CLINIMIX
(amino acids in dextrose) Injections

CLINIMIX E
(amino acids with electrolytes in dextrose with calcium) Injections

CLINIMIX and CLINIMIX E injections

A Premix Option for Flexible PN Therapy

INDICATIONS

CLINIMIX (amino acids in dextrose) Injections and CLINIMIX E (amino acids with electrolytes in dextrose with calcium) Injections are indicated as a source of calories and protein (and electrolytes for CLINIMIX E) for patients requiring parenteral nutrition when oral or enteral nutrition is not possible, insufficient, or contraindicated. CLINIMIX and CLINIMIX E may be used to treat negative nitrogen balance in patients.

Please see inside back cover for Indications and Important Risk information.
Please see accompanying Package Inserts for full Prescribing Information.

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CLINIMIX
(amino acids in dextrose) Injections

CLINIMIX E
(amino acids with electrolytes in dextrose with calcium) Injections

A Premix Option for **Flexible PN Therapy**

CLINIMIX and CLINIMIX E Injections. Source of calories and protein (and a source of electrolytes for CLINIMIX E) in a lipid compatible container.

- The CLINIMIX E Injections formulations are consistent with A.S.P.E.N. electrolyte dosing guidelines for adult patients.[1,2]

Please see inside back cover for Indications and Important Risk information. Please see accompanying Package Inserts for full Prescribing Information.

CLINIMIX
(amino acids in dextrose) Injections

CLINIMIX E
(amino acids with electrolytes in dextrose with calcium) Injections

CLINIMIX and CLINIMIX E Injections can provide adequate nutrients, lipid flexibility, and are available in multiple formulations

Essential Protein

- Up to 100 grams of protein/2L bag — highest concentration of protein/L in premix bag

Lipid Flexibility

- Underfilled bag allows for the addition of lipids to the bag or, can deliver lipids separately via IV piggyback

Multiple Formulations

- Central and peripheral formulations; 1 and 2-liter volumes
- With and without electrolytes
- 78% of custom compounded adult formulations can be met by the use of CLINIMIX Injection products[3]
- Can be used in pediatric and adult patients
- Extended shelf life:
  - 2 years room temperature (while in overwrap)
  - 9 days under refrigeration out of overwrap (or activated with no additives)

Quality Manufacturing Process

- Manufactured under cGMP processes, to ensure the identity, strength, quality, and purity of the drug products
- Terminally sterilized; terminally sterilized products represent the lowest risk of microbial contamination for sterile pharmaceutical products (USP<1022>)[4]
- Not made with natural rubber latex

Flexible Lipid Addition

The nutritional needs of your patients will be different based on how critically ill they may be. CLINIMIX sulfite-free (Amino Acid in Dextrose) Injections and CLINIMIX E (amino acids with electrolytes in dextrose with calcium) Injections gives you the power to choose when and how to provide IV fat emulsions.

For 2-in-1 therapy, CLINIMIX (amino acids in dextrose) Injections and CLINIMIX E (amino acids with electrolytes in dextrose with calcium) Injections may be admixed in the pharmacy and lipids may be piggybacked at the appropriate time during infusion. Infusing lipids separately also allows a visual check for precipitates and particulate matter prior to administration.

For 3-in-1 therapy, lipids can be directly added to the CLINIMIX and/or CLINIMIX E Injections bag.

Managing Electrolytes

Standardized Parenteral Nutrition (PN) with Electrolytes can be an appropriate choice.

- A.S.P.E.N. suggests managing short-term fluid and electrolyte abnormalities with parenteral nutrition is inappropriate[2]
- Managing additional electrolyte needs outside of the parenteral nutrition bag is recommended
- A.S.P.E.N. PN Safety Summit recommends standardization of parenteral nutrition formulation processes[6]

Metabolic complications have been reported, such as acid-base, electrolyte, and blood glucose imbalances, elevated liver enzymes, osmotic diuresis and dehydration.

Nutrient	A.S.P.E.N. Daily Electrolyte Guidelines for Adult Parenteral Nutrition[5]*	CLINIMIX E Injections 2 Liter Bag Contains**
Calcium	10–15 mEq	**9 mEq**
Magnesium	8–20 mEq	**10 mEq**
Phosphorus	20–40 mmol	**30 mmol**
Sodium	1–2 mEq/kg	**70 mEq**
Potassium	1–2 mEq/kg	**60 mEq**

* Individual dosing needs vary.

** Product codes: 2B7713, 2B7714, 2B7716, 2B7717, 2B7719, 2B7721, 2B7722 and 2B7723

An Essential Component of Your Dual PN System

Custom compounding may be essential for certain high risk patient populations. However, supplementing your compounding operations with premix nutrition delivers additional flexibility:

- Eliminates the delay to starting PN therapy for orders arriving on weekends or orders received after cutoff times
- Immediately available in disaster situations
- Extended shelf life minimizes risk of expiration prior to use

- *In a 2006 A.S.P.E.N. survey of PN ordering and compounding, 60% of those surveyed reported 1–5 errors per month related to PN.[7]*
- *Standardizing PN formulas may help improve clinician prescribing of a balanced formula to help meet patient nutritional goals.[8]*

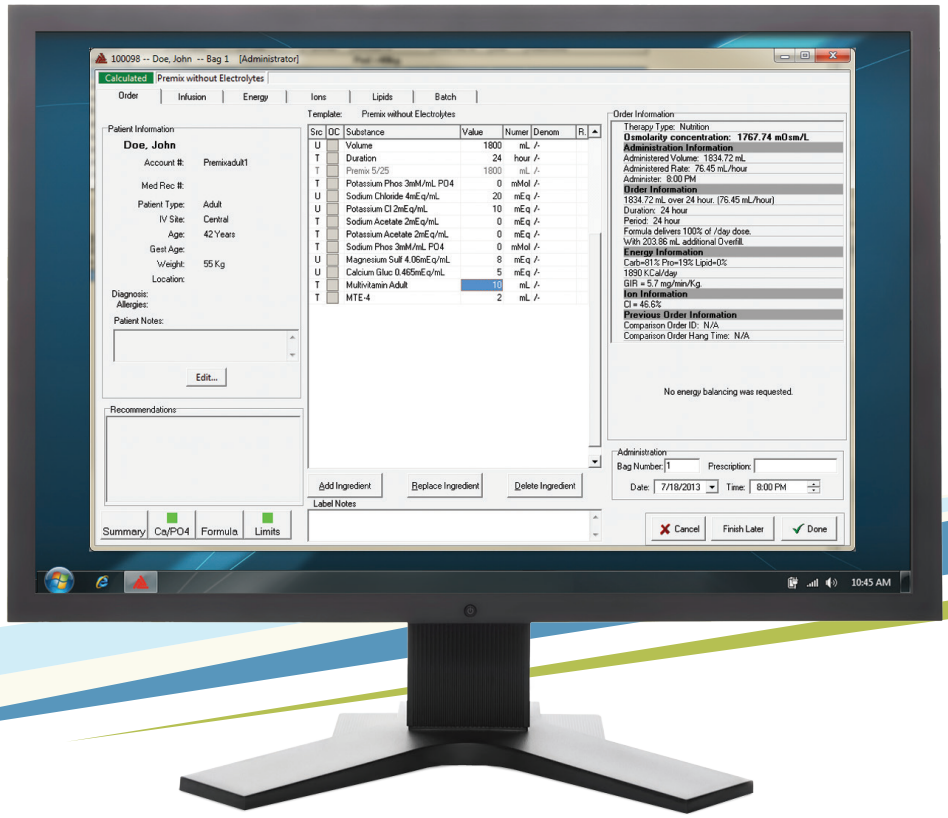
Eliminate Manual Calculations with ABACUS Order Entry and Calculation Software

ABACUS Software simplifies the ordering, calculation and labeling process. It conducts up to 17 safety checks, helping to minimize the risk of errors during the formulation ordering process.

ABACUS Software supports the ordering of premixed solutions for parenteral nutrition. Users simply select a premix template, enter the volume and choose a formula. ABACUS Software automatically calculates the infusion rate and duration.

ABACUS
Order Entry & Calculation Software

- Additives are calculated and documented within the software
- Printed Label includes all ingredients; premix components + additives
- Eliminates the need for manual calculations
- Ability to calculate overfill and unused volume for Premix orders
- Ability to create multiple order templates for Home Infusion/Alternate Care facilities



Patient Label Example

18-Jul-13 **General Hospital** 11:01 AM
Facility Address - Phone

Acct : **Premixadult1**

DOE, JOHN Patient Bag #: **1**

Location: / Order No: **100098**

Order Volume: **1,834.72 mL** Compound Volume: **2,038.58 mL**

Premix 5/25	1,800	mL
Sodium Chloride	20	mEq
Potassium Chloride	10	mEq
Magnesium Sulfate	8	mEq
Calcium Gluconate	5	mEq
Multivitamin Adult	10	mL
MTE-4	2	mL

** Approximate Concentrations with Additives **

Protein	4.91	%	Magnesium	4.36	mEq/L
Dextrose	24.53	%	Phosphate	0	mMol/L
Sodium	10.9	mEq/L	Acetate	41.21	mEq/L
Potassium	5.45	mEq/L	Chloride	35.97	mEq/L
Calcium	2.73	mEq/L			

Nitrogen	14.87 gm	Protein	360 Kcal (19.05 %)
Non-Prot KCal	1,530 Kcal	Dextrose	1,530.0 Kcal (80.95 %)
Total KCal	1,890 Kcal		

Admixture contains: 1,834.72 mL plus 203.86 mL Overfill

Flow Rate: 1,834.72 mL at 76.45 mL/hr for 24 hours

Final Solution Osmolarity: 1,768 mOsm/L

***** CENTRAL LINE ONLY *****

Prepared By:_____ Date:_____ Checked By:_____

Delivery Time: 7/18/13 20:00:00 Do Not Use After: 7/21/13 20:00:00

Serial No: 100098

The ABACUS Software is intended as an adjunct tool for pharmacy practice. It is not intended to replace the professional judgement or knowledge of a pharmacist or pharmacy technician.

Please see inside back cover for Indications and Important Risk information. Please see accompanying Package Inserts for full Prescribing Information.

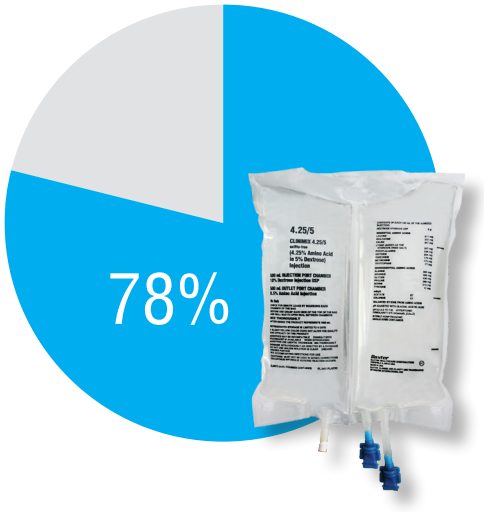
Ask for Your PN Order Analysis Today

A PN order analysis can help determine not only if these products will meet your needs, but also which product codes might be most appropriate for your patients' requirements.

Data shows that **78% of adult PN orders could be filled by CLINIMIX Injections formulas**† based on daily needs of:

- Protein
- Calories
- Volume

Maintenance vitamins, additional electrolytes, and trace elements are not included and should be administered as required.



† 56,672 TPN orders analyzed over 1,000 facilities. Formulas considered a match if within 10% of target. Does not include CLINIMIX E formulations.

Over 15 Years of Customer Satisfaction*

More than 4789 U.S. Healthcare facilities have used CLINIMIX and/or CLINIMIX E Injections

Over 6.5 million bags manufactured and sold in the U.S.

* Customer data on file, 2014. Baxter Healthcare Corporation.

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INDICATIONS

CLINIMIX (amino acids in dextrose) Injections and CLINIMIX E (amino acids with electrolytes in dextrose with calcium) Injections are indicated as a source of calories and protein (and electrolytes for CLINIMIX E) for patients requiring parenteral nutrition when oral or enteral nutrition is not possible, insufficient, or contraindicated. CLINIMIX and CLINIMIX E may be used to treat negative nitrogen balance in patients.

IMPORTANT RISK INFORMATION

- CLINIMIX and CLINIMIX E Injections are contraindicated in patients with known hypersensitivity to one or more amino acids or dextrose; in patients with inborn errors of amino acid metabolism due to risk of severe metabolic and neurologic complications; and in patients with pulmonary edema or acidosis due to low cardiac output. In addition, CLINIMIX E is contraindicated in neonates (less than 28 days of age) receiving concomitant treatment with ceftriaxone, even if separate infusion lines are used, due to the risk of fatal ceftriaxone calcium salt precipitation in the neonate's bloodstream.
- Pulmonary vascular precipitates causing pulmonary vascular emboli and pulmonary distress have been reported in patients receiving parenteral nutrition. Excessive addition of calcium and phopshate increases the risk of the formation of calcium phosphate precipitates. The solution should be inspected for precipitates before admixing, after admixing, and again before administration. If signs of pulmonary distress occur, stop the infusion and initiate a medical evaluation.
- Precipitation of ceftriaxone-calcium can occur when ceftriaxone is mixed with CLINIMIX E, in the same intravenous administration line. Do not administer ceftriaxone simultaneously with CLINIMIX E via a Y-site.
- Stop infusion immediately and treat patient accordingly if signs or symptoms of a hypersensitivity reaction develop.
- Monitor for signs and symptoms of early infections.
- Refeeding severely undernourished patients may result in refeeding syndrome. Thiamine deficiency and fluid retention may also develop. Monitor severely undernourished patients and slowly increase nutrient intakes.
- CLINIMIX and CLINIMIX E solutions containing more than 5% dextrose have an osmolarity of ≥ 900 mOsm/L and must be infused through a central catheter.
- CLINIMIX and CLINIMIX E contain no more than 25 mcg/L of aluminum which may reach toxic levels with prolonged administration in patients with renal impairment. Preterm infants are at greater risk because their kidneys are immature, and they require large amounts of calcium and phosphate solutions which contain aluminum. Patients with renal impairment, including preterm infants, 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.
- Parenteral Nutrition Associated Liver Disease (PNALD) has been reported in patients who receive parenteral nutrition for extended periods of time, especially preterm infants. If CLINIMIX and CLINIMIX E treated patients develop liver test abnormalities consider discontinuation or dosage reduction.
- Use CLINIMIX and CLINIMIX E with caution in patients with cardiac insufficiency or renal impairment due to increased risk of electrolyte and fluid volume imbalance.
- Monitor renal and liver function parameters, ammonia levels, fluid and electrolyte status, serum osmolarity, blood glucose, blood count and coagulation parameters throughout treatment. In situations of severely elevated electrolyte levels, stop CLINIMIX and CLINIMIX E until levels have been corrected.
- Adverse reactions include diuresis, extravasation, glycosuria, hyperglycemia, and hyperosmolar coma.

Please see accompanying Package Inserts for full Prescribing Information.

Conversion is Easy

Thousands of hospitals have successfully incorporated CLINIMIX (amino acids in dextrose) Injections and CLINIMIX E (amino acids with electrolytes in dextrose with calcium) Injections into their pharmacy operations. Baxter can assist you with all aspects of your conversion process.

- Product Education; inservicing; tools and resources to inform and support the implementation process
- Help identify formulations by conducting a TPN Order Analysis of a sampling of your historical PN orders to determine the most appropriate CLINIMIX and CLINIMIX E formulations
- Bag activation training video and poster; available at www.baxtermedicationdeliveryproducts.com

Place your order now. Call your Baxter representative at 1-888-229-0001

Visit www.clinimix.com

Your global PN leader for more than 80 years.

1. CLINIMIX and CLINIMIX E Injections Package Insert (2016)
2. Sacks et al. Parenteral Nutrition Implementation and Management. The A.S.P.E.N. Nutrition Support Practice Manual 2nd Edition, 108-117. (2005)
3. Baxter Clinimix Challenge. Data on file. (2014)
4. Tirumalai, R. Terminally Sterilized Pharmaceutical Products-Parametric Release. *Pharmacopeia*. Retrieved from http://www.pharmacopeia.cn/v29240/usp29nf24s0_c1222.html (2005)
5. McClave et al. Guidelines for the Provision and Assessment of Nutrition Support Therapy in the Adult Critically Ill Pt: Society of Critical Care Medicine and American Society for Parenteral and Nutrition. *Journal of Parenteral and Enteral Nutrition*, 33, 277-316. (2009).
6. Gervasio, J. Compounding vs Standardized Commercial Parenteral Nutrition Product: Pros and Cons. *Journal of Parenteral and Enteral Nutrition*, 36, 40S-41S. (2012).
7. Mirtallo, Jay. Parenteral Nutrition: Can Outcomes be Improved? *Journal of Parenteral and Enteral Nutrition*, 37,181-189. (2013)
8. Kochevar et al. A.S.P.E.N Statement on Parenteral Nutrition Standardization. *Journal of Parenteral and Enteral Nutrition*, 31,441-448. (2007).

Please see inside back cover for Indications and Important Risk information.
Please see accompanying Package Inserts for full Prescribing Information.

www.baxter.com

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USMP/78/14-0032(1) 1/17

Baxter

HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use CLINIMIX safely and effectively. See full prescribing information for CLINIMIX.

CLINIMIX (amino acids in dextrose) injection, for intravenous use Initial U.S. Approval: 1997

---------- INDICATIONS AND USAGE ----------
CLINIMIX is indicated as a source of calories and protein for patients requiring parenteral nutrition when oral or enteral nutrition is not possible, insufficient, or contraindicated. CLINIMIX may be used to treat negative nitrogen balance in patients. (1)

---------- DOSAGE AND ADMINISTRATION ----------
See full prescribing information for information on preparation, administration, instructions for use, dosing considerations, including the recommended dosage in adults and pediatrics, and dosage modifications in patients with renal impairment. (2.1, 2.2, 2.3, 2.4, 2.5, 2.6, 2.7, 2.8)

---------- DOSAGE FORMS AND STRENGTHS ----------
CLINIMIX injection is available in multiple strengths. See full prescribing information for detailed description of each formulation. (3, 11)

---------- CONTRAINDICATIONS ----------
- Known hypersensitivity to one or more amino acids or dextrose. (4)
- Inborn errors of amino acid metabolism. (4)
- Patients with pulmonary edema or acidosis due to low cardiac output. (4)

---------- WARNINGS AND PRECAUTIONS ----------
- Pulmonary Embolism due to Pulmonary Vascular Precipitates: if signs of pulmonary distress occur, stop the infusion and initiate a medical evaluation. (5.1)
- Hypersensitivity Reactions: monitor for signs and symptoms and discontinue infusion if reactions occur. (5.2)
- Risk of Infections, Refeeding Complications, and Hyperglycemia or Hyperosmolar Hyperglycemic State: monitor for signs and symptoms; monitor laboratory parameters. (5.3, 5.4, 5.5)
- Vein Damage and Thrombosis: solutions with osmolarity of ≥ 900 mOsm/L must be infused through a central catheter. (2.2, 5.6)
- Hepatobiliary Disorders: monitor liver function parameters and ammonia levels. (5.7)
- Aluminum Toxicity: increased risk in patients with renal impairment, including preterm infants. (5.8, 8.4)
- Parenteral Nutrition Associated Liver Disease: increased risk in patients who receive parenteral nutrition for extended periods of time, especially preterm infants; monitor l iver function tests, if abnormalities occur consider discontinuation or dosage reduction. (5.9, 8.4)
- Electrolyte Imbalance and Fluid Overload: patients with cardiac insufficiency or renal impairment may require adjustment of fluid, protein and electrolyte content. (5.10, 8.4)

---------- ADVERSE REACTIONS ----------
Adverse reactions include diuresis, extravasation, glycosuria, hyperglycemia, and hyperosmolar coma. (6)

To report SUSPECTED ADVERSE REACTIONS, contact Baxter Healthcare Corporation at 1-866-888-2472 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch

---------- USE IN SPECIFIC POPULATIONS ----------
Pediatric Use: increased risk of hypoglycemia/hyperglycemia: monitor serum glucose concentrations. (8.4)

See 17 for PATIENT COUNSELING INFORMATION. **Revised: 9/2016**

FULL PRESCRIBING INFORMATION: CONTENTS*

*Sections or subsections omitted from the full prescribing information are not listed.

FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

CLINIMIX is indicated as a source of calories and protein for patients requiring parenteral nutrition when oral or enteral nutrition is not possible, insufficient, or contraindicated. CLINIMIX may be used to treat negative nitrogen balance in patients.

2 DOSAGE AND ADMINISTRATION

2.1 Preparation Prior to Administration

- Tear protective foil overwrap across top at slit and remove solution container. Small amounts of moisture may be found on the solution container from water permeating from inside the container. The amount of permeated water is insufficient to affect the solution significantly. If larger amounts of water are found, the container should be checked for tears or leaks.
- Inspect the bag prior to activation. 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. Evaluate the following:
  - If the outlet or additive port protectors are damaged, detached, or not present, discard container as solution path sterility may be impaired.
  - Check to ensure seal between chambers is intact, solutions are contained in separate chambers, and the content of the individual chambers is clear, colorless or slightly yellow. Discard if the seal is broken or if the solution is bright yellow or yellowish brown.
  - Check for minute leaks by separately squeezing each chamber. If external leaks or leakage between the chambers are found, discard solution as sterility or stability may be impaired.
- Lipids and/or additives can be introduced to the container after opening seal between chambers. Because additives may be incompatible, evaluate all additions to the plastic container for compatibility. Activate chambers of bag prior to introduction of additives. Mix thoroughly when additives have been introduced. Supplemental medication may be added with a 19 to 22 gauge needle through the medication port.
- Calcium and phosphate ratios must be considered. Excess addition of calcium and phosphate, especially in the form of mineral salts, may result in the formation of calcium phosphate precipitates *[see Warnings and Precautions (5.1)].*
- Inspect the bag to ensure precipitates have not formed during the mixing or addition of additives. A slight yellow color does not alter the quality and efficacy of this product. If lipid has been added, ensure the emulsion has not separated. Separation of the emulsion can be visibly identified by a yellowish streaking or the accumulation of yellowish droplets in the mixed emulsion. Discard the admixture if any of the above are observed.

2.2 Important Administration Instructions

- Set the vent to the closed position on a vented intravenous administration set to prevent air embolism.
- Use a dedicated line without any connections to avoid air embolism.
- CLINIMIX is for intravenous infusion only into a central or peripheral vein. The choice of a central or peripheral venous route should depend on the osmolarity of the final infusate. Solutions with osmolarity of 900 mOsm/L or greater must be infused through a central catheter *[see Warnings and Precautions (5.6)]*.
  - For central vein infusion only: CLINIMIX 4.25/10, 4.25/20, 4.25/25, 5/15, 5/20, 5/25
  - For central or peripheral vein infusion: CLINIMIX 2.75/5 and 4.25/5
- The solution should be inspected for precipitates before admixing, after admixing, and again before administration.
- Use a 0.22 micron filter for administration of CLINIMIX. If a lipid is also administered, use a 1.2 micron filter.
- If lipid emulsion is added, do not use administration sets and lines that contain di-2-ethylhexyl phthalate (DEHP). Administration sets that contain polyvinyl chloride (PVC) components have DEHP as a plasticizer.

2.3 Instructions for Use

1. Open by tearing protective foil overwrap across top at slit and remove solution container.
2. Lay the bag onto a flat surface. Grasp the container firmly on each side of the top of the bag (**Figure 1**).
3. Starting from the top squeeze and roll bag to open seal between chambers until the peel-seal is completely broken as shown in **Figure 2**.
4. If the seal has not been separated completely flip the bag over and repeat process.
5. Mix the contents thoroughly by inverting the bag upside down to ensure a homogenous admixture (**Figure 3**).
6. Once the bag is mixed, check for leaks.
7. Make additions (if prescribed).

Because additives may be incompatible, evaluate all additions to the bag for compatibility and stability of the resulting preparation. Consult with pharmacist, if available. Questions about compatibility may be directed to Baxter. If it is deemed advisable to introduce additives, use aseptic technique. For information on adding lipid emulsions *see Dosage and Administration (2.4).*

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 (**Figure 3**). For high density medication (high specific gravity), such as potassium chloride, squeeze ports while ports are upright and mix thoroughly. 8. Inspect final solution for discoloration and particulate matter. Check for leaks.

9. Spike and hang bag.

a. Suspend container from eyelet support.

b. Twist off protector from outlet port at bottom of container (**Figure 4**).

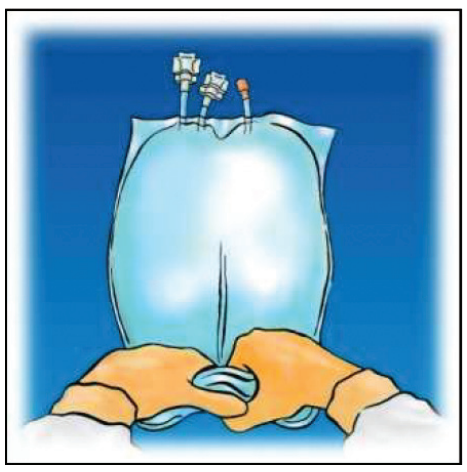
c. Attach administration set. Refer to complete directions accompanying set.

For single dose only. Discard unused portion.

Figures 1-4:

1. Lay the bag onto a flat surface. Grasp the bag firmly with both hands at the top corners.

2. Starting from the top, squeeze and roll the bag down toward the bottom until the peel seal is broken down the center. You should feel or hear an audible pop as the peel seal dividing the chambers is broken, which allows the components from each chamber to mix.



3. Mix by turning the bag upsidedown at least 3 times.

4. Hang the bag. Twist off the protector from the administration outlet. Firmly plug the spike connector.

Instructions on Storage

Storage After Removal of Overwrap:

Once removed from the protective foil overwrap, mixed (peel seal activated) or unmixed (peel seal intact) CLINIMIX Injection solutions may be stored under refrigeration for up to 9 days.

Storage Once any Additive is Added:

Use promptly after mixing. Any storage with additives should be under refrigeration and limited to a brief period of time, less than 24 hours. After removal from refrigeration, use promptly and complete the infusion within 24 hours. Any remaining mixture must be discarded.

2.4 Preparation and Addition of Lipid Emulsion

1. Prior to adding lipid emulsion, mix amino acid and dextrose injection as shown in **Figures 1-3**.
2. Prepare lipid emulsion transfer set following instructions provided.
3. Attach transfer set to lipid emulsion container using aseptic technique.
4. Twist off protector on the additive port of the container.
5. Attach the transfer set to the exposed additive port.
6. Open clamp on transfer set.
7. After completing transfer, use appropriate plastic clamp or metal ferrule to seal off additive port tube.
8. Remove transfer set.
9. Mix contents of container thoroughly. Inspect final solution for discoloration and particulate matter. Check for leaks.

Storage Once Lipids are Added:

Use promptly after mixing. Any storage with additives should be under refrigeration and limited to a brief period of time, no longer than 24 hours. After removal from refrigeration, use promptly and complete the infusion within 24 hours. Any mixture remaining must be discarded.

2.5 Dosing Considerations

- The dosage of CLINIMIX should be individualized based on the patient's clinical condition (ability to adequately metabolize amino acids and dextrose), body weight and nutritional/fluid requirements, as well as additional energy given orally/enterally to the patient. Prior to initiating CLINIMIX the following patient information should be reviewed:, review of all medications, gastrointestinal function and laboratory data such as electrolytes (including magnesium, calcium, and phosphorus), glucose, urea/creatinine, liver panel, complete blood count and triglyceride level (if adding lipid emulsion). Refer to the complete prescribing information of lipid emulsion for dosing information.
- CLINIMIX formulations have varying concentrations of protein and carbohydrate; thus infusion rates to achieve requirements will vary. Protein, caloric, fluid and electrolyte requirements all need to be taken into consideration when determining individual patient dosage needs.
- The dosage selection is based only on the recommended protein requirements. The maximum dextrose infusion rates and calorie and fluid requirements must also be considered when determining the clinically appropriate infusion rate for patients.
- CLINIMIX meets the total nutritional requirements for protein and dextrose in stable patients, and can be individualized to meet specific needs with the addition of nutrients.
- Total daily fluid requirements can be met beyond the volume of amino acids solution by supplementing with non-carbohydrate or carbohydrate-containing electrolyte solutions. 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.
- Prior to administration of CLINIMIX correct severe fluid, electrolyte and acid-base disorders.
- Monitor levels of serum potassium during therapy. It may be necessary to add potassium to the CLINIMIX admixture.
- Lipid emulsion administration should be considered with prolonged use (more than 5 days) of CLINIMIX in order to prevent essential fatty acid deficiency (EFAD). Serum lipids should be monitored for evidence of EFAD in patients maintained on fat-free parenteral nutrition. See prescribing information of lipid emulsion.
- The flow rate should be increased gradually. The flow rate must be adjusted taking into account the dose being administered, the daily volume intake, and the duration of the infusion.

2.6 Recommended Dosage in Adults

The recommended daily nutritional requirements for protein and dextrose compared to the amount of nutrition provided by CLINIMIX are shown in **Table 1**.

As indicated on an individual basis, maintenance vitamins, electrolytes, trace elements and other components (including lipids) should be administered as required to prevent deficiencies and complications from developing.

The maximum infusion rates in adult patients are show in **Table 2**.

In addition to meeting protein needs, the administration rate should be governed, especially during the first few day of therapy, by the patient's tolerance to dextrose. Daily intake of amino acids and dextrose should be increased gradually to the maximum required dose as indicated by frequent determinations of blood glucose levels.

Table 1: Nutritional Comparison –Adult Patients

	Recommended Nutritional Requirements[1]		Recommended Clinimix Adult Dosage							
	Stable Patients	Critically Ill Patients*	Clinimix 2.75/5	Clinimix 4.25/5	Clinimix 4.25/10	Clinimix 4.25/20	Clinimix 4.25/25	Clinimix 5/15	Clinimix 5/20	Clinimix 5/25
Fluid (mL/kg/day)	30 to 40	Minimum needed to deliver adequate nutrition	29 to 40	19 to 40	19 to 40	19 to 40	19 to 40	16 to 40	16 to 40	16 to 40
Protein** (g/kg/day) (Nitrogen g/kg/day)	0.8 to 1 (0.13 to 0.16)	1.5 to 2 (0.24 to 0.32)	0.8 to 1.1 (0.13 to 0.18)	0.8 to 1.7 (0.13 to 0.27)	0.8 to 1.7 (0.13 to 0.27)	0.8 to 1.7 (0.13 to 0.27)	0.8 to 1.7 (0.13 to 0.27)	0.8 to 2 (0.13 to 0.32)	0.8 to 2 (0.13 to 0.32)	0.8 to 2 (0.13 to 0.32)
Dextrose (g/kg/day)	≤10	≤5.8	1.45 to 2	0.95 to 2	1.9 to 4	3.8 to 8	4.75 to 10	2.4 to 6	3.2 to 8	4 to 10

* Do not use in patients with conditions that are contraindicated [see Contraindications (4)].
** Protein is provided as amino acids. When infused intravenously amino acids are metabolized and utilized as the building blocks of protein.

Table 2: Maximum Infusion Rate in Adult Patients:

		Maximum Infusion Rates in Adults Patients							
		Clinimix 2.75/5	Clinimix 4.25/5	Clinimix 4.25/10	Clinimix 4.25/20	Clinimix 4.25/25	Clinimix 5/15	Clinimix 5/20	Clinimix 5/25
Maximum Infusion Rate (mL/kg/hour)		3.6	2.4	2.4	1.25	1	1.67	1.25	1
Corresponding infusion rate	**Amino Acid (g/kg/hour)**	0.1*	0.1*	0.1*	0.05	0.04	0.08	0.06	0.05
	Dextrose (g/kg/hour)	0.18	0.12	0.24	0.25*	0.25*	0.25*	0.25*	0.25*

*Rate limiting factor

2.7 Dosage Modifications in Patients with Renal Impairment

Prior to administration, correct severe fluid or electrolyte imbalances. Closely monitor serum electrolyte levels and adjust the volume of CLINIMIX administered as required *[see Warnings and Precautions (5.10)].*

Patients with renal impairment not needing dialysis require 0.6 to 0.8 g of protein/kg/day. Serum electrolyte levels should be closely monitored. Patients on hemodialysis or continuous renal replacement therapy should receive 1.2 to 1.8 g of protein/kg/day up to a maximum of 2.5 g of protein/kg/day based on nutritional status and estimated protein losses.[2] The CLINIMIX dosage can be adjusted based on the severity of renal impairment, supplementing protein as indicated. If required, additional amino acids may be added to the CLINIMIX bag or infused separately. Compatibility of additions should be evaluated by a pharmacist and questions may be directed to Baxter.

2.8 Recommended Dosage in Pediatric Patients

The dosage and constant infusion rate of intravenous dextrose must be selected with caution in pediatric patients, particularly neonates and low weight infants, because of the increased risk of hyperglycemia/hypoglycemia *[see Use in Specific Populations (8.4)].* Frequent monitoring of serum glucose concentrations is required when dextrose is prescribed to pediatric patients, particularly neonates and low birth weight infants. The infusion rate and volume should be determined by the consulting physician experienced in pediatric intravenous fluid therapy.

In pediatric patients, CLINIMIX is dosed on the basis of protein provided as amino acids. The recommended dosage, by age group is provided in **Tables 3–6**. Infusion rates are based on protein and do not take carbohydrates, fluid or electrolytes into consideration.

This product does not contain the amino acids cysteine and taurine, considered conditionally essential for neonates and infants. If possible, these amino acids should be added to this product if used in this pediatric population.

Table 3: Preterm and Term Infants Less than 1 Month of Age

	Recommended Nutritional Requirements[1]	Recommended Clinimix Dosage in Preterm and Term Infants Less than 1 Month of Age							
		Clinimix 2.75/5	Clinimix 4.25/5	Clinimix 4.25/10	Clinimix 4.25/20	Clinimix 4.25/25	Clinimix 5/15	Clinimix 5/20	Clinimix 5/25
Infusion Rate Range (mL/kg/hr)		4.5 to 6	2.9 to 3.9	2.9 to 3.9	2.9 to 3.9	2.9 to 3.3	2.5 to 3.3	2.5 to 3.3	2.5 to 3.3
Fluid (mL/kg/day)	100 to 150	108 to 144	70 to 94	70 to 94	70 to 94	70 to 79	60 to 79	60 to 79	60 to 79
Protein* (g/kg/day) (Nitrogen g/kg/day)	3 to 4 (0.48 to 0.64)	3 to 4 (0.48 to 0.64)	3 to 4 (0.48 to 0.64)	3 to 4 (0.48 to 0.64)	3 to 4 (0.48 to 0.64)	3 to 3.4 (0.48 to 0.54)	3 to 4 (0.48 to 0.64)	3 to 4 (0.48 to 0.64)	3 to 4 (0.48 to 0.64)
Dextrose (g/kg/day)	7 to 20	5.4 to 7.2	3.5 to 4.7	7 to 9.4	14 to 18.8	17.5 to 19.8	9 to 11.9	12 to 15.8	15 to 19.8

* Protein is provided as amino acids. When infused intravenously amino acids are metabolized and utilized as the building blocks of protein.

Table 4: Pediatric Patients 1 Month to Less than 1 Year of Age

	Recommended Nutritional Requirements[1]	Recommended Clinimix Dosage in Pediatric Patients 1 Month to Less than 1 Year of Age							
		Clinimix 2.75/5	Clinimix 4.25/5	Clinimix 4.25/10	Clinimix 4.25/20	Clinimix 4.25/25	Clinimix 5/15	Clinimix 5/20	Clinimix 5/25
Infusion Rate Range (mL/kg/hr)		3 to 4.5	2 to 2.9	2 to 2.9	2 to 2.9	2 to 2.9	1.7 to 2.5	1.7 to 2.5	1.7 to 2.5
Fluid (mL/kg/day)	100 mL/kg for the first 10 kg + 50 mL/kg for the second 10 kg.	72 to 108	48 to 70	48 to 70	48 to 70	48 to 70	41 to 60	41 to 60	41 to 60
Protein* (g/kg/day) (Nitrogen g/kg/day)	2 to 3 (0.32 to 0.48)	2 to 3 (0.32 to 0.48)	2 to 3 (0.32 to 0.48)	2 to 3 (0.32 to 0.48)	2 to 3 (0.32 to 0.48)	2 to 3 (0.32 to 0.48)	2 to 3 (0.32 to 0.48)	2 to 3 (0.32 to 0.48)	2 to 3 (0.32 to 0.48)
Dextrose (g/kg/day)	7 to 20	3.6 to 5.4	2.4 to 3.5	4.8 to 7	9.6 to 14	12 to 17.5	6.1 to 9	8.2 to 12	10.2 to 15

* Protein is provided as amino acids. When infused intravenously amino acids are metabolized and utilized as the building blocks of protein.

Table 5: Pediatric Patients 1 Year to Less than 11 Years of Age

	Recommended Nutritional Requirements[1]	Recommended Clinimix Dosage in Pediatric Patients 1 Year to Less than 11 Years of Age							
		Clinimix 2.75/5	Clinimix 4.25/5	Clinimix 4.25/10	Clinimix 4.25/20	Clinimix 4.25/25	Clinimix 5/15	Clinimix 5/20	Clinimix 5/25
Infusion Rate Range (mL/kg/hr)		1.5 to 3	1 to 2	1 to 2	1 to 2	1 to 2	0.8 to 1.7	0.8 to 1.7	0.8 to 1.7

* Protein is provided as amino acids. When infused intravenously amino acids are metabolized and utilized as the building blocks of protein.

Table 6: Pediatric Patients 11 Years to 17 Years of Age

	Recommended Nutritional Requirements[1]	Recommended Clinimix Dosage in Pediatric Patients 11 Years to 17 Years of Age							
		Clinimix 2.75/5	Clinimix 4.25/5	Clinimix 4.25/10	Clinimix 4.25/20	Clinimix 4.25/25	Clinimix 5/15	Clinimix 5/20	Clinimix 5/25
Infusion Rate Range (mL/kg/hr)		1.2 to 2.3	0.8 to 1.5	0.8 to 1.5	0.8 to 1.5	0.8 to 1.5	0.7 to 1.3	0.7 to 1.3	0.7 to 1.3
Fluid (mL/kg/day)	100 mL/kg for the first 10 kg + 50 mL/kg for the second 10 kg + 20 mL/kg for weight > 20 kg	29 to 55	19 to 36	19 to 36	19 to 36	19 to 36	17 to 31	17 to 31	17 to 31
Protein* (g/kg/day) (Nitrogen g/kg/day)	0.8 to 1.5 (0.13 to 0.24)	0.8 to 1.5 (0.13 to 0.24)	0.8 to 1.5 (0.13 to 0.24)	0.8 to 1.5 (0.13 to 0.24)	0.8 to 1.5 (0.13 to 0.24)	0.8 to 1.5 (0.13 to 0.24)	0.8 to 1.5 (0.13 to 0.24)	0.8 to 1.5 (0.13 to 0.24)	0.8 to 1.5 (0.13 to 0.24)
Dextrose (g/kg/day)	5 to 9	1.4 to 2.8	1 to 1.8	1.9 to 3.6	3.8 to 7.2	4.8 to 9	2.5 to 4.7	3.4 to 6.2	4.2 to 7.8

* Protein is provided as amino acids. When infused intravenously amino acids are metabolized and utilized as the building blocks of protein.

2.9 Discontinuation of CLINIMIX

To reduce the risk of hypoglycemia after discontinuation, a gradual decrease in flow rate in the last hour of infusion should be considered.

3 DOSAGE FORMS AND STRENGTHS

CLINIMIX injection is available in 1000 mL and 2000 mL dual chamber bags. The individual chambers contain essential and nonessential amino acids and dextrose. **Table 7** describes the individual components of CLINIMIX.

Table 7 Ingredients per 100mL of CLINIMIX

Strength of CLINIMIX		CLINIMIX 2.75/5 sulfite-free (2.75% Amino Acid in 5% Dextrose) Injection	CLINIMIX 4.25/5 sulfite-free (4.25% Amino Acid in 5% Dextrose) Injection	CLINIMIX 4.25/10 sulfite-free (4.25% Amino Acid in 10% Dextrose) Injection	CLINIMIX 4.25/20 sulfite-free (4.25% Amino Acid in 20% Dextrose) Injection	CLINIMIX 4.25/25 sulfite-free (4.25% Amino Acid in 25% Dextrose) Injection	CLINIMIX 5/15 sulfite-free (5% Amino Acid in 15% Dextrose) Injection	CLINIMIX 5/20 sulfite-free (5% Amino Acid in 20% Dextrose) Injection	CLINIMIX 5/25 sulfite-free (5% Amino Acid in 25% Dextrose) Injection
	Dextrose Hydrous, USP (g/100 mL)	5	5	10	20	25	15	20	25
	Amino Acids (g/100 mL)	2.75	4.25	4.25	4.25	4.25	5	5	5
	Total Nitrogen (mg/100 mL)	454	702	702	702	702	826	826	826
Essential Amino Acids (mg/100 mL)	Leucine	201	311	311	311	311	365	365	365
	Isoleucine	165	255	255	255	255	300	300	300
	Valine	160	247	247	247	247	290	290	290
	Lysine (added as the hydrochloride salt)	159	247	247	247	247	290	290	290
	Phenylalanine	154	238	238	238	238	280	280	280
	Histidine	132	204	204	204	204	240	240	240
	Threonine	116	179	179	179	179	210	210	210
	Methionine	110	170	170	170	170	200	200	200
	Tryptophan	50	77	77	77	77	90	90	90
Nonessential Amino Acids (mg/100 mL)	Alanine	570	880	880	880	880	1035	1035	1035
	Arginine	316	489	489	489	489	575	575	575
	Glycine	283	438	438	438	438	515	515	515
	Proline	187	289	289	289	289	340	340	340
	Serine	138	213	213	213	213	250	250	250
	Tyrosine	11	17	17	17	17	20	20	20
Anion Profile (mEq/L)1	Acetate[2]	24	37	37	37	37	42	42	42
	Chloride[3]	11	17	17	17	17	20	20	20
	pH [4] (Range)	6.0 (4.5 to 7.0)	6.0 (4.5 to 7.0)	6.0 (4.5 to 7.0)	6.0 (4.5 to 7.0)	6.0 (4.5 to 7.0)	6.0 (4.5 to 7.0)	6.0 (4.5 to 7.0)	6.0 (4.5 to 7.0)
	Osmolarity (mOsmol/L) (calc)	525	675	930	1435	1685	1255	1505	1760
Caloric Content (kcal/L)	From Dextrose	170	170	340	680	850	510	680	850
	From Amino Acids	110	170	170	170	170	200	200	200
	TOTAL (Dextrose and Amino Acids)	280	340	510	850	1020	710	880	1050

1. Balanced by ions from amino acids.
2. Derived from glacial acetic acid (for pH adjustment) and sodium acetate.
3. Contributed by calcium chloride, lysine hydrochloride, magnesium chloride, and sodium chloride.
4. pH of sulfite-free amino acid injection in the outlet port chamber was adjusted with glacial acetic acid.

4 CONTRAINDICATIONS

The use of CLINIMIX is contraindicated in:

- Patients with known hypersensitivity to one or more amino acids or dextrose *[see Warnings and Precautions (5.2)].*
- Patients with inborn errors of amino acid metabolism due to risk of severe metabolic and neurologic complications.
- Patients with pulmonary edema or acidosis due to low cardiac output.

5 WARNINGS AND PRECAUTIONS

5.1 Pulmonary Embolism due to Pulmonary Vascular Precipitates

Pulmonary vascular precipitates causing pulmonary vascular emboli and pulmonary distress have been reported in patients receiving parenteral nutrition. In some cases, fatal outcomes due to pulmonary embolism have occurred. CLINIMIX contains no added phosphorus. Patients, especially those with hypophosphatemia, may require the addition of phosphate. To prevent hypocalcemia, calcium supplementation should always accompany phosphate administration. Excessive addition of calcium and phosphate increases the risk of the formation of calcium phosphate precipitates. Precipitates have been reported even in the absence of phosphate salt in the solution. Precipitation following passage through an in-line filter and suspected in vivo precipitate formation has also been reported. If signs of pulmonary distress occur, stop the infusion and initiate a medical evaluation. In addition to inspection of the solution *[see Dosage and Administration (2.1, 2.2, 2.3, 2.4)],* the infusion set and catheter should also periodically be checked for precipitates.

5.2 Hypersensitivity Reactions

Hypersensitivity/infusion reactions including anaphylaxis have been reported with CLINIMIX. Stop infusion immediately and treat patient accordingly if any signs or symptoms of a hypersensitivity reaction develop. Signs or symptoms may include: hypotension, hypertension, peripheral cyanosis, tachycardia, dyspnea, vomiting, nausea, urticaria, rash, pruritus, erythema, hyperhidrosis, pyrexia, and chills.

5.3 Risk of Infections

Patients who require parenteral nutrition are at high risk of infections because the nutritional components of these solutions can support microbial growth. Infection and sepsis may also occur as a result of the use of intravenous catheters to administer parenteral nutrition.

The risk of infection is increased in patients with malnutrition-associated immunosuppression, hyperglycemia exacerbated by dextrose infusion, long-term use and poor maintenance of intravenous catheters, or immunosuppressive effects of other concomitant conditions, drugs, or other components of the parenteral formulation (e.g., lipid emulsion).

To decrease the risk of infection, ensure aseptic technique in catheter placement and maintenance, as well as aseptic technique in the preparation and administration of the nutritional formula.

Monitor for signs and symptoms (including fever and chills) of early infections, including laboratory test results (including leukocytosis and hyperglycemia) and frequent checks of the parenteral access device and insertion site for edema, redness and discharge.

5.4 Refeeding Syndrome

Refeeding severely undernourished patients may result in refeeding syndrome, characterized by the intracellular shift of potassium, phosphorus, and magnesium as the patient becomes anabolic. Thiamine deficiency and fluid retention may also develop. To prevent these complications, monitor severely undernourished patients and slowly increase nutrient intakes.

5.5 Hyperglycemia or Hyperosmolar Hyperglycemic State

When using CLINIMIX in patients with diabetes mellitus, impaired glucose tolerance may worsen hyperglycemia. Administration of dextrose at a rate exceeding the patient's utilization rate may lead to hyperglycemia, coma, and death. Patients with underlying confusion and renal impairment who receive dextrose infusions, may be at greater risk of developing hyperosmolar hyperglycemic state. Monitor blood glucose levels and treat hyperglycemia to maintain optimum levels while administering CLINIMIX. Insulin may be administered or adjusted to maintain optimal blood glucose levels during CLINIMIX administration.

5.6 Vein Damage and Thrombosis

Solutions with osmolarity of 900 mOsm/L or greater must be infused through a central catheter. CLINIMIX solutions containing more than 5% dextrose have an osmolarity greater than or equal to 900 mOsm/L. CLINIMIX 4.25/10, 4.25/20, 4.25/25, 5/15, 5/20, and 5/25 are indicated for administration into a central vein only, such as the superior vena cava *[see Dosage and Administration (2.2)].* The infusion of hypertonic nutrient injections into a peripheral vein may result in vein irritation, vein damage, and/or thrombosis.

CLINIMIX 2.75/5 and 4.25/5 are indicated for peripheral administration, or may be infused into a central vein *[see Dosage and Administration (2.2)].* The primary complication of peripheral access is venous thrombophlebitis, which manifests as pain, erythema, tenderness or a palpable cord. Remove the catheter as soon as possible, if thrombophlebitis develops.

5.7 Hepatobiliary Disorders

Hepatobiliary disorders are known to develop in some patients without preexisting liver disease who receive parenteral nutrition, including cholecystitis, cholelithiasis, cholestasis, hepatic steatosis, fibrosis and cirrhosis, possibly leading to hepatic failure. The etiology of these disorders is thought to be multifactorial and may differ between patients.

Increase in blood ammonia levels and hyperammonemia may occur in patients receiving amino acid solutions. In some patients this may indicate hepatic insufficiency or the presence of an inborn error of amino acid metabolism *[see Contraindications (4).]*

Monitor liver function parameters and ammonia levels. Patients developing signs of hepatobiliary disorders should be assessed early by a clinician knowledgeable in liver diseases in order to identify possible causative and contributory factors, and possible therapeutic and prophylactic interventions.

5.8 Aluminum Toxicity

CLINIMIX contains no more than 25 mcg/L of aluminum. However, with prolonged parenteral administration in patients with renal impairment, the aluminum contained in CLINIMIX may reach toxic levels. Preterm infants are at a greater risk because their kidneys are immature, and they require large amounts of calcium and phosphate solutions, which contain aluminum.

Patients with renal impairment, including preterm infants, 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.

5.9 Risk of Parenteral Nutrition Associated Liver Disease

Parenteral Nutrition Associated Liver Disease (PNALD) has been reported in patients who receive parenteral nutrition for extended periods of time, especially preterm infants, and can present as cholestasis or steatohepatitis. The exact etiology is unknown and is likely multifactorial. If CLINIMIX treated patients develop liver test abnormalities consider discontinuation or dosage reduction.

5.10 Electrolyte Imbalance and Fluid Overload

Patients with renal impairment, such as pre-renal azotemia, renal obstruction, and protein-losing nephropathy may be at increased risk of electrolyte and fluid volume imbalance. Patients with cardiac insufficiency due to left ventricular systolic dysfunction are susceptible to excess fluid accumulation. Use CLINIMIX with caution in patients with cardiac insufficiency or renal impairment. CLINIMIX dosage may require adjustment with specific attention to fluid, protein, and electrolyte content in these patients.

Monitor renal function parameters. Patients developing signs of renal impairment should be assessed early by a clinician knowledgeable in renal disease in order to determine the appropriate CLINIMIX dosage and other treatment options.

5.11 Monitoring/Laboratory Tests

Monitor fluid and electrolyte status, serum osmolarity, blood glucose, liver and kidney function, blood count and coagulation parameters throughout treatment.

Patients receiving CLINIMIX should be monitored frequently and their electrolyte requirements individualized.

6 ADVERSE REACTIONS

The following serious adverse reactions are discussed in greater detail in other sections of the prescribing information.

- Pulmonary embolism due to pulmonary vascular precipitates *[see Warnings and Precautions (5.1)]*
- Hypersensitivity reactions *[see Warnings and Precautions (5.2)]*
- Risk of Infections *[see Warnings and Precautions (5.3)]*
- Refeeding syndrome *[see Warnings and Precautions (5.4)]*
- Hyperglycemia or hyperosmolar hyperglycemic state *[see Warnings and Precautions (5.5)]*
- Vein damage and thrombosis *[see Warnings and Precautions (5.6)]*
- Hepatobiliary disorders [see Warnings and Precautions (5.7)]
- Parenteral Nutrition Associated Liver Disease *[see Warnings and Precautions (5.9)]*
- Electrolyte imbalance and fluid overload *[see Warnings and Precautions (5.10)]*

The following adverse reactions from voluntary reports or clinical studies have been reported with CLINIMIX. Because many of these reactions were reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

- Diuresis
- Extravasation
- Glycosuria
- Hyperglycemia
- Hyperosmolar coma

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

There are no adequate or well-controlled studies in pregnant women with CLINIMIX. Additionally, animal reproduction studies have not been conducted with amino acids and electrolytes and dextrose. It is not known whether CLINIMIX can cause fetal harm when administered to a pregnant woman.

The estimated background risk of major birth defects and miscarriage for the indicated population is unknown. However, the estimated background risk in the U.S. general population of major birth defects is 2 to 4% and of miscarriage is 15 to 20% of clinically recognized pregnancies.

Clinical Considerations

Disease-Associated Maternal and/or Embryo-Fetal Risk

Based on clinical practice guidelines, parenteral nutrition should be considered in cases of severe maternal malnutrition where nutritional requirements cannot be fulfilled by the enteral route because of the risks to the fetus associated with severe malnutrition, such as preterm delivery, low birth weight, intrauterine growth restriction, congenital malformations and perinatal mortality.

8.2 Lactation

Risk Summary

It is not known whether CLINIMIX is present in human milk. There are no data on the effects of CLINIMIX on the breastfed infant or on milk production. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for CLINIMIX and any potential adverse effects on the breastfed child from CLINIMIX or from the underlying maternal condition.

8.4 Pediatric Use

Safety and effectiveness of CLINIMIX in pediatric patients have not been established by adequate and wellcontrolled studies. Use of dextrose, amino acid infusions and electrolytes in pediatric patients is based on clinical practice *[see Dosage and Administration (2.8)]*.

Newborns, especially those born premature and with low birth weight, are at increased risk of developing hypo – or hyperglycemia and therefore need close monitoring during treatment with intravenous glucose solutions to ensure adequate glycemic control in order to avoid potential long term adverse effects. Hypoglycemia in the newborn can cause prolonged seizures, coma and brain damage. Hyperglycemia has been associated with intraventricular hemorrhage, late onset bacterial and fungal infection, retinopathy of prematurity, necrotizing enterocolitis, bronchopulmonary dysplasia, prolonged length of hospital stay, and death. Plasma electrolyte concentrations should be closely monitored in the pediatric population as this population may have impaired ability to regulate fluids and electrolytes.

Because of immature renal function, preterm infants receiving prolonged treatment with CLINIMIX may be at risk of aluminum toxicity *[see Warnings and Precautions (5.8)]*.

Patients, including pediatric patients, may be at risk for Parenteral Nutrition Associated Liver Disease (PNALD) *[see Warnings and Precautions (5.9)]*.

Hyperammonemia is of special significance in infants (birth to two years). 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 *[See Warnings and Precautions (5.7)]*.

8.5 Geriatric Use

Clinical studies of CLINIMIX did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from other younger subjects. Other reported clinical experience has not identified differences in responses between the elderly and younger patients.

In general, dose selection for an elderly patient should be cautious, usually starting at the low end of the dosing range, reflecting the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or drug therapy.

10 OVERDOSAGE

An increased infusion rate of CLINIMIX can cause hyperglycemia, hyperosmolality, and adverse effects on water and electrolyte balance *[see Warnings and Precautions (5.5, 5.10)]*.

Severe hyperglycemia and severe dilutional hyponatremia, and their complications, can be fatal.

Discontinue infusion and institute appropriate corrective measures in the event of overhydration or solute overload during therapy, with particular attention to respiratory and cardiovascular systems.

For current information on the management of poisoning or overdosage, contact the National Poison Control Center at 1-800-222-1222 or www.poison.org.

11 DESCRIPTION

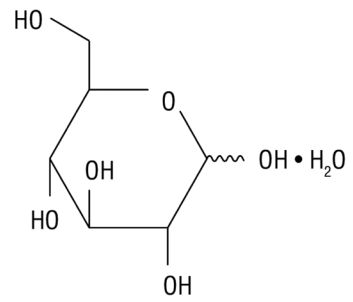
CLINIMIX sulfite-free (amino acids in dextrose) injection for intravenous use consists of sterile, nonpyrogenic, hypertonic solutions in a dual chamber container.

The outlet port chamber contains essential and nonessential amino acids. The formulas for the individual amino acids found in CLINIMIX sulfite-free (Amino Acid in Dextrose) Injections are provided in **Table 8**.

Table 8: Formulas for Amino Acids

Essential Amino Acids	
Leucine	$(CH_3)_2$ $CHCH_2CH$ (NH_2) $COOH$
Isoleucine	CH_3CH_2CH (CH_3) CH (NH_2) $COOH$
Valine	$(CH_3)_2$ $CHCH$ (NH_2) $COOH$
Lysine (added as the hydrochloride salt)	H_2N $(CH_2)_4$ CH (NH_2) $COOH$
Phenylalanine	(C_6H_5) CH_2 CH (NH_2) $COOH$
Histadine	$(C_3H_3N_2)$ CH_2CH (NH_2) $COOH$
Threonine	CH_3CH (OH) CH (NH_2) COO
Methionine	CH_3S $(CH_2)_2$ CH (NH_2) $COOH$
Tryptophan	(C_8H_6N) CH_2 CH (NH_2) $COOH$
Nonessential Amino Acids	
Alanine	CH_3CH (NH_2) $COOH$
Arginine	H_2NC (NH) NH $(CH_2)_3$ CH (NH_2) $COOH$
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) $COOH$

The injection port chamber contains dextrose. Dextrose, USP, is chemically designated D-glucose, monohydrate ($C_6H_{12}O_6 \cdot H_2O$) and has the following structure:



Dextrose Hydrous, USP
(D-Glucose monohydrate)

Dextrose is derived from corn.

See **Table 7** for composition, pH, osmolarity, ionic concentration and caloric content of the admixed product *[see Dosage Forms and Strengths (3)]*.

The dual chamber container is a lipid-compatible plastic container (PL 2401 Plastic).

CLINIMIX contains no more than 25 mcg/L of aluminum.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

CLINIMIX is used as a supplement of nutrition in patients, providing macronutrients (amino acids and dextrose) parenterally.

The amino acids provide the structural units that make up proteins and are used to synthesize proteins and other biomolecules or are oxidized to urea and carbon dioxide as a source of energy.

The administered dextrose is oxidized to carbon dioxide and water, yielding energy.

12.3 Pharmacokinetics

The disposition of infused amino acids and dextrose, are essentially the same as those absorbed from ordinary food.

15 REFERENCES

1. Ayers Phil, et al. A.S.P.E.N. *Parenteral Nutrition Handbook*, 2nd ed. 2014, pg. 123.
2. Mueller CM ed. The A.S.P.E.N. *Nutrition Support Core Curriculum*, 2nd ed. 2012. Chapter 29. Wolk R, Foulks C. Renal Disease, pg. 500.

16 HOW SUPPLIED/STORAGE AND HANDLING

CLINIMIX (amino acids in dextrose) injection (sulfite-free) is available in 1000 mL and 2000mL volumes (**See Table 9**).

Table 9: CLINIMIX Formulations

After mixing, the product represents	1000 mL Code and NDC Number	2000 mL Code and NDC Number
CLINIMIX 2.75/5 sulfite-free (2.75% Amino Acid in 5% Dextrose) Injection	Code 2B7725 NDC 0338-1132-03	Code 2B7701 NDC 0338-1083-04
CLINIMIX 4.25/5 sulfite-free (4.25% Amino Acid in 5% Dextrose) Injection	Code 2B7726 NDC 0338-1133-03	Code 2B7704 NDC 0338-1089-04
CLINIMIX 4.25/10 sulfite-free (4.25% Amino Acid in 10% Dextrose) Injection	Code 2B7727 NDC 0338-1134-03	Code 2B7705 NDC 0338-1091-04
CLINIMIX 4.25/20 sulfite-free (4.25% Amino Acid in 20% Dextrose) Injection	Code 2B7728 NDC 0338-1135-03	Code 2B7706 NDC 0338-1093-04
CLINIMIX 4.25/25 sulfite-free (4.25% Amino Acid in 25% Dextrose) Injection	Code 2B7729 NDC 0338-1136-03	Code 2B7707 NDC 0338-1095-04
CLINIMIX 5/15 sulfite-free (5% Amino Acid in 15% Dextrose) Injection	Code 2B7730 NDC 0338-1137-03	Code 2B7709 NDC 0338-1099-04
CLINIMIX 5/20 sulfite-free (5% Amino Acid in 20% Dextrose) Injection	Code 2B7731 NDC 0338-1138-03	Code 2B7710 NDC 0338-1101-04
CLINIMIX 5/25 sulfite-free (5% Amino Acid in 25% Dextrose) Injection	Code 2B7732 NDC 0338-1139-03	Code 2B7711 NDC 0338-1103-04

Minimize exposure of CLINIMIX to heat and avoid excessive heat.
Protect from freezing.

Store CLINIMIX at room temperature (25°C/77°F) (may briefly store at up to 40°C/104°F).

Refrigerated storage is limited to 9 days once the protective foil overwrap has been opened.

Do not use if the protective foil overwrap has been previously opened or damaged.

For storage of admixed solutions *see Dosage and Administration (2.3, 2.4).*

17 PATIENT COUNSELING INFORMATION

Inform patients, caregivers, or home healthcare providers of the following risks of CLINIMIX:

- Pulmonary embolism due to pulmonary vascular precipitates *[see Warnings and Precautions (5.1)]*
- Hypersensitivity reactions *[see Warnings and Precautions (5.2)]*
- Risk of Infections *[see Warnings and Precautions (5.3)]*
- Refeeding syndrome *[see Warnings and Precautions (5.4)]*
- Hyperglycemia or hyperosmolar hyperglycemic state *[see Warnings and Precautions (5.5)]*
- Vein damage and thrombosis *[see Warnings and Precautions (5.6)]*
- Hepatobiliary disorders *[see Warnings and Precautions (5.7)]*
- Aluminum toxicity *[see Warnings and Precautions (5.8)]*
- Parenteral Nutrition Associated Liver Disease (PNALD) *[see Warnings and Precautions (5.9)]*
- *Electrol*yte imbalance and fluid overload *[see Warnings and Precautions (5.10)]*

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HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use CLINIMIX E safely and effectively. See full prescribing information for CLINIMIX E.

CLINIMIX E (amino acids with electrolytes in dextrose with calcium) injection, for intravenous use Initial U.S. Approval: 1997

---------- INDICATIONS AND USAGE ----------
CLINIMIX E is indicated as a source of calories, protein, and electrolytes for patients requiring parenteral nutrition when oral or enteral nutrition is not possible, insufficient, or contraindicated. CLINIMIX E may be used to treat negative nitrogen balance in patients. (1)

---------- DOSAGE AND ADMINISTRATION ----------
See full prescribing information for information on preparation, administration, instructions for use, dosing considerations, including the recommended dosage in adults and pediatrics, and dosage modifications in patients with renal impairment. (2.1, 2.2, 2.3, 2.4, 2.5, 2.6, 2.7, 2.8)

---------- DOSAGE FORMS AND STRENGTHS ----------
CLINIMIX E injection is available in multiple strengths. See full prescribing information for detailed description of each formulation. (3, 11)

---------- CONTRAINDICATIONS ----------
- Concomitant treatment with ceftriaxone in neonates (age less than 28 days). (4)
- Known hypersensitivity to one or more amino acids or dextrose. (4)
- Inborn errors of amino acid metabolism. (4)
- Patients with pulmonary edema or acidosis due to low cardiac output. (4)

---------- WARNINGS AND PRECAUTIONS ----------
- Pulmonary Embolism due to Pulmonary Vascular Precipitates: if signs of pulmonary distress occur, stop the infusion and initiate a medical evaluation. (5.1)

Precipitation with Ceftriaxone: do not administer ceftriaxone simultaneously with CLINIMIX E via a Y-site. (4, 5.2, 8.4)
Hypersensitivity Reactions: monitor for signs and symptoms and discontinue infusion if reactions occur. (5.3)
Risk of Infections, Refeeding Complications, and Hyperglycemia or Hyperosmolar Hyperglycemic State: monitor for signs and symptoms; monitor laboratory parameters. (5.4, 5.5, 5.6)
Vein Damage and Thrombosis: solutions with osmolarity of ≥ 900 mOsm/L must be infused through a central catheter. (2.2, 5.7)
Hepatobiliary Disorders: monitor liver function parameters and ammonia levels. (5.8)
Aluminum Toxicity: increased risk in patients with renal impairment, including preterm infants. (5.9, 8.4)
Parenteral Nutrition Associated Liver Disease: increased risk in patients who receive parenteral nutrition for extended periods of time, especially preterm infants; monitor liver function tests, if abnormalities occur consider discontinuation or dosage reduction. (5.10, 8.4)
Electrolyte Imbalance and Fluid Overload: patients with cardiac insufficiency or renal impairment may require adjustment of fluid, protein and electrolyte content. (5.11, 8.4)

---------- ADVERSE REACTIONS ----------
Adverse reactions include diuresis, extravasation, glycosuria, hyperglycemia, and hyperosmolar coma. (6)

To report SUSPECTED ADVERSE REACTIONS, contact Baxter Healthcare Corporation at 1-866-888-2472 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch

---------- USE IN SPECIFIC POPULATIONS ----------
Pediatric Use: increased risk of hypoglycemia/hyperglycemia: monitor serum glucose concentrations. (8.4)
See 17 for PATIENT COUNSELING INFORMATION.

See 17 for PATIENT COUNSELING INFORMATION. **Revised: 9/2016**

FULL PRESCRIBING INFORMATION: CONTENTS*

*Sections or subsections omitted from the full prescribing information are not listed.

FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

CLINIMIX E is indicated as a source of calories, protein, and electrolytes for patients requiring parenteral nutrition when oral or enteral nutrition is not possible, insufficient, or contraindicated. CLINIMIX E may be used to treat negative nitrogen balance in patients.

2 DOSAGE AND ADMINISTRATION

2.1 Preparation Prior to Administration

- Tear protective foil overwrap across top at slit and remove solution container. Small amounts of moisture may be found on the solution container from water permeating from inside the container. The amount of permeated water is insufficient to affect the solution significantly. If larger amounts of water are found, the container should be checked for tears or leaks.
- Inspect the bag prior to activation. 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. Evaluate the following
  - If the outlet or additive port protectors are damaged, detached, or not present, discard container as solution path sterility may be impaired.
  - Check to ensure seal between chambers is intact, solutions are contained in separate chambers, and the content of the individual chambers is clear, colorless or slightly yellow. Discard if the seal is broken or if the solution is bright yellow or yellowish brown.
  - Check for minute leaks by separately squeezing each chamber. If external leaks or leakage between the chambers are found, discard solution as sterility or stability may be impaired.
- Lipids and/or additives can be introduced to the container after opening seal between chambers. Because additives may be incompatible, evaluate all additions to the plastic container for compatibility. Activate chambers of bag prior to introduction of additives. Mix thoroughly when additives have been introduced. Supplemental medication may be added with a 19 to 22 gauge needle through the medication port.
- Calcium and phosphate ratios must be considered. Excess addition of calcium and phosphate, especially in the form of mineral salts, may result in the formation of calcium phosphate precipitates *[see Warnings and Precautions (5.1)].*
- Inspect the bag to ensure precipitates have not formed during the mixing or addition of additives. A slight yellow color does not alter the quality and efficacy of this product. If lipid has been added, ensure the emulsion has not separated. Separation of the emulsion can be visibly identified by a yellowish streaking or the accumulation of yellowish droplets in the mixed emulsion. Discard the admixture if any of the above are observed.

2.2 Important Administration Instructions

- Set the vent to the closed position on a vented intravenous administration set to prevent air embolism.
- Use a dedicated line without any connections to avoid air embolism.
- CLINIMIX E is for intravenous infusion only into a central or peripheral vein. The choice of a central or peripheral venous route should depend on the osmolarity of the final infusate. Solutions with osmolarity of 900 mOsm/L or greater must be infused through a central catheter *[see Warnings and Precautions (5.7)].*
  - For central vein infusion only: CLINIMIX E 2.75/10, 4.25/10, 4.25/25, 5/15, 5/20, 5/25
  - For central or peripheral vein infusion: CLINIMIX E 2.75/5 and 4.25/5
- The solution should be inspected for precipitates before admixing, after admixing, and again before administration.
- Use a 0.22 micron filter for administration of CLINIMIX E. If a lipid is also administered, use a 1.2 micron filter.
- If lipid emulsion is added, do not use administration sets and lines that contain di-2-ethylhexyl phthalate (DEHP). Administration sets that contain polyvinyl chloride (PVC) components have DEHP as a plasticizer.
- Ceftriaxone must not be administered simultaneously with calcium-containing intravenous solutions such as CLINIMIX E via a Y-site. However, in patients other than neonates, ceftriaxone and CLINIMIX E may be administered sequentially if the infusion lines are thoroughly flushed between infusions with a compatible fluid *[see Contraindications (4), Warnings and Precautions (5.2)].*

2.3 Instructions for Use

1. Open by tearing protective foil overwrap across top at slit and remove solution container.
2. Lay the bag onto a flat surface. Grasp the container firmly on each side of the top of the bag (**Figure 1**).
3. Starting from the top squeeze and roll bag to open seal between chambers until the peel-seal is completely broken as shown in **Figure 2**.
4. If the seal has not been separated completely flip the bag over and repeat process.
5. Mix the contents thoroughly by inverting the bag upside down to ensure a homogenous admixture (**Figure 3**).
6. Once the bag is mixed, check for leaks.
7. Make additions (if prescribed).

Because additives may be incompatible, evaluate all additions to the bag for compatibility and stability of the resulting preparation. Consult with pharmacist, if available. Questions about compatibility may be directed to Baxter. If it is deemed advisable to introduce additives, use aseptic technique. For information on adding lipid emulsions see Dosage and Administration (2.4).

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 (**Figure 3**). For high density medication (high specific gravity), such as potassium chloride, squeeze ports while ports are upright and mix thoroughly.

8. Inspect final solution for discoloration and particulate matter. Check for leaks.
9. Spike and hang bag.

a. Suspend container from eyelet support.

b. Twist off protector from outlet port at bottom of container (**Figure 4**).

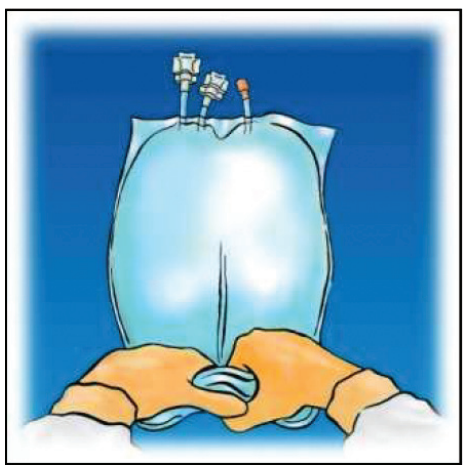
c. Attach administration set. Refer to complete directions accompanying set.

For single dose only. Discard unused portion.

Figures 1-4:

1. Lay the bag onto a flat surface. Grasp the bag firmly with both hands at the top corners.

2. Starting from the top, squeeze and roll the bag down toward the bottom until the peel seal is broken down the center. You should feel or hear an audible pop as the peel seal dividing the chambers is broken, which allows the components from each chamber to mix.



3. Mix by turning the bag upsidedown at least 3 times.

4. Hang the bag. Twist off the protector from the administration outlet. Firmly plug the spike connector.

Instructions on Storage

Storage After Removal of Overwrap:

Once removed from the protective foil overwrap, mixed (peel seal activated) or unmixed (peel seal intact), CLINIMIX E Injection solutions may be stored under refrigeration for up to 9 days.

Storage Once any Additive is Added:

Use promptly after mixing. Any storage with additives should be under refrigeration and limited to a brief period of time, less than 24 hours. After removal from refrigeration, use promptly and complete the infusion within 24 hours. Any remaining mixture must be discarded.

2.4 Preparation and Addition of Lipid Emulsion

1. Prior to adding lipid emulsion, mix amino acid and dextrose injection as shown in **Figures 1-3**.
2. Prepare lipid emulsion transfer set following instructions provided.
3. Attach transfer set to lipid emulsion container using aseptic technique.
4. Twist off protector on the additive port of the container.
5. Attach the transfer set to the exposed additive port.
6. Open clamp on transfer set.
7. After completing transfer, use appropriate plastic clamp or metal ferrule to seal off additive port tube.
8. Remove transfer set.
9. Mix contents of container thoroughly. Inspect final solution for discoloration and particulate matter. Check for leaks.

Storage Once Lipids are Added:

Use promptly after mixing. Any storage with additives should be under refrigeration and limited to a brief period of time, no longer than 24 hours. After removal from refrigeration, use promptly and complete the infusion within 24 hours. Any mixture remaining must be discarded.

2.5 Dosing Considerations

- The dosage of CLINIMIX E should be individualized based on the patient's clinical condition (ability to adequately metabolize amino acids and dextrose), body weight and nutritional/fluid requirements, as well as additional energy given orally/enterally to the patient. Prior to initiating CLINIMIX E the following patient information should be reviewed: review of all medications, gastrointestinal function and laboratory data such as electrolytes (including magnesium, calcium, and phosphorus), glucose, urea/creatinine, liver panel, complete blood count and triglyceride level (if adding lipid emulsion). Refer to the complete prescribing information of lipid emulsion for dosing information.
- CLINIMIX E formulations have varying concentrations of protein, carbohydrate and a standard concentration of electrolytes; thus infusion rates to achieve requirements will vary. Protein, caloric, fluid and electrolyte requirements all need to be taken into consideration when determining individual patient dosage needs.
- The dosage selection is based only on the recommended protein requirements. The maximum dextrose infusion rates and calorie and fluid requirements must also be considered when determining the clinically appropriate infusion rate for patients.
- CLINIMIX E meets the total nutritional requirements for protein and dextrose in stable patients, and can be individualized to meet specific needs with the addition of nutrients.
- Total daily fluid requirements can be met beyond the volume of amino acids solution by supplementing with non-carbohydrate or carbohydrate-containing electrolyte solutions. 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.
- Prior to administration of CLINIMIX E correct severe fluid, electrolyte and acid-base disorders.
- Monitor levels of serum potassium during therapy. It may be necessary to add additional potassium to the CLINIMIX E admixture.
- Lipid emulsion administration should be considered with prolonged use (more than 5 days) of CLINIMIX E in order to prevent essential fatty acid deficiency (EFAD). Serum lipids should be monitored for evidence of EFAD in patients maintained on fat-free parenteral nutrition. See prescribing information of lipid emulsion.
- The flow rate should be increased gradually. The flow rate must be adjusted taking into account the dose being administered, the daily volume intake, and the duration of the infusion.

2.6 Recommended Dosage in Adults

The recommended daily nutritional requirements for protein and dextrose compared to the amount of nutrition provided by CLINIMIX E are shown in **Table 1**.

As indicated on an individual basis, maintenance vitamins, additional electrolytes, trace elements and other components (including lipids) should be administered as required to prevent deficiencies and complications from developing.

The maximum infusion rates in adult patients are show in **Table 2**.

In addition to meeting protein needs, the administration rate should be governed, especially during the first few day of therapy, by the patient's tolerance to dextrose. Daily intake of amino acids and dextrose should be increased gradually to the maximum required dose as indicated by frequent determinations of blood glucose levels.

Table 1: Nutritional Comparison –Adult Patients

	Recommended Nutritional Requirements[1]		Recommended Clinimix E Adult Dosage							
	Stable Patients	Critically Ill Patients*	Clinimix E 2.75/5	Clinimix E 2.75/10	Clinimix E 4.25/5	Clinimix E 4.25/10	Clinimix E 4.25/25	Clinimix E 5/15	Clinimix E 5/20	Clinimix E 5/25
Fluid (mL/kg/day)	30 to 40	Minimum needed to deliver adequate nutrition	29 to 40	29 to 40	19 to 40	19 to 40	19 to 40	16 to 40	16 to 40	16 to 40
Protein** (g/kg/day) (Nitrogen g/kg/day)	0.8 to 1 (0.13 to 0.16)	1.5 to 2 (0.24 to 0.32)	0.8 to 1.1 (0.13 to 0.18)	0.8 to 1.1 (0.13 to 0.18)	0.8 to 1.7 (0.13 to 0.27)	0.8 to 1.7 (0.13 to 0.27)	0.8 to 1.7 (0.13 to 0.27)	0.8 to 2 (0.13 to 0.32)	0.8 to 2 (0.13 to 0.32)	0.8 to 2 (0.13 to 0.32)
Dextrose (g/kg/day)	≤10	≤5.8	1.45 to 2	2.9 to 4	0.95 to 2	1.9 to 4	4.75 to 10	2.4 to 6	3.2 to 8	4 to 10

* Do not use in patients with conditions that are contraindicated [see Contraindications (4)].
** Protein is provided as amino acids. When infused intravenously amino acids are metabolized and utilized as the building blocks of protein.

Table 2: Maximum Infusion Rate in Adult Patients:

		Maximum Infusion Rates in Adults Patients							
		Clinimix E 2.75/5	Clinimix E 2.75/10	Clinimix E 4.25/5	Clinimix E 4.25/10	Clinimix E 4.25/25	Clinimix E 5/15	Clinimix E 5/20	Clinimix E 5/25
Maximum Infusion Rate (mL/kg/hour)		3.6	2.5	2.4	2.4	1	1.67	1.25	1
Corresponding infusion rate	**Amino Acid (g/kg/hour)**	0.1*	0.07	0.1*	0.1*	0.04	0.08	0.06	0.05
	Dextrose (g/kg/hour)	0.18	0.25*	0.12	0.24	0.25*	0.25*	0.25*	0.25*

*Rate limiting factor

2.7 Dosage Modifications in Patients with Renal Impairment

Prior to administration, correct severe fluid or electrolyte imbalances. Closely monitor serum electrolyte levels and adjust the volume of CLINIMIX E administered as required *[see Warnings and Precautions (5.11)].*

Patients with renal impairment not needing dialysis require 0.6 to 0.8 g of protein/kg/day. Serum electrolyte levels should be closely monitored. Patients on hemodialysis or continuous renal replacement therapy should receive 1.2 to 1.8 g of protein/kg/day up to a maximum of 2.5 g of protein/kg/day based on nutritional status and estimated protein losses.2 The CLINIMIX E dosage can be adjusted based on the severity of renal impairment, supplementing protein as indicated. If required, additional amino acids may be added to the CLINIMIX E bag or infused separately. Compatibility of additions should be evaluated by a pharmacist and questions may be directed to Baxter.

2.8 Recommended Dosage in Pediatric Patients

The dosage and constant infusion rate of intravenous dextrose must be selected with caution in pediatric patients, particularly neonates and low weight infants, because of the increased risk of hyperglycemia/hypoglycemia [see Use in Specific Populations (8.4)]. Frequent monitoring of serum glucose concentrations is required when dextrose is prescribed to pediatric patients, particularly neonates and low birth weight infants. The infusion rate and volume should be determined by the consulting physician experienced in pediatric intravenous fluid therapy.

In pediatric patients, CLINIMIX E is dosed on the basis of protein provided as amino acids. The recommended dosage, by age group is provided in **Tables 3–6**. Infusion rates are based on protein and do not take carbohydrates, fluid or electrolytes into consideration.

This product does not contain the amino acids cysteine and taurine, considered conditionally essential for neonates and infants. If possible, these amino acids should be added to this product if used in this pediatric population.

Table 3: Preterm and Term Infants Less than 1 Month of Age

	Recommended Nutritional Requirements[1]	Recommended Clinimix Dosage in Preterm and Term Infants Less than 1 Month of Age							
		Clinimix E 2.75/5	Clinimix E 2.75/10	Clinimix E 4.25/5	Clinimix E 4.25/10	Clinimix E 4.25/25	Clinimix E 5/15	Clinimix E 5/20	Clinimix E 5/25
Infusion Rate Range (mL/kg/hr)		4.5 to 6	4.5 to 6	2.9 to 3.9	2.9 to 3.9	2.9 to 3.3	2.5 to 3.3	2.5 to 3.3	2.5 to 3.3
Fluid (mL/kg/day)	100 to 150	108 to 144	108 to 144	70 to 94	70 to 94	70 to 79	60 to 79	60 to 79	60 to 79
Protein* (g/kg/day) (Nitrogen g/kg/day)	3 to 4 (0.48 to 0.64)	3 to 4 (0.48 to 0.64)	3 to 4 (0.48 to 0.64)	3 to 4 (0.48 to 0.64)	3 to 4 (0.48 to 0.64)	3 to 3.4 (0.48 to 0.54)	3 to 4 (0.48 to 0.64)	3 to 4 (0.48 to 0.64)	3 to 4 (0.48 to 0.64)
Dextrose (g/kg/day)	7 to 20	5.4 to 7.2	10.8 to 14.4	3.5 to 4.7	7 to 9.4	17.5 to 19.8	9 to 11.9	12 to 15.8	15 to 19.8

* Protein is provided as amino acids. When infused intravenously amino acids are metabolized and utilized as the building blocks of protein.

Table 4: Pediatric Patients 1 Month to Less than 1 Year of Age

	Recommended Nutritional Requirements[1]	Recommended Clinimix E Dosage in Pediatric Patients 1 Month to Less than 1 Year of Age							
		Clinimix E 2.75/5	Clinimix E 2.75/10	Clinimix E 4.25/5	Clinimix E 4.25/10	Clinimix E 4.25/25	Clinimix E 5/15	Clinimix E 5/20	Clinimix E 5/25
Infusion Rate Range (mL/kg/hr)		3 to 4.5	3 to 4.5	2 to 2.9	2 to 2.9	2 to 2.9	1.7 to 2.5	1.7 to 2.5	1.7 to 2.5
Fluid (mL/kg/day)	100 mL/kg for the first 10 kg + 50 mL/kg for the second 10 kg.	72 to 108	72 to 108	48 to 70	48 to 70	48 to 70	41 to 60	41 to 60	41 to 60
Protein* (g/kg/day) (Nitrogen g/kg/day)	2 to 3 (0.32 to 0.48)	2 to 3 (0.32 to 0.48)	2 to 3 (0.32 to 0.48)	2 to 3 (0.32 to 0.48)	2 to 3 (0.32 to 0.48)	2 to 3 (0.32 to 0.48)	2 to 3 (0.32 to 0.48)	2 to 3 (0.32 to 0.48)	2 to 3 (0.32 to 0.48)
Dextrose (g/kg/day)	7 to 20	3.6 to 5.4	7.2 to 10.8	2.4 to 3.5	4.8 to 7	12 to 17.5	6.1 to 9	8.2 to 12	10.2 to 15

* Protein is provided as amino acids. When infused intravenously amino acids are metabolized and utilized as the building blocks of protein.

Table 5: Pediatric Patients 1 Year to Less than 11 Years of Age

	Recommended Nutritional Requirements[1]	Recommended Clinimix E Dosage in Pediatric Patients 1 Year to Less than 11 Years of Age							
		Clinimix E 2.75/5	Clinimix E 2.75/10	Clinimix E 4.25/5	Clinimix E 4.25/10	Clinimix E 4.25/25	Clinimix E 5/15	Clinimix E 5/20	Clinimix E 5/25
Infusion Rate Range (mL/kg/hr)		1.5 to 3	1.5 to 3	1 to 2	1 to 2	1 to 2	0.8 to 1.7	0.8 to 1.7	0.8 to 1.7
Fluid (mL/kg/day)	100 mL/kg for the first 10 kg + 50 mL/kg for the second 10 kg + 20 mL/kg for weight > 20 kg	36 to 72	36 to 72	24 to 48	24 to 48	24 to 48	19 to 41	19 to 41	19 to 41
Protein* (g/kg/day) (Nitrogen g/kg/day)	1 to 2 (0.16 to 0.32)	1 to 2 (0.16 to 0.32)	1 to 2 (0.16 to 0.32)	1 to 2 (0.16 to 0.32)	1 to 2 (0.16 to 0.32)	1 to 2 (0.16 to 0.32)	1 to 2 (0.16 to 0.32)	1 to 2 (0.16 to 0.32)	1 to 2 (0.16 to 0.32)
Dextrose (g/kg/day)	7 to 14	1.8 to 3.6	3.6 to 7.2	1.2 to 2.4	2.4 to 4.8	6 to 12	2.9 to 6.1	3.8 to 8.2	4.8 to 10.2

* Protein is provided as amino acids. When infused intravenously amino acids are metabolized and utilized as the building blocks of protein.

Table 6: Pediatric Patients 11 Years to 17 Years of Age

	Recommended Nutritional Requirements[1]	Recommended Clinimix E Dosage in Pediatric Patients 11 Years to 17 Years of Age							
		Clinimix E 2.75/5	Clinimix E 2.75/10	Clinimix E 4.25/5	Clinimix E 4.25/10	Clinimix E 4.25/25	Clinimix E 5/15	Clinimix E 5/20	Clinimix E 5/25
Infusion Rate Range (mL/kg/hr)		1.2 to 2.3	1.2 to 2.3	0.8 to 1.5	0.8 to 1.5	0.8 to 1.5	0.7 to 1.3	0.7 to 1.3	0.7 to 1.3
Fluid (mL/kg/day)	100 mL/kg for the first 10 kg + 50 mL/kg for the second 10 kg + 20 mL/kg for weight > 20 kg	29 to 55	29 to 55	19 to 36	19 to 36	19 to 36	17 to 31	17 to 31	17 to 31
Protein* (g/kg/day) (Nitrogen g/kg/day)	0.8 to 1.5 (0.13 to 0.24)	0.8 to 1.5 (0.13 to 0.24)	0.8 to 1.5 (0.13 to 0.24)	0.8 to 1.5 (0.13 to 0.24)	0.8 to 1.5 (0.13 to 0.24)	0.8 to 1.5 (0.13 to 0.24)	0.8 to 1.5 (0.13 to 0.24)	0.8 to 1.5 (0.13 to 0.24)	0.8 to 1.5 (0.13 to 0.24)
Dextrose (g/kg/day)	5 to 9	1.4 to 2.8	2.9 to 5.5	1.9 to 3.6	3.8 to 7.2	4.8 to 9	2.5 to 4.7	3.4 to 6.2	4.2 to 7.8

* Protein is provided as amino acids. When infused intravenously amino acids are metabolized and utilized as the building blocks of protein.

2.9 Discontinuation of CLINIMIX

To reduce the risk of hypoglycemia after discontinuation, a gradual decrease in flow rate in the last hour of infusion should be considered.

3 DOSAGE FORMS AND STRENGTHS

CLINIMIX E injection is available in 1000 mL and 2000 mL dual chamber bags. The individual chambers contain essential and nonessential amino acids with electrolytes and dextrose with calcium. Table 7 describes the individual components of CLINIMIX E.

Table 7 Ingredients per 100mL of CLINIMIX

Strength of CLINIMIX E		CLINIMIX E 2.75/5 sulfite-free (2.75% Amino Acid in 5% Dextrose) Injection	CLINIMIX E 2.75/10 sulfite-free (2.75% Amino Acid in 10% Dextrose) Injection	CLINIMIX E 4.25/5 sulfite-free (4.25% Amino Acid in 5% Dextrose) Injection	CLINIMIX E 4.25/10 sulfite-free (4.25% Amino Acid in 10% Dextrose) Injection	CLINIMIX E 4.25/25 sulfite-free (4.25% Amino Acid in 25% Dextrose) Injection	CLINIMIX E 5/15 sulfite-free (5% Amino Acid in 15% Dextrose) Injection	CLINIMIX E 5/20 sulfite-free (5% Amino Acid in 20% Dextrose) Injection	CLINIMIX E 5/25 sulfite-free (5% Amino Acid in 25% Dextrose) Injection
	Dextrose Hydrous, USP (g/100 mL)	5	10	5	10	25	15	20	25
	Amino Acids (g/100 mL)	2.75	2.75	4.25	4.25	4.25	5	5	5
	Total Nitrogen (mg/100 mL)	454	454	702	702	702	826	826	826
Essential Amino Acids (mg/100 mL)	Leucine	201	201	311	311	311	365	365	365
	Isoleucine	165	165	255	255	255	300	300	300
	Valine	160	160	247	247	247	290	290	290
	Lysine (added as the hydrochloride salt)	159	159	247	247	247	290	290	290
	Phenylalanine	154	154	238	238	238	280	280	280
	Histidine	132	132	204	204	204	240	240	240
	Threonine	116	116	179	179	179	210	210	210
	Methionine	110	110	170	170	170	200	200	200
	Tryptophan	50	50	77	77	77	90	90	90
Nonessential Amino Acids (mg/100 mL)	Alanine	570	570	880	880	880	1035	1035	1035
	Arginine	316	316	489	489	489	575	575	575
	Glycine	283	283	438	438	438	515	515	515
	Proline	187	187	289	289	289	340	340	340
	Serine	138	138	213	213	213	250	250	250
	Tyrosine	11	11	17	17	17	20	20	20
Electrolytes (mg/100 mL)	Sodium Acetate Trihydrate, USP	217	217	297	297	297	340	340	340
	Dibasic Potassium Phosphate, USP	112	112	77	77	77	59	59	59
	Sodium Chloride, USP	11	17	17	17	17	20	20	20
	Magnesium Chloride, USP	51	51	51	51	51	51	51	51
	Calcium Chloride Dihydrate, USP	33	33	33	33	33	33	33	33
Electrolyte Profile (mEq/L)[1]	Sodium	35	35	35	35	35	35	35	35
	Potassium	30	30	30	30	30	30	30	30
	Magnesium	5	5	5	5	5	5	5	5
	Calcium	4.5 (2.2 mmol/L)	4.5 (2.2 mmol/L)	4.5 (2.2 mmol/L)	4.5 (2.2 mmol/L)	4.5 (2.2 mmol/L)	4.5 (2.2 mmol/L)	4.5 (2.2 mmol/L)	4.5 (2.2 mmol/L)
	Acetate[2]	51	51	70	70	70	80	80	80
	Chloride[3]	39	39	39	39	39	39	39	39
	Phosphate (as $HPO_4^{=}$)	30 (15 mmol/L)	30 (15 mmol/L)	30 (15 mmol/L)	30 (15 mmol/L)	30 (15 mmol/L)	30 (15 mmol/L)	30 (15 mmol/L)	30 (15 mmol/L)
	pH[4] (Range)	6.0 (4.5 to 7.0)	6.0 (4.5 to 7.0)	6.0 (4.5 to 7.0)	6.0 (4.5 to 7.0)	6.0 (4.5 to 7.0)	6.0 (4.5 to 7.0)	6.0 (4.5 to 7.0)	6.0 (4.5 to 7.0)
	Osmolarity (mOsmol/L) (calc)	665	920	815	1070	1825	1395	1650	1900
Caloric Content (kcal/L)	From Dextrose	170	340	170	340	850	510	680	850
	From Amino Acids	110	110	170	170	170	200	200	200
	TOTAL (Dextrose and Amino Acids)	280	450	340	510	1020	710	880	1050

1. Balanced by ions from amino acids.
2. Derived from glacial acetic acid (for pH adjustment) and sodium acetate.
3. Contributed by calcium chloride, lysine hydrochloride, magnesium chloride, and sodium chloride.
4. pH of sulfite-free amino acid injection with electrolytes in the outlet port chamber was adjusted with glacial acetic acid.

4 CONTRAINDICATIONS

The use of CLINIMIX E is contraindicated in:

- Neonates (less than 28 days of age) receiving concomitant treatment with ceftriaxone, even if separate infusion lines are used, due to the risk of fatal ceftriaxone calcium salt precipitation in the neonate's bloodstream *[see Warnings and Precautions (5.2), Use in Specific Populations (8.4)]*.
- Patients with known hypersensitivity to one or more amino acids or dextrose *[see Warnings and Precautions (5.3)].*
- Patients with inborn errors of amino acid metabolism due to risk of severe metabolic and neurologic complications.
- Patients with pulmonary edema or acidosis due to low cardiac output.

5 WARNINGS AND PRECAUTIONS

5.1 Pulmonary Embolism due to Pulmonary Vascular Precipitates

Pulmonary vascular precipitates causing pulmonary vascular emboli and pulmonary distress have been reported in patients receiving parenteral nutrition. In some cases, fatal outcomes due to pulmonary embolism have occurred. Patients, especially those with hypophosphatemia, may require the addition of phosphate. To prevent hypocalcemia, calcium supplementation should always accompany phosphate administration. Excessive addition of calcium and phosphate increases the risk of the formation of calcium phosphate precipitates. Precipitates have been reported even in the absence of phosphate salt in the solution. Precipitation following passage through an in-line filter and suspected in vivo precipitate formation has also been reported. If signs of pulmonary distress occur, stop the infusion and initiate a medical evaluation. In addition to inspection of the solution *[see Dosage and Administration (2.1, 2.2, 2.3, 2.4)],* the infusion set and catheter should also periodically be checked for precipitates.

5.2 Precipitation with Ceftriaxone

Precipitation of ceftriaxone-calcium can occur when ceftriaxone is mixed with calcium-containing parenteral nutrition solutions, such as CLINIMIX E, in the same intravenous administration line. Do not administer ceftriaxone simultaneously with CLINIMIX E via a Y-site.

Deaths have occurred in neonates (less than 28 days of age) who received concomitant intravenous calcium-containing solutions with ceftriaxone resulting from calcium-ceftriaxone precipitates in the lungs and kidneys, even when separate infusion lines were used. CLINIMIX E is contraindicated in neonates receiving ceftriaxone *[see Contraindications (4),Use in Specific Populations (8.4)]*.

In patients older than 28 days (including adults), ceftriaxone and CLINIMIX E may be administered sequentially if the infusion lines are thoroughly flushed between infusions with a compatible fluid.

5.3 Hypersensitivity Reactions

Hypersensitivity/infusion reactions including anaphylaxis have been reported with CLINIMIX E. Stop infusion immediately and treat patient accordingly if any signs or symptoms of a hypersensitivity reaction develop. Signs or symptoms may include: hypotension, hypertension, peripheral cyanosis, tachycardia, dyspnea, vomiting, nausea, urticaria, rash, pruritus, erythema, hyperhidrosis, pyrexia, and chills.

5.4 Risk of Infections

Patients who require parenteral nutrition are at high risk of infections because the nutritional components of these solutions can support microbial growth. Infection and sepsis may also occur as a result of the use of intravenous catheters to administer parenteral nutrition.

The risk of infection is increased in patients with malnutrition-associated immunosuppression, hyperglycemia exacerbated by dextrose infusion, long-term use and poor maintenance of intravenous catheters, or immunosuppressive effects of other concomitant conditions, drugs, or other components of the parenteral formulation (e.g., lipid emulsion).

To decrease the risk of infection, ensure aseptic technique in catheter placement and maintenance, as well as aseptic technique in the preparation and administration of the nutritional formula.

Monitor for signs and symptoms (including fever and chills) of early infections, including

laboratory test results (including leukocytosis and hyperglycemia) and frequent checks of the parenteral access device and insertion site for edema, redness and discharge.

5.5 Refeeding Syndrome

Refeeding severely undernourished patients may result in refeeding syndrome, characterized by the intracellular shift of potassium, phosphorus, and magnesium as the patient becomes anabolic. Thiamine deficiency and fluid retention may also develop. To prevent these complications, monitor severely undernourished patients and slowly increase nutrient intakes.

5.6 Hyperglycemia or Hyperosmolar Hyperglycemic State

When using CLINIMIX E in patients with diabetes mellitus, impaired glucose tolerance may worsen hyperglycemia. Administration of dextrose at a rate exceeding the patient's utilization rate may lead to hyperglycemia, coma, and death. Patients with underlying confusion and renal impairment who receive dextrose infusions, may be at greater risk of developing hyperosmolar hyperglycemic state. Monitor blood glucose levels and treat hyperglycemia to maintain optimum levels while administering CLINIMIX E. Insulin may be administered or adjusted to maintain optimal blood glucose levels during CLINIMIX E administration.

5.7 Vein Damage and Thrombosis

Solutions with osmolarity of 900 mOsm/L or greater must be infused through a central catheter. CLINIMIX E solutions containing more than 5% dextrose have an osmolarity greater than or equal to 900 mOsm/L. CLINIMIX E 2.75/10, 4.25/10, 4.25/25, 5/15, 5/20, and 5/25 are indicated for administration into a central vein only, such as the superior vena cava *[see Dosage and Administration (2.2)]*. The infusion of hypertonic nutrient injections into a peripheral vein may result in vein irritation, vein damage, and/or thrombosis.

CLINIMIX E 2.75/5 and 4.25/5 are indicated for peripheral administration, or may be infused into a central vein *[see Dosage and Administration (2.2)]*. The primary complication of peripheral access is venous thrombophlebitis, which manifests as pain, erythema, tenderness or a palpable cord. Remove the catheter as soon as possible, if thrombophlebitis develops.

5.8 Hepatobiliary Disorders

Hepatobiliary disorders are known to develop in some patients without preexisting liver disease who receive parenteral nutrition, including cholecystitis, cholelithiasis, cholestasis, hepatic steatosis, fibrosis and cirrhosis, possibly leading to hepatic failure. The etiology of these disorders is thought to be multifactorial and may differ between patients.

Increase in blood ammonia levels and hyperammonemia may occur in patients receiving amino acid solutions. In some patients this may indicate hepatic insufficiency or the presence of an inborn error of amino acid metabolism *[see Contraindications (4)]*.

Monitor liver function parameters and ammonia levels. Patients developing signs of hepatobiliary disorders should be assessed early by a clinician knowledgeable in liver diseases in order to identify possible causative and contributory factors, and possible therapeutic and prophylactic interventions.

5.9 Aluminum Toxicity

CLINIMIX E contains no more than 25 mcg/L of aluminum. However, with prolonged parenteral administration in patients with renal impairment, the aluminum contained in CLINIMX E may reach toxic levels. Preterm infants are at a greater risk because their kidneys are immature, and they require large amounts of calcium and phosphate solutions, which contain aluminum.

Patients with renal impairment, including preterm infants, 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.

5.10 Risk of Parenteral Nutrition Associated Liver Disease

Parenteral Nutrition Associated Liver Disease (PNALD) has been reported in patients who receive parenteral nutrition for extended periods of time, especially preterm infants, and can present as cholestasis or steatohepatitis. The exact etiology is unknown and is likely multifactorial. If CLINIMIX E treated patients develop liver test abnormalities consider discontinuation or dosage reduction.

5.11 Electrolyte Imbalance and Fluid Overload

Patients with renal impairment, such as pre-renal azotemia, renal obstruction, and protein-losing nephropathy may be at increased risk of electrolyte and fluid volume imbalance. Patients with cardiac insufficiency due to left ventricular systolic dysfunction are susceptible to excess fluid accumulation. Use CLINIMIX E with caution in patients with cardiac insufficiency or renal impairment. CLINIMIX E dosage may require adjustment with specific attention to fluid, protein, and electrolyte content in these patients.

Monitor renal function parameters. Patients developing signs of renal impairment should be assessed early by a clinician knowledgeable in renal disease in order to determine the appropriate CLINIMIX E dosage and other treatment options.

5.12 Monitoring/Laboratory Tests

Monitor fluid and electrolyte status, serum osmolarity, blood glucose, liver and kidney function, blood count and coagulation parameters throughout treatment. In situations of severely elevated electrolyte levels, stop CLINIMIX E until levels have been corrected.

6 ADVERSE REACTIONS

The following serious adverse reactions are discussed in greater detail in other sections of the prescribing information.

- Pulmonary embolism due to pulmonary vascular precipitates *[see Warnings and Precautions (5.1)]*
- Death in neonates due to calcium-ceftriaxone precipitates *[see Warnings and Precautions (5.2)]*
- Hypersensitivity reactions *[see Warnings and Precautions (5.3)]*
- Risk of Infections [see Warnings and Precautions (5.4)]
- Refeeding syndrome *[see Warnings and Precautions (5.5)]*
- Hyperglycemia or hyperosmolar hyperglycemic state *[see Warnings and Precautions (5.6)]*
- Vein damage and thrombosis *[see Warnings and Precautions (5.7)]*
- Hepatobiliary disorders *[see Warnings and Precautions (5.8)]*
- Parenteral Nutrition Associated Liver Disease (PNALD) *[see Warnings and Precautions (5.10)]*
- Electrolyte imbalance and fluid overload *[see Warnings and Precautions (5.11)]*

The following adverse reactions from voluntary reports or clinical studies have been reported with CLINIMIX E. Because many of these reactions were reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

- Diuresis
- Extravasation
- Glycosuria
- Hyperglycemia
- Hyperosmolar coma

7 DRUG INTERACTIONS

7.1 Drugs that Can Cause Hyperkalemia

Because of its potassium content, CLINIMIX E should be administered with caution in patients treated with agents or products that can cause hyperkalemia or increase the risk of hyperkalemia, such as potassium sparing diuretics (amiloride, spironolactone, triamterene), with ACE inhibitors, angiotensin II receptor antagonists, or the immunosuppressants tacrolimus and cyclosporine.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

There are no adequate or well-controlled studies in pregnant women with CLINIMIX E. Additionally, animal reproduction studies have not been conducted with amino acids and electrolytes and dextrose. It is not known whether CLINIMIX E can cause fetal harm when administered to a pregnant woman.

The estimated background risk of major birth defects and miscarriage for the indicated population is unknown. However, the estimated background risk in the U.S. general population of major birth defects is 2 to 4% and of miscarriage is 15 to 20% of clinically recognized pregnancies.

Clinical Considerations

Disease-Associated Maternal and/or Embryo-Fetal Risk

Based on clinical practice guidelines, parenteral nutrition should be considered in cases of severe maternal malnutrition where nutritional requirements cannot be fulfilled by the enteral route because of the risks to the fetus associated with severe malnutrition, such as preterm delivery, low birth weight, intrauterine growth restriction, congenital malformations and perinatal mortality.

8.2 Lactation

Risk Summary

It is not known whether CLINIMIX E is present in human milk. There are no data on the effects of CLINIMIX E on the breastfed infant or on milk production. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for CLINIMIX E and any potential adverse effects on the breastfed child from CLINIMIX E or from the underlying maternal condition.

8.4 Pediatric Use

Safety and effectiveness of CLINIMIX E in pediatric patients have not been established by adequate and well-controlled studies. Use of dextrose, amino acid infusions and electrolytes in pediatric patients is based on clinical practice *[see Dosage and Administration (2.8)]*.

Deaths have occurred in neonates (less than 28 days of age) who received concomitant intravenous calcium-containing solutions with ceftriaxone resulting from calcium-ceftriaxone precipitates in the lungs and kidneys, even when separate infusion lines were used. CLINIMIX E is contraindicated in neonates receiving ceftriaxone *[see Contraindications (4), Warnings and Precautions (5.2)]*.

Newborns, especially those born premature and with low birth weight, are at increased risk of developing hypo – or hyperglycemia and therefore need close monitoring during treatment with intravenous glucose solutions to ensure adequate glycemic control in order to avoid potential long term adverse effects. Hypoglycemia in the newborn can cause prolonged seizures, coma and brain damage. Hyperglycemia has been associated with intraventricular hemorrhage, late onset bacterial and fungal infection, retinopathy of prematurity, necrotizing enterocolitis, bronchopulmonary dysplasia, prolonged length of hospital stay, and death. Plasma electrolyte concentrations should be closely monitored in the pediatric population as this population may have impaired ability to regulate fluids and electrolytes.

Because of immature renal function, preterm infants receiving prolonged treatment with CLINIMIX E, may be at risk of aluminum toxicity *[see Warnings and Precautions (5.9)]*.

Patients, including pediatric patients, may be at risk for Parenteral Nutrition Associated Liver Disease (PNALD) *[see Warnings and Precautions (5.10)]*.

Hyperammonemia is of special significance in infants (birth to two years). 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 *[see Warnings and Precautions (5.8)]*.

8.5 Geriatric Use

Clinical studies of CLINIMIX E did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from other younger subjects. Other reported clinical experience has not identified differences in responses between the elderly and younger patients.

In general, dose selection for an elderly patient should be cautious, usually starting at the low end of the dosing range, reflecting the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or drug therapy.

10 OVERDOSAGE

An increased infusion rate of CLINIMIX E can cause hyperglycemia, hyperosmolality, and adverse effects on water and electrolyte balance *[see Warnings and Precautions (5.6, 5.11)]*.

Severe hyperglycemia and severe dilutional hyponatremia, and their complications, can be fatal.

Discontinue infusion and institute appropriate corrective measures in the event of overhydration or solute overload during therapy, with particular attention to respiratory and cardiovascular systems.

For current information on the management of poisoning or overdosage, contact the National Poison Control Center at 1-800-222-1222 or www.poison.org.

11 DESCRIPTION

CLINIMIX E sulfite-free (amino acids with electrolytes in dextrose with calcium) injection for intravenous use consists of sterile, nonpyrogenic, hypertonic solutions in a dual chamber container.

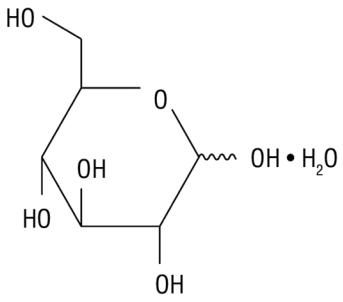
The outlet port chamber contains essential and nonessential amino acids with electrolytes. The formulas for the individual electrolytes and amino acids are provided in **Table 8**.

Table 8: Formulas for Amino Acids

Electrolytes	
Sodium Acetate	$C_2H_3NaO_2 \cdot 3H_2O$
Potassium Phosphate, dibasic	K_2HPO_4
Magnesium Chloride	$MgCl_2 \cdot 6H_2O$
Sodium Chloride	NaCl
Essential Amino Acids	
Leucine	$(CH_3)_2$ $CHCH_2CH$ (NH_2) $COOH$
Isoleucine	CH_3CH_2CH (CH_3) CH (NH_2) $COOH$
Valine	$(CH_3)_2$ $CHCH$ (NH_2) $COOH$
Lysine (added as the hydrochloride salt)	H_2N $(CH_2)_4$ CH (NH_2) $COOH$
Phenylalanine	(C_6H_5) CH_2 CH (NH_2) $COOH$
Histadine	$(C_3H_3N_2)$ CH_2CH (NH_2) $COOH$
Threonine	CH_3CH (OH) CH (NH_2) COO

Methionine	$CH_3S\ (CH_2)_2\ CH\ (NH_2)\ COOH$
Tryptophan	$(C_8H_6N)\ CH_2\ CH\ (NH_2)\ COOH$
Nonessential Amino Acids	
Alanine	$CH_3CH\ (NH_2)\ COOH$
Arginine	$H_2NC\ (NH)\ NH\ (CH_2)_3\ CH\ (NH_2)\ COOH$
Glycine	H_2NCH_2COOH
Proline	$[(CH_2)_3\ NH\ CH]\ COOH$
Serine	$HOCH_2CH\ (NH_2)\ COOH$
Tyrosine	$[C_6H_4\ (OH)]\ CH_2CH\ (NH_2)\ COOH$

The injection port chamber contains dextrose with calcium. The formula for Calcium Chloride is: C_aC_{l2}•$2H_2O$. Dextrose, USP, is chemically designated D-glucose, monohydrate (C6H12O6 • H2O) and has the following structure:



Dextrose Hydrous, USP
(D-Glucose monohydrate)

Dextrose is derived from corn.

See **Table 7** for composition, pH, osmolarity, ionic concentration and caloric content of the admixed product *[see Dosage Forms and Strengths (3)].*

The dual chamber container is a lipid-compatible plastic container (PL 2401 Plastic).

CLINIMIX E contains no more than 25 mcg/L of aluminum.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

CLINIMIX E is used as a supplement of nutrition in patients, providing macronutrients (amino acids and dextrose) and micronutrients (electrolytes) parenterally.

The amino acids provide the structural units that make up proteins and are used to synthesize proteins and other biomolecules or are oxidized to urea and carbon dioxide as a source of energy.

The administered dextrose is oxidized to carbon dioxide and water, yielding energy.

12.3 Pharmacokinetics

The disposition of infused amino acids, dextrose, and electrolytes are essentially the same as those absorbed from food.

15 REFERENCES

1. Ayers Phil, et al. A.S.P.E.N. Parenteral Nutrition Handbook, 2nd ed. 2014, pg. 123.
2. Mueller CM ed. The A.S.P.E.N. Nutrition Support Core Curriculum, 2nd ed. 2012. Chapter 29. Wolk R, Foulks C. Renal Disease, pg. 500.

16 HOW SUPPLIED/STORAGE AND HANDLING

CLINIMIX E (amino acids with electrolytes in dextrose with calcium) injection (sulfite-free) is available in 1000 mL and 2000 mL volumes **(See Table 9)**.

Table 9: CLINIMIXE Formulations

After mixing, the product represents	1000 mL Code and NDC Number	2000 mL Code and NDC Number
CLINIMIX E 2.75/5 sulfite-free (2.75% Amino Acid with Electrolytes in 5% Dextrose with Calcium) Injection	Code 2B7735 NDC 0338-1142-03	Code 2B7713 NDC 0338-1107-04
CLINIMIX E 2.75/10 sulfite-free (2.75% Amino Acid with Electrolytes in 10% Dextrose with Calcium) Injection	Code 2B7736 NDC 0338-1143-03	Code 2B7714 NDC 0338-1109-04
CLINIMIX E 4.25/5 sulfite-free (4.25% Amino Acid with Electrolytes in 5% Dextrose with Calcium) Injection	Code 2B7737 NDC 0338-1144-03	Code 2B7716 NDC 0338-1113-04
CLINIMIX E 4.25/10 sulfite-free (4.25% Amino Acid with Electrolytes in 10% Dextrose with Calcium) Injection	Code 2B7738 NDC 0338-1145-03	Code 2B7717 NDC 0338-1115-04
CLINIMIX E 4.25/25 sulfite-free (4.25% Amino Acid with Electrolytes in 25% Dextrose with Calcium) Injection	Code 2B7739 NDC 0338-1146-03	Code 2B7719 NDC 0338-1119-04
CLINIMIX E 5/15 sulfite-free (5% Amino Acid with Electrolytes in 15% Dextrose with Calcium) Injection	Code 2B7740 NDC 0338-1147-03	Code 2B7721 NDC 0338-1123-04
CLINIMIX E 5/20 sulfite-free (5% Amino Acid with Electrolytes in 20% Dextrose with Calcium) Injection	Code 2B7741 NDC 0338-1148-03	Code 2B7722 NDC 0338-1125-04
CLINIMIX E 5/25 sulfite-free (5% Amino Acid with Electrolytes in 25% Dextrose with Calcium) Injection	Code 2B7742 NDC 0338-1149-03	Code 2B7723 NDC 0338-1127-04

Minimize exposure of CLINIMIX E to heat and avoid excessive heat.

Protect from freezing.

Store CLINIMIX E at room temperature (25°C/77°F) (may briefly store at up to 40°C/104°F).

Refrigerated storage is limited to 9 days once the protective foil overwrap has been opened.

Do not use if the protective foil overwrap has been previously opened or damaged.

For storage of admixed solutions see Dosage and Administration (2.3, 2.4).

17 PATIENT COUNSELING INFORMATION

Inform patients, caregivers, or home healthcare providers of the following risks of CLINIMIX E:

- Pulmonary embolism due to pulmonary vascular precipitates *[see Warnings and Precautions (5.1)]*
- Death in neonates due to calcium-ceftriaxone precipitates *[see Warnings and Precautions (5.2)]*
- Hypersensitivity reactions *[see Warnings and Precautions (5.3)]*
- Risk of Infections *[see Warnings and Precautions (5.4)]*
- Refeeding syndrome *[see Warnings and Precautions (5.5)]*
- Hyperglycemia or hyperosmolar hyperglycemic state *[see Warnings and Precautions (5.6)]*
- Vein damage and thrombosis *[see Warnings and Precautions (5.7)]*
- Hepatobiliary disorders *[see Warnings and Precautions (5.8)]*
- Aluminum toxicity *[see Warnings and Precautions (5.9)]*
- Parenteral Nutrition Associated Liver Disease (PNALD) *[see Warnings and Precautions (5.10)]*
- Electrolyte imbalance and fluid overload *[see Warnings and Precautions (5.11)]*

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