

AMINOSYN® II 4.25% in 25% Dextrose Injection

R_x only

AN AMINO ACID INJECTION IN DEXTROSE INJECTION

NOTE: These solutions are hypertonic. See **WARNINGS** and **PRECAUTIONS**.

Nutrimix® Dual-chamber Flexible Container

The Upper Chamber Contains 500 mL of Aminosyn II 8.5% (An Amino Acid Injection)

The Lower Chamber Contains 500 mL of 50% Dextrose Injection, USP

DESCRIPTION

Upper Chamber: Aminosyn II 8.5%, an amino acid injection, 500 mL.

Aminosyn II 8.5% is a sterile, nonpyrogenic solution for intravenous infusion. The formulation is described in the table below.

Lower Chamber: 50% Dextrose Injection, USP, 500 mL.

50% Dextrose Injection, USP (concentrated dextrose in water) is a sterile, nonpyrogenic, hypertonic solution of Dextrose, USP in water for injection. The table below indicates the characteristics of this concentrated solution.

The container must be used only after removing the clamp and thoroughly mixing the contents of the two chambers. The solution resulting from mixing the contents of the upper and the lower chamber will be 4.25% amino acids in 25% dextrose. Mixing the contents of the upper and lower chambers yields a concentrated source of amino acids and carbohydrate calories for intravenous infusion. Headspace contains Nitrogen gas. The composition of this admixture is described in the table below.

	Solution Composition per 100 mL		
	Upper Chamber	Lower Chamber	Admixture
Dextrose, hydrous (g)		50	25
Essential Amino Acids (mg)			
Isoleucine	561		280
Leucine	850		425
Lysine (as acetate salt)*	893		446
Methionine	146		73
Phenylalanine	253		126
Threonine	340		170
Tryptophan	170		85
Valine	425		212
Nonessential Amino Acids (mg)			
Alanine	844		422
Arginine	865		432
L-Aspartic Acid	595		298
L-Glutamic Acid	627		314
Histidine	255		128
Proline	614		307
Serine	450		225
N-Acetyl-L-Tyrosine	230		115
Glycine	425		212
Total Amino Acids (g)	8.5		4.25
Protein Equivalent (g)	8.5		4.25
Total Nitrogen (g)	1.3		0.65


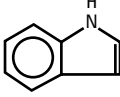


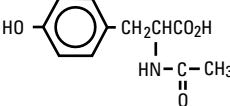
*Amount cited is for lysine alone and does not include the acetate salt.

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	Upper Chamber	Lower Chamber	Admixture
Electrolytes (mEq/liter)			
Sodium ^a (Na ⁺)	38		19
Acetate ^b (C ₂ H ₃ O ₂ ⁻)	61.1		30.6
Sodium hydrosulfite (mg/100 mL)	60		30
Osmolarity mOsmol/liter (actual)	780	1997	1522
pH	5.8	4.3	5.8
pH range	5.0 to 6.5 ^c	3.2 to 6.5	5.0 to 6.5

The formulas for the individual amino acids are as follows:

<u>Essential Amino Acids</u>	
Isoleucine	CH ₃ CH ₂ CH(CH ₃)CH(NH ₂)COOH
Leucine	(CH ₃) ₂ CHCH ₂ CH(NH ₂)COOH
Lysine Acetate	H ₂ N(CH ₂) ₄ CH(NH ₂)COOH • CH ₃ COOH
Methionine	CH ₃ S(CH ₂) ₂ CH(NH ₂)COOH
Phenylalanine	 CH ₂ CH(NH ₂)COOH
Threonine	CH ₃ CH(OH)CH(NH ₂)COOH
Tryptophan	 CH ₂ CH(NH ₂)COOH
Valine	(CH ₃) ₂ CHCH(NH ₂)COOH
<u>Nonessential Amino Acids</u>	
Alanine	CH ₃ CH(NH ₂)COOH
Arginine	H ₂ NC(NH)NH(CH ₂) ₃ CH(NH ₂)COOH
L-Aspartic Acid	HOOCCH ₂ CH(NH ₂)COOH
L-Glutamic Acid	HOOC(CH ₂) ₂ CH(NH ₂)COOH
Glycine	H ₂ NCH ₂ COOH
Histidine	 CH ₂ CH(NH ₂)COOH
Proline	 HOCH ₂ CH(NH ₂)COOH
Serine	HOCH ₂ CH(NH ₂)COOH
N-Acetyl-L-Tyrosine	

^a Includes sodium from the pH adjustor sodium hydroxide and the antioxidant, sodium hydrosulfite.

^b Includes acetate from lysine acetate.

^c May contain sodium hydroxide for pH adjustment.

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Dextrose, USP is chemically designated D-glucose, monohydrate ($C_6H_{12}O_6 \cdot H_2O$), a hexose sugar freely soluble in water.

The flexible plastic container is fabricated from a specially formulated nonplasticized thermoplastic copolyester (CR3). Water can permeate from inside the container into the overwrap but not in amounts sufficient to affect the solution significantly. Solutions inside the plastic container also can leach out certain of its chemical components in very small amounts before the expiration period is attained. However, the safety of the plastic has been confirmed by tests in animals according to USP biological standards for plastic containers.

CLINICAL PHARMACOLOGY

The Aminosyn II 4.25% in 25% Dextrose Injection admixture, obtained upon mixing thoroughly the contents of the two chambers, provides carbohydrate calories and crystalline amino acids to stimulate protein synthesis, to limit protein catabolism, to minimize liver glycogen depletion and to promote wound healing. The infusion of this mixture through a central venous line should be considered to meet the protein and calorie requirements for patients receiving prolonged total parenteral nutrition. I.V. lipids may be infused simultaneously to provide adequate calories, if desired.

INDICATIONS AND USAGE

Aminosyn II 4.25% in 25% Dextrose Injection is indicated for central vein infusion in the prevention of nitrogen loss and negative nitrogen balance in cases where (a) the gastrointestinal tract by the oral, gastrostomy or jejunostomy route cannot or should not be used, (b) gastrointestinal absorption of nutrients is impaired or (c) metabolic requirements for protein and calories are substantially increased as with extensive burns and (d) morbidity and mortality may be reduced by replacing amino acids lost from tissue breakdown, thereby preserving tissue reserves, as in acute renal failure. In such patients intravenous feeding for more than a few days would be expected.

The addition of supplemental electrolytes will be required in accordance with the prescription of the attending physician.

CONTRAINDICATIONS

This preparation should not be used in patients with hepatic coma or metabolic disorders involving impaired nitrogen utilization.

WARNINGS

The Aminosyn II 4.25% in 25% Dextrose Injection admixture is hypertonic and may not be administered by peripheral vein.

Concentrated dextrose solutions, if administered too rapidly, may result in significant hyperglycemia and possible hyperosmolar syndrome, characterized by mental confusion and loss of consciousness.

Intravenous infusion of amino acids may induce a rise in blood urea nitrogen (BUN), especially in patients with impaired hepatic or renal function. Appropriate laboratory tests should be performed periodically and infusion discontinued if BUN levels exceed normal postprandial limits and continue to rise. It should be noted that a modest rise in BUN normally occurs as a result of increased protein intake.

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

Administration of amino acid solutions in the presence of impaired renal function may augment an increasing BUN, as does any protein dietary component.

Solutions containing sodium ion should be used with great care, if at all, in patients with congestive heart failure, severe renal insufficiency and in clinical states in which there exists edema with sodium retention.

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Solutions containing potassium ions should be used with great care, if at all, in patients with hyperkalemia, severe renal failure and in conditions in which potassium retention is present.

Solutions containing acetate ion should be used with great care in patients with metabolic or respiratory alkalosis. Acetate should be administered with great care in those conditions in which there is an increased level or an impaired utilization of this ion, such as severe hepatic insufficiency.

Aminosyn II 4.25% in 25% Dextrose Injection contains sodium hydrosulfite, a sulfite that may cause allergic-type reactions including anaphylactic symptoms and life-threatening or less severe asthmatic episodes in certain susceptible people. The overall prevalence of sulfite sensitivity in the general population is unknown and probably low. Sulfite sensitivity is seen more frequently in asthmatic than in nonasthmatic people.

This solution (4.25% Aminosyn II) is too concentrated for administration to infants.

Instances of asymptomatic hyperammonemia have been reported in patients without overt liver dysfunction. The mechanisms of this reaction are not clearly defined, but may involve genetic defects and immature or subclinically impaired liver function.

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

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

PRECAUTIONS

Special care must be taken when administering concentrated glucose to diabetic or prediabetic patients. To control and minimize hyperglycemia and consequent glycosuria, it is desirable to monitor blood and urine glucose and, if necessary, add insulin.

Because of its antianabolic activity, concurrent administration of tetracycline may reduce the nitrogen sparing effects of infused amino acids.

Intravenously administered amino acids should be used with caution in patients with history of renal disease, pulmonary disease, or with cardiac insufficiency so as to avoid excessive fluid accumulation.

Nitrogen intake should be carefully monitored in patients with impaired renal function.

Aminosyn II 4.25% in 25% Dextrose Injection is indicated for long-term total parenteral nutrition and whenever it is essential to provide, together with amino acids, adequate amounts of exogenous calories. Concentrated dextrose is an effective source of such calories. Such strongly hypertonic nutrient solutions should be administered only through an indwelling catheter with the tip located in a large vein: i.e., the superior vena cava.

SPECIAL PRECAUTIONS FOR CENTRAL INFUSIONS

**ADMINISTRATION BY CENTRAL VENOUS CATHETER SHOULD BE USED ONLY BY THOSE FAMILIAR
WITH THIS TECHNIQUE AND ITS COMPLICATIONS.**

Central vein infusion of nutrient solutions requires a knowledge of nutrition as well as clinical expertise in recognition and treatment of complications. Attention must be given 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.

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SUMMARY HIGHLIGHTS OF COMPLICATIONS

(See also Current Medical Literature).

1. Technical:

The placement of a central venous catheter should be regarded as a surgical procedure. One should be fully acquainted with various techniques of catheter insertion. For details of technique 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 and air and catheter emboli.

2. Septic:

The constant risk of sepsis is present during administration of total parenteral nutrition. It is imperative that the preparation of the solution and the placement and care of catheters be accomplished under strict aseptic conditions.

Solutions should be used promptly after mixing. Storage should be under refrigeration and limited to a brief period of time, preferably less than 24 hours.

Administration time for a single container and set should never exceed 24 hours.

3. Metabolic:

The following metabolic complications have been reported: Metabolic acidosis and alkalosis, hypophosphatemia, hypocalcemia, osteoporosis, hyperglycemia, hyperosmolar nonketotic states and dehydration, glycosuria, rebound hypoglycemia, osmotic diuresis and dehydration, elevated liver enzymes, hypo- and hypervitaminosis, electrolyte imbalances and hyperammonemia in children. Frequent evaluations are necessary especially during the first few days of therapy to prevent or minimize these complications.

Administration of glucose at a rate exceeding the patient's utilization rate may lead to hyperglycemia, coma and death.

Pregnancy Category C. Animal reproduction studies have not been conducted with Aminosyn II 4.25% in 25% Dextrose Injection. It is not known whether this admixture can cause fetal harm when administered to a pregnant woman or can affect reproductive capacity. Aminosyn II 4.25% in 25% Dextrose Injection should be given to pregnant women only if clearly needed.

Geriatric Use

Clinical Studies of Aminosyn II in Dextrose Injection have not been performed to determine whether patients over 65 years of age respond differently from younger subjects. Other reported clinical experience has not identified differences in responses between elderly and younger patients. In general, dose selection for an elderly patient should be cautious, reflecting the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy. This drug is known to be substantially excreted by the kidney, and the risk for adverse reactions to this drug may be greater in patients with impaired renal function. Because elderly patients are more likely to have decreased renal function, care should be taken in dose selection, and it may be useful to monitor renal function.

Pediatric Usage

Due to their concentration, these solutions are not recommended for use in pediatric patients less than 1 year old. Frequent monitoring of serum glucose concentrations is required when dextrose is prescribed to pediatric patients, particularly neonates and low birth weight infants.

CLINICAL EVALUATION AND LABORATORY DETERMINATIONS, AT THE DISCRETION OF THE ATTENDING PHYSICIAN, ARE NECESSARY FOR PROPER MONITORING DURING ADMINISTRATION. Do not withdraw venous blood for blood chemistries through the infusion site, as interference with estimations of nitrogen-containing substances may occur. Blood studies should include glucose, urea nitrogen, serum

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electrolytes, ammonia, cholesterol, acid-base balance, serum proteins, kidney and liver function tests, osmolality and hemogram. White blood count and blood cultures are to be determined if indicated. Urinary osmolality and glucose should be determined as necessary.

Do not use unless the solutions are clear and container is undamaged. Discard unused portion.

Do not use if solution in either chamber is discolored or if clamp is open or missing.

This product contains no more than 25 mcg/L of aluminum.

ADVERSE REACTIONS

Hyperosmolar syndrome, resulting from excessively rapid administration of concentrated dextrose may cause mental confusion and/or loss of consciousness.

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

Generalized flushing, fever and nausea also have been reported during peripheral infusions of amino acid solutions.

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.

OVERDOSAGE

In the event of overhydration or solute overload, re-evaluate the patient and institute appropriate corrective measures. See WARNINGS and PRECAUTIONS.

DOSAGE AND ADMINISTRATION

The total daily dose of Aminosyn II 4.25% in 25% Dextrose Injection to be infused depends on daily protein and caloric requirements and on the patient's metabolic and clinical response. 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. To prevent rebound hypoglycemia, a solution containing 5% dextrose should be administered when hypertonic dextrose infusions are abruptly discontinued.

As reported in the literature, the dosage and constant infusion rate of intravenous dextrose must be selected with caution in pediatric patients, particularly neonates and low birth weight infants, because of the increased risk of hyperglycemia/ hypoglycemia.

As with all intravenous fluid therapy, the parenteral administration of a solution of amino acids and dextrose requires an accurate estimate of the total fluid and electrolytes needed to compensate for the patient's measurable urinary and other (i.e., nasogastric suction, fistula drainage, diarrhea) daily losses. After estimating the total daily fluid (water) requirements, the appropriate volume to be infused to meet the daily protein requirement of the patient, can be determined. The balance of fluid needed beyond the volume of the amino acid/dextrose solution can be provided by other solutions suitable for intravenous infusion. Lipid emulsion can be administered to provide up to 3 g fat/kg/day, infused simultaneously with Aminosyn II 4.25% in 25% Dextrose Injection by means of a Y-connector located near the infusion site, using separate flow controls for each solution. Aminosyn II 4.25% in 25% Dextrose Injection should not be premixed with fat emulsion. Vitamins and trace minerals may be added to the amino acid/dextrose solution as needed.

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

The total daily dose of the amino acid/dextrose solution to be infused depends on daily protein requirements and on the patient's metabolic and clinical response. The daily determination of nitrogen balance and accurate body weights, corrected for fluid balance, are probably the best means of assessing individual protein requirements.

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Adults

The daily nutrient requirements of an average adult patient, not hypermetabolic, in an acceptable weight range and with restricted physical activity, are about 30 kcal/kg of body weight, 12 to 18 grams of nitrogen and between 2500 and 3000 mL of fluids. In depleted and severely traumatized patients such as burned patients or patients who have received major surgery with complications, the requirements for nutrients and fluids may be significantly higher. In such cases, 4000 calories and 25 grams of nitrogen or more may be required daily to achieve nitrogen balance. The fluid losses through drainages and wound surface must be taken into account in calculating the fluid requirements of these patients.

Fat emulsion administration should be considered when prolonged 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.

Each gram of dextrose provides approximately 3.4 calories — 1000 mL of Aminosyn II 4.25% in 25% Dextrose Injection will provide 6.5 grams of nitrogen and 850 calories. The infusion rate of Aminosyn II 4.25% in 25% Dextrose Injection should be 2 mL/min initially and may be gradually increased to deliver the required amounts of amino acids and calories. If nutrient administration falls behind schedule, under no circumstances should an attempt to “catch up” to planned intake be made. The rate of nutrient infusion is governed by the protein requirements and by the patient’s glucose tolerance estimated by glucose levels in plasma and urine. The maximum rate at which dextrose can be infused without producing glycosuria is 0.5 g/kg/hour; at a rate of 0.8 g/kg/hour, about 95% of the infused dextrose is retained. Administration of exogenous insulin may be required in order to control hyperglycemia and glycosuria which may occur upon infusion of concentrated glucose solutions. When concentrated dextrose infusion is abruptly interrupted rebound hypoglycemia may occur, which can be prevented by the administration of 5% or 10% dextrose solutions. Part of the caloric requirements may be met by the infusion of I.V. fat emulsions.

SERUM ELECTROLYTES SHOULD BE MONITORED AS INDICATED.

Electrolytes should be added to the nutrient solution as indicated by the patient’s clinical condition and laboratory determinations of plasma values. Major electrolytes are sodium, chloride, potassium, phosphate, magnesium and calcium. Adding 20 mL of TPN Electrolytes (List 5779) to the amino acid chamber and 5 mL of Potassium Phosphate (List 7296) to the dextrose chamber will result in final admixture concentrations (in mEq/L) as follows: 54 sodium, 42 potassium, 35 chloride, 5 magnesium, 4.5 calcium, 60.1 acetate, and 15 (mM) phosphate. Alternate electrolyte additives may be used at the clinician’s discretion.

Vitamins, including folic acid and vitamin K are required additives. The trace element supplements should be given when long-term parenteral nutrition is undertaken.

Calcium and phosphorus are added to the solution as indicated. The usual dose of phosphate added to a liter of TPN solution (containing 25% dextrose) is 12 mM. This requirement is related to the carbohydrate calories delivered. Iron is added to the solution or given intramuscularly in depot form as indicated. Vitamin B₁₂, vitamin K and folic acid are given intramuscularly or added to the solution as desired.

Calcium and phosphate additives are potentially incompatible when added to the TPN admixture. However, if one additive is added to the amino acid solution, and the other to the concentrated dextrose solution, and if the contents of both chambers are mixed before they are combined, then the likelihood of physical incompatibility is reduced.

In patients with hyperchloremic or other metabolic acidosis, sodium and potassium may be added as the acetate or lactate salts to provide bicarbonate alternates.

In adults, hypertonic mixtures of amino acids and dextrose may be safely administered by continuous infusion through a central venous catheter with the tip located in the vena cava.

Pediatric

Pediatric requirements for parenteral nutrition are constrained by the greater relative fluid requirements of the infant and greater caloric requirements per kilogram. A 4.25% amino acid solution is too concentrated

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for use in pediatric patients less than one year old, who generally receive a 2.5% amino acid solution. However, older pediatric patients can receive Aminosyn II 4.25% in 25% Dextrose Injection. The suggested amino acid dosage level for children between 4 and 12 years of age is 2 g/kg/day; for 13 to 15 years of age, 1.7 g/kg/day; and for 16 years of age and above, 1.5 g/kg/day. Energy requirements for children between 1 and 7 years of age are approximately 75 to 90 kcal/kg/day; for children 7 to 12 years of age, 60 to 75 kcal/kg/day; and for ages 12 to 18 years, 30 to 60 kcal/kg/day. Energy intake may be supplemented with intravenous fat emulsion. In cases of malnutrition or stress, these requirements may be increased.

Supplemental electrolytes and vitamin additives should be administered as deemed necessary by careful monitoring of blood chemistries and nutritional status. Iron supplementation is more critical in the child than the adult because of the increasing red cell mass required by the growing child. Serum lipids should be monitored for evidence of essential fatty acid deficiency in patients maintained on fat-free TPN. Bicarbonate should not be administered during infusion of the nutritional solution unless deemed absolutely necessary.

To ensure the precise delivery of the small volumes of fluid necessary for total parenteral nutrition in children, accurately calibrated and reliable infusion systems should be used.

Drug Interactions

Additives may be incompatible. Consult with pharmacist, if available. When introducing additives, use aseptic technique, mix thoroughly and do not store.

INSTRUCTIONS FOR USE

DO NOT USE IF AMINOSYN II IS DISCOLORED OR IF CLAMP IS OPEN OR MISSING. COLOR VARIATION IN THE DEXTROSE INJECTION FROM PALE YELLOW TO YELLOW IS NORMAL AND DOES NOT ALTER EFFICACY.

To Open:

Tear outer wrap at notch. After removing the overwrap, check for minute leaks by squeezing the container firmly. If leaks are found, discard solution as sterility may be impaired. If supplemental medication is desired, follow directions below before preparing for administration.

To Add Medication:

1. Prepare the appropriate additive port.
2. Using aseptic technique and an additive delivery needle of appropriate length, puncture resealable additive port at target area through inner diaphragm and inject. Withdraw needle after injecting medication.
3. The additive ports should be protected by covering with additive caps.
4. Mix container contents thoroughly.

Preparation for Administration

(Use aseptic technique)

1. Open clamp between the two chambers. Completely drain all the solution and air into the lower chamber. To achieve this, stretch the side wall of the emptied top chamber.
2. Close flow control clamp of administration set.
3. Remove cover from outlet port at bottom of container.
4. Insert piercing pin of administration set into port with a twisting motion until the set is firmly seated.
NOTE: See full directions on administration set carton.
5. Suspend from hanger at top of container.
6. Squeeze and release drip chamber to establish proper fluid level in chamber.
7. Open flow control clamp to expel air from set. Close flow control clamp.
8. Connect to central infusion catheter.
9. Regulate rate of administration with flow control clamp. Ensure that all solution and air are in the lower chamber when reading fluid levels.

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WARNING: Do not use flexible container in series connections.

HOW SUPPLIED

Aminosyn® II 4.25% in 25% Dextrose Injection is supplied in a 1000 mL volume dual-chamber flexible container (List No. 7702). Aminosyn II 4.25% in 25% Dextrose Injection is obtained by opening the clamp separating the two chambers and mixing the contents of the upper chamber, 500 mL of Aminosyn II 8.5% and the lower chamber, 500 mL of 50% Dextrose Injection, USP.

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); however, brief exposure up to 40°C does not adversely affect the product.

Avoid exposure to light.

To prevent breakage, handle cold or refrigerated (2°C to 8°C) co-polyester (CR3) containers with care.

Revised: May, 2004

