazardous polymerization: Data not available
Incompatibilities (specific materials to avoid): not established

11. Toxicological Information

See patient package insert in shipping carton for complete information regarding adverse and overdose effects in humans: The following side/adverse effects have been selected on the basis of their potential clinical significance and are not necessarily inclusive.

Get medical attention	May require medical attention if bothersome
Diuresis, hyperglycemia, glycosuria, and/or hyperosmolar coma.	Prolonged discomfort or pain at sites of use.

12. Ecological Information

Based on chemical composition, individual units of this product can be treated in an acclimatized biological waste treatment plant system. Consult your local POTW or wastewater treatment plant supervisor for more information.
Environmental impact rating (0-4): no data
Acute aquatic toxicity: no data
Degradability: no data
Log bioconcentrations factor: data not available
Log octanol/water partition coefficient: approx. that of water

13. Disposal Considerations

Solution: Most intravenous solutions can be disposed of down the drain with approval from the local, publicly owned treatment works, based on the data provided in section 12. Admixtures with additives may require additional treatment prior to disposal. Always consult the publicly owned treatment system in your area or your sewage treatment plant operator prior to disposing of this, or any other materials, in the local drains. This product is not considered a hazardous waste per 40CFR 261.20-24., however, please be advised that state and local regulations for waste disposal may be more restrictive or otherwise different from Federal regulations.
Plastic container: May be disposed as regular waste unless contaminated with infectious materials, blood-borne pathogens or cytotoxic (cancer) drugs.

14. Transport Information

This product cannot be shipped with hazardous materials.
DOT Hazardous Material regulations do not apply to this product.

Transportation and Hazardous Materials Description:

DOT shipping name:	not applicable
DOT Hazard Class:	not applicable
UN/NA Number:	not applicable
Product RQ (lbs):	not applicable
DOT label:	not applicable
DOT Placard	not applicable
Freight class bulk	not applicable
Freight class package:	not applicable
Product label:	not applicable

15. Regulatory Information

Federal Regulatory Information:

CERCLA Section 103 (40 CFR 302.4), reportable quantity	not applicable
CERCLA/Superfund (40 CFR 117.302)	not applicable
OSHA Process Safety (29 CFR 1910.119)	not applicable
RCRA Status: If discarded in its purchased form, this product would not be a hazardous waste either by listing or by characteristic. However, under RCRA, it is the responsibility of the product user to determine at the time of disposal, whether a material containing the product or derived from the product should be classified as a hazardous waste. (40 CFR 261.20-24)	not applicable
SARA Section 302 (40 CFR 355.30), extremely hazardous substances	not applicable
SARA Section 304 (40 CFR 355.40)	not applicable
SARA Hazard categories, Title III sections 311 and 312 (40 CFR 370.21)	
Acute hazard	No
Chronic hazard	No
Fire hazard	No
Reactivity hazard	No
Sudden release hazard	No
SARA Section 313 (40 CFR 370.65), toxic chemicals	not applicable
TSCA status	mixture not in inventory

State Regulatory Information:

California Proposition 65	mixture not on list
Other states:	May be more restrictive or otherwise different.

16. Other Information

Patient Package Inserts, which describe Clinimix™ E (sulfite-free Amino Acid with Electrolytes in Dextrose with Calcium) Injections in Clarity™ Dual Chamber Container are provided with each shipping carton of product.

Abbreviations:
CERCLA: Comprehensive Environmental Response, Compensation and Liability Act. Administered by EPA.
OSHA: Occupational Safety and Health Administration, US Department of Labor which regulates workplace conditions.
RCRA: Resource Conservation and Recovery Act. Administered by EPA.
SARA: Superfund Amendments and Reauthorization Act of 1986. Title III is also known as the Emergency Planning and Community Right-to-Know Act. Administered by EPA.
TSCA: Toxic Substances Control Act.
ACGIH: American Conference of Governmental Industrial Hygienists.
NIOSH: National Institute for Occupational Safety and Health.
DOT: Department of Transportation.

To the best of our knowledge, the information contained herein is accurate. However, neither Baxter Healthcare Corporation nor any of its divisions or subsidiaries assumes any legal responsibility for use or reliance upon these data. Final determination of suitability of any material is the sole responsibility of the user. All materials may present unknown hazards and should be used with caution. Although certain hazards are described herein, we cannot guarantee that these are the only hazards which exist.

Baxter Healthcare Corporation, Clintec Nutrition Division, Deerfield, Illinois 60015 Tel: 1-800-422-2751

ITEM 3

IV. ENVIRONMENTAL ASSESSMENT

1. Date

March 21, 1996

2. Name of applicant

Baxter Healthcare Corporation

3. Address

I.V. Systems Division (Headquarters): Route 120 and Wilson Rd.
Round Lake, IL 600[illegible]

Manufacturing Facility: Road 144, KM 20.6
Jayuya, Puerto Rico 00664

4. Description of the proposed action

The applicant requests approval to manufacture and market Travasol II® - sulfite-free (Amino Acid) with Electrolytes in Dextrose with Calcium Injections in new Clinimix™, dual-chambered, single-dose plastic containers. The body of the containers are constructed of a new, multilayered plastic film designated as PL 2401. The two chambers of the dual-chambered configuration are separated by a peel seal. The upper chamber is filled with 1 L of dextrose (10% - 70%) with 9 mEq/L calcium; the lower chamber is filled with 1 L of Travasol® II (5.5%, 8.5% and10%) with electrolytes. Prior to administration, the seal is opened and the amino acid and dextrose solutions are mixed together. The total capacity of the container is 3 L to allow for the addition of up to 1 L of lipid emulsion after seal activation. The following configurations are proposed:

		Dextrose with 9 mEq/L Calcium (upper chamber)						
		10%	**20%**	**30%**	**40%**	**50%**	**60%**	**70%**
Travasol® II (Amino Acid) with electrolytes (lower chamber)	**5.5%**	X	X	X	X	X	X	X
	8.5%	X	X	X	X	X	X	X
	10%	X	X	X	X	X	X	X

ITEM 3.IV.4.

Except for the inclusion of calcium (as calcium chloride) in the dextrose chamber, the proposed products are stable solutions of the same ingredients in the same concentrations as those that have been available for many years packaged in glass and plastic containers including the current Quick Mix® dual-chambered, PVC container. Calcium is an essential nutrient typically added to TPN admixtures by pharmacists in concentrations similar to that contained in the proposed product. Baxter amino acid solutions packaged in glass are covered by NDA 17-493, 5.5%, 8.5% & 10% Travasol® in PL 146®. Baxter's amino acid and dextrose solutions packaged in the current Quick Mix™ PVC container system are covered by NDA 19-520, Travasol® (5.5% & 8.5%) in Dextrose (10%, 20%, 30%, 40%, 50%) Injection in PL 146® (Quick Mix™) and NDA 20-147, 2.75% and 4.25% Travasol® (Amino Acid) with Electrolytes and Dextrose Injection in Quick Mix™ Dual Chamber PL 146® Plastic Container.

Travasol II® with Electrolytes in Dextrose Injection with Calcium are sterile, nonpyrogenic, hypertonic solutions that are indicated as a caloric component in a parenteral nutrition regimen and as the protein (nitrogen) source for offsetting nitrogen loss or for 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 excessive burns. The product is steam sterilized. The new PL 2401 container system used to package the solution is the subject of the submission. The request for approval is submitted as a new drug application.

The proposed products will be used and disposed of primarily within hospitals and related institutions located within both urban and rural environments throughout the United States and Puerto Rico.

The manufacturing facility is described in **Confidential Addendum 1**. The facility is situated in a rural, mountainous area. The facility is in a residential and light industry community. Annual rainfall is approximately 72.8 inches and the average ambient temperature is 80°F. There are no surface water bodies in the vicinity of the area. Due to the geologic conditions of the Zone, the drainage is mainly underground.

Process and sanitary waste from the facility is discharged to a regional wastewater treatment plant. The type of environment present at this location specific to the drug product manufacturing and packaging operations is described in **Confidential Addendum 1**.

ITEM 3.IV.

5. Identification of chemical substances that are the subject of the proposed action

a. Drug Product Solution Components

Travasol II® - sulfite-free (Amino Acid) Injections with Electrolytes in the lower chamber are solutions of essential and nonessential amino acids. The Dextrose Injections with 9 mEq/L Calcium in the upper chamber are solutions for fluid replenishment and caloric supply. The product is steam sterilized. The drug name, chemical name (as applicable), molecular formula and molecular weight for the amino acids, electrolytes and dextrose which comprise the admixed drug product are listed in **Table 1**.

Table 1

Contents of Admixed Product:
Travasol II® - sulfite-free (Amino Acid) Injection with Electrolytes in Dextrose Injection with Calcium

Name	Chemical Name	Molecular Formula	Molecular Weight
Alanine	L-α-aminopropanoic acid	$C_3H_7NO_2$	89.09
Arginine	L-2-amino-5-guanidinovaleric acid	$C_6H_{14}N_4O_2$	174.20
Glycine	aminoacetic acid	$C_2H_5NO_2$	75.07
Histidine	L-α-amino-4 (or 5) imidazolepropionic acid	$C_6H_9N_3O_2$	155.16
Isoleucine	L-2-amino-3-methylvaleric acid	$C_6H_{13}NO_2$	131.17
Leucine	L-2-amino-4-methylvaleric acid	$C_6H_{13}NO_2$	131.17
Lysine Hydrochloride	L-2,6-diaminohexanoic acid hydrochloride	$C_6H_{14}N_2O_2 \cdot HCl$	182.65
Methionine	L-2-amino-4-methylthiobutanoic acid	$C_5H_{11}NO_2S$	149.21

ITEM 3.IV.5.a.

Table 1 (cont.)

Contents of Admixed Product:
Travasol II® - sulfite-free (Amino Acid) Injection with Electrolytes in Dextrose Injection with Calcium

Name	Chemical Name	Molecular Formula	Molecular Weight
Phenylalanine	L-α-amino-β-phenylpropionic acid	$C_9H_{11}NO_2$	165.19
Proline	L-2-pyrrolidine carboxylic acid	$C_5H_9NO_2$	115.13
Serine	L-2-amino-3-hydroxypropionic acid	$C_3H_7NO_3$	105.09
Threonine	L-2-amino-3-hydroxybutyric acid	$C_4H_9NO_3$	119.12
Tryptophan	L-2-amino-3-indolylpropanoic acid	$C_{11}H_{12}N_2O_2$	204.23
Tyrosine	L-α-amino-p-hydroxyhydro-cinnamic acid	$C_9H_{11}NO_3$	181.19
Valine	L-2-aminoisovaleric acid	$C_5H_{11}NO_2$	117.15
Dextrose, Hydrous USP	same	$C_6H_{12}O_6 . H_2O$	198.17
Sodium Acetate Trihydrate, USP	same	$C_2H_3NaO_2 . 3H_2O$	136.08
Dibasic Potassium Phosphate, USP	same	K_2HPO_4	174.18
Magnesium Chloride Hexahydrate, USP	same	$MgCl_2 . 3H_2O$	203.30
Calcium Chloride Dihydrate, USP	same	$CaCl_2 . 2H_2O$	147.02

ITEM 3.IV.5.

b. Drug Product Container Components

A full description of the container and its components is provided in **Confidential Addendum 2.**

The plastic container does not contain any of the chemicals listed on the EPA Toxicity Characteristic Leachate procedure (TCLP) 40 CFR §261. The extractable substances identified also do not appear on this list. The use and disposal of the proposed product will be similar to the use and disposal of existing products.

6. Introduction of substances into the environment

The introduction of substances into the environment is described below in terms of substances emitted, control procedures for expected emissions, applicable regulations, statement of compliance, and effect of application approval on compliance with current emission requirements.

a. Substances Emitted

The primary modes of introduction of chemical substances into the environment as a result of drug product formulation of Travasol II® - sulfite-free (Amino Acid) with Electrolytes in Dextrose with Calcium Injections in PL 2401 containers include air emissions, organic and aqueous liquid wastes and solid waste materials. Minimal introduction of chemical substances to the terrestrial compartment will occur as detailed below.

Air Emissions - The chemical substances that may be emitted into the atmosphere as a result of production of Travasol II® - sulfite-free (Amino Acid) with Electrolytes in Dextrose with Calcium Injections in PL 2401 containers are listed in **Confidential Addendum 2.**

Liquid Emissions - Organic and inorganic substances identified in **Confidential Addendum 2** may also be emitted to the aquatic environment as a result of drug product manufacture. In all instances, the wastewater generated will be discharged in conformance with the applicable environmental interim limits and will be sent to the local publicly owned wastewater treatment plant. Liquid from product that is off-specification will be sent to the wastewater treatment plant in the same manner as production waste.

ITEM 3.IV.6.a.

Solid Emissions - Solid waste generation will include dust collector residues and filter, empty containers from raw materials, packaging components and a small amount of drug product waste. Control of solid waste generation from the facility will include collection of these wastes for recycling of unusable packaging components, as appropriate. Alternatively, non-hazardous solid waste will be land filled at a properly permitted facility. Plastic material from product that is off-specification or returned to the plant will be disposed to the landfill with other nonhazardous wastes.

b. Control Procedures for Expected Emissions

Air Emissions Controls - Any dust produced by the manufacturing and packaging operation will be collected by filters. Exhaust air from manufacturing and packaging areas will be collected by HEPA filtration with a control efficiency of 99.97%. Approval of this proposed action will not impact the facility's ability to comply with all applicable air emission requirements.

Liquid Emissions Controls - The site's interim wastewater limits for biological oxygen demand (BOD) and chemical oxygen demand (COD) are listed in **Confidential Addendum 1**. Approval of the proposed action will not impact the facility's ability to comply with all applicable liquid emissions requirements. No new permit limits are anticipated as a result of the proposed action.

Each Baxter facility has developed spill procedures based upon the chemicals that are stored at the facility. The spill procedures take into account total quantity and diversity of the chemicals including any federal requirements for above-ground storage of fuel oils. The procedures describe plans for any potential spill, clean-up and prevention of spills. No parts of the spill procedures deal specifically with these products because they include only non-hazardous materials.

Solid Waste Emissions Controls - Solid Waste Management is controlled by a local Environmental Quality Board (EQB). Any Federal Resource Conservation and Recovery Act hazardous waste generated will be handled as required by the regulation. There are no numerical permit limits or standards associated with the solid waste generation that limit the facility or will be impacted by the proposed action.

ITEM 3.IV.6.b.

Employee Protection - Material Safety Data Sheets are available on-site for all chemicals as required by the Occupational Safety Act of 1971, the Hazards Communication Act of 1985, and Title 29 Code of Federal Regulations (CFR) Part 1910. Employees associated with the manufacture of drug product have appropriate MSDSs available for their review. Employee protective clothing such as gloves, uniforms and safety glasses are used during the manufacturing process to assure compliance with the Occupational Safety Act of 1971, the Hazard Communication Act of 1985 and Title 29 CFR Subpart I.

c. Applicable Emission Citations

Air Citations - The manufacturing and packaging operation will be in compliance with the state air requirements, and the Federal Clean Air Act. There are no additional permits required for the production of this drug product. There are no other permit limits or standards that are applicable to the proposed action. Approval of the proposed action will not impact the facility's ability to comply with the above stated requirements.

Liquid Citations - The effluent from the site is discharged as described in **Confidential Addendum 1.** The wastewater is subject to the pretreatment standards for existing sources of the Pharmaceutical Manufacturing Category under Title 40 of the Code of Federal Regulations Part 439 (Subcategory D for mixing, compounding, and formulation). The BOD limits for the site average daily wastewater discharge is provided in **Confidential Addendum 1.** Approval of the proposed action will not impact the facility's ability to comply with these regulatory levels.

Solid Citations - Solid waste management at the facility requires conformance with conditions set forth by agencies listed in **Confidential Addendum 1.** These requirements assure comprehensive control for management of waste throughout the plant including returned market packages, and are subject to the requirements of the Federal Resource Conservation and Recovery Act and the Federal Hazardous and Solid Waste Amendments. These regulations do not limit the quantity of solid waste produced. Approval of the proposed action will not impact the facility's ability to comply with the above stated requirements.

ITEM 3.IV.6.

d. Effect of Application Approval on Compliance with Current Emission Requirements

Baxter Healthcare Corporation is in compliance with all emission requirements set forth in permits, consent decrees, and administrative orders applicable to the manufacturing and packaging of Travasol II® - sulfite-free (Amino Acid) with Electrolytes in Dextrose with Calcium Injections.

7. Fate of emitted substances in the environment

The use of the proposed product is not expected to alter significantly the concentration and distribution of the product, its metabolites, or degradation products. Likewise, minimal impact is expected from the use of the PL 2401 plastic container.

Similar amino acid solutions have been manufactured at the same facility proposed for these products. Amino acid solutions are non-toxic and are not expected to adversely impact wastewater, air or soil. Denaturing prior to discharge is not required for this drug solution.

Waste plastic material is not a hazardous waste. Plastic materials which cannot be reprocessed are collected and sent to the landfill as part of the facility's normal nonhazardous waste. There is no special requirement to permit this disposal. Additionally, there is no requirement for handling the waste in another manner. Landfills used by the facility are regularly inspected to assure operation according to required standards.

As a direct or indirect result of the use and/or disposal of this product, there will be no emissions into the air other than those already generated by the manufacturing plant. Most larger institutions incinerate this product after use. No new or different emissions will be generated from hospitals, or other user facilities, following normal incineration procedures.

No discharges to water systems by product user facilities are expected as a result of the use and/or disposal of this product, other than routine disposal of unused drug solutions to local publicly owned waste water treatment plants. The drug product components (solution and container) do not contain any of the chemicals listed on the EPA Toxicity Characteristic Leachate procedure (TCLP) 40 CFR §261.

Some medical institutions may utilize local landfills for disposal of the product after use. Plastic materials, in general, are inert to landfilling.

ITEM 3.IV.

8. Environmental effects of released substances

Substances emitted into the environment as a consequence of the use of the proposed product are not expected to adversely affect the environment. The drug product components (solution and container) do not contain any of the chemicals listed on the EPA Toxicity Characteristic Leachate procedure (TCLP) 40 CFR §261.

Amino acid solutions are non-toxic and are not expected to adversely impact wastewater, air or soil. They have been used for many years in clinical settings. No new pharmacological or clinical studies were required to establish safety of the drug solution.

Waste plastic material is not a hazardous waste and is inert to landfilling. The safety of the plastic container materials for the intended use was evaluated using USP Physicochemical and Biological tests, extraction studies and pharmacotoxicological assessments. No new or different emissions will be generated from hospitals, or other user facilities, following normal incineration procedures.

9. Use of resources and energy

The raw materials utilized to manufacture the proposed product are common chemicals that are in ample commercial supply. Energy commitment for dosage form production in the United States is nominal and not excessive. No effects upon endangered or threatened species and upon property listed in or eligible for listing in the National Register of Historic Places are anticipated.

At this time, based upon expected efficiencies in the manufacturing process, energy use is predicted to be no greater than current use.

10. Mitigation measures

No potential adverse environmental impacts are foreseen with the production and use of the drug product. The manufacture, distribution and use of the drug product take place under highly regulated and controlled conditions which further mitigate against negative environmental consequences.

11. Alternatives to the proposed action

No alternatives to this action have been developed other than no action. No action would forego potential environmental benefits described in **Confidential Addendum 2.**

ITEM 3.IV.

12. Baxter Healthcare Corporation Preparers

Pat Bartholomew - Director, Environmental Affairs
Marcia Marconi - Vice President, Regulatory Affairs

Qualifications for the above listed individuals are provided in **Confidential Addendum 3.**

13. Certification

The undersigned official certifies that to the best of Baxter's knowledge the information presented here is true, accurate and complete.

Marcia Marconi (RC)	2/7/97
Marcia Marconi, Vice President, Regulatory Affairs	Date

14. A bibliography of the referenced literature articles

No literature articles have been referenced.

AUG - 9 1996

REVIEW FOR HFD-510
OFFICE OF NEW DRUG CHEMISTRY
MICROBIOLOGY STAFF
MICROBIOLOGIST'S REVIEW #1 OF NDA 20-678
August 2, 1996

A. 1. **NDA 20-678**
APPLICANT: Baxter Healthcare Corporation
Route 120 & Wilson Road
Round Lake, Illinois 60073-0490

2. PRODUCT NAME: Travasol® II - sulfite-free (Amino Acid) with Electrolytes in Dextrose with Calcium Injections in Clinimix™ Dual Chamber (PL 2401) Container (Amino Acids, Electrolytes, Dextrose, USP)

3. DOSAGE FORM AND ROUTE OF ADMINISTRATION: The products are sterile LVP Clinimix™ Dual Chamber (PL 2401) flexible plastic containers constructed of two 1.5L compartments separated by a peel seal. The upper compartment contains a 1L dextrose/calcium solution, while the lower contains a 1L amino acid/electrolyte solution. For intravenous injection.

4. METHODS OF STERILIZATION:

5. PHARMACOLOGICAL CATEGORY and/or PRINCIPAL INDICATION:
The products are indicated for providing a substantial portion of the essential elements for a total parenteral nutrition (TPN) regimen (amino acids, dextrose, calcium, and electrolytes) and to allow for the direct addition of fat emulsion.

6. DRUG PRIORITY CLASSIFICATION: 3-S

B. 1. **DATE OF INITIAL SUBMISSION:** April 1, 1996

2. DATE OF AMENDMENT: (none)

3. RELATED DOCUMENT: DMF 977

4. ASSIGNED FOR REVIEW: April 15, 1996

C. **REMARKS:** The 21 formulations do not contain any new drug substances, but represent an increased number of amino acid/dextrose configurations over the currently marketed Travasol® Quick Mix® PL146 products. In addition, the PL 2401 products contain serine in the amino acid solution, and calcium in the dextrose solution, whereas the currently marketed PL 146 products lack both of these ingredients. However, the Dual Chamber PL 2401 has not been previously used (or submitted for FDA review) as a container for any drug product. The container closure system, therefore, is the focus of the NDA 20-678 submission.

D. **CONCLUSIONS:** The application is recommended "as approvable", as provided in 21 CFR §314.110(a), for reasons of sterility assurance.

Neal Sweeney 8/2/96
Neal Sweeney, Ph.D.

PLK 8/9/96

cc: Original NDA 20-678
HFD-510/S.McCort
HFD-805/Consult File/Sweeney

Drafted by: N. Sweeney, August 2, 1996
R/D initialed by P. Cooney, August 2, 1996

REVIEW FOR HFD-510
OFFICE OF NEW DRUG CHEMISTRY
MICROBIOLOGY STAFF
MICROBIOLOGIST'S REVIEW #2 OF NDA 20-678
February 10, 1996

A. 1. **NDA 20-678**
APPLICANT: Baxter Healthcare Corporation
Route 120 & Wilson Road
Round Lake, Illinois 60073-0490

2. **PRODUCT NAME:** Travasol® II - sulfite-free (Amino Acid) with Electrolytes in Dextrose with Calcium Injections in Clinimix™ Dual Chamber (PL 2401) Container (Amino Acids, Electrolytes, Dextrose, USP)

3. **DOSAGE FORM AND ROUTE OF ADMINISTRATION:** The products are sterile LVP Clinimix™ Dual Chamber (PL 2401) flexible plastic containers constructed of two 1.5L compartments separated by a peel seal. The upper compartment contains a 1L dextrose/calcium solution, while the lower contains a 1L amino acid/electrolyte solution. For intravenous injection.

4. **METHODS OF STERILIZATION:**

5. **PHARMACOLOGICAL CATEGORY and/or PRINCIPAL INDICATION:**
The products are indicated for providing a substantial portion of the essential elements for a total parenteral nutrition (TPN) regimen (amino acids, dextrose, calcium, and electrolytes) and to allow for the direct addition of fat emulsion.

6. **DRUG PRIORITY CLASSIFICATION:** 3-S

B. 1. **DATE OF INITIAL SUBMISSION:** April 1, 1996 (Subject of Microbiologist's Review #1)

2. **DATE OF AMENDMENT:** February , 1997

3. **RELATED DOCUMENT:** DMF 977

4. **ASSIGNED FOR REVIEW:** April 15, 1996

C. **REMARKS:**

D. CONCLUSIONS: The application is recommended for approval for issues concerning sterility assurance.

Neal Sweeney 2/10/97

Neal Sweeney, Ph.D.

DHC 2/12/97

cc: Original NDA 20-678
HFD-510/CSO/S. McCort
HFD-805/Consult File/N. Sweeney

Drafted by: N. Sweeney, February 10, 1996
R/D initialed by P. Cooney, February 10, 1996