HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use NOURESS ™ safely and effectively. See full prescribing information for NOURESS.

NOURESS (cysteine hydrochloride injection), for intravenous use
Initial U.S. Approval: 1971

INDICATIONS AND USAGE

NOURESS is a sulfur-containing amino acid indicated for use as an additive to amino acids solutions to meet nutritional requirements of neonates (preterm and term infants less than one month of age) requiring total parenteral nutrition. (1)

DOSAGE AND ADMINISTRATION

- NOURESS is for *intravenous infusion after dilution and admixing* only. (2.1)
- See full prescribing information for information on preparation, administration, and instructions for use. (2.1, 2.2, 2.3, 2.4)
- The recommended dosage in neonates is based upon the recommended daily protein (amino acid) requirements: 22 mg NOURESS/g amino acids. The corresponding volume is 0.44 mL NOURESS/g amino acids. (2.5)

DOSAGE FORMS AND STRENGTHS

Injection: 500 mg/10 mL (50 mg/mL) cysteine hydrochloride, USP in a single-dose vial. (3)

CONTRAINDICATIONS

- Hypersensitivity to one or more amino acids (4)
- Inborn errors of amino acid metabolism (4)
- 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)
- Vein Damage and Thrombosis: Solutions with osmolarity of 900 mOsm/L or more must be infused through a central catheter (2.1, 5.2)
- Increased Blood Urea Nitrogen (BUN): Monitor laboratory parameters and discontinue if BUN exceeds normal postprandial limits and continues to increase. (5.3)
- Acid-Base Imbalance: Monitor laboratory parameters and supplement with electrolytes as needed. (5.4)
- Hepatobiliary Disorders: Neurocognitive delay possible in infants; monitor liver function parameters and ammonia levels. (5.5, 8.4)
- Aluminum Toxicity: Increased risk in patients with renal impairment, including preterm infants. (5.6, 8.4)
- Monitoring and Laboratory Tests: Monitor fluid and electrolytes, serum osmolarity, blood glucose, kidney and liver function, blood count, and coagulation parameters throughout treatment. (5.7)

ADVERSE REACTIONS

Most common adverse reactions are local reactions (warm sensation, erythema, phlebitis, and thrombosis at the infusion site), generalized flushing, fever, nausea, and metabolic acidosis. (6)

To report SUSPECTED ADVERSE REACTIONS, contact Avadel at 1-877-638-4579 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

See 17 for PATIENT COUNSELING INFORMATION.

Revised: 12/2019

FULL PRESCRIBING INFORMATION: CONTENTS*

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

FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

NOURESS is indicated for use as an additive to amino acids solutions to meet nutritional requirements of neonates (preterm and term infants less than one month of age) requiring total parenteral nutrition.

2 DOSAGE AND ADMINISTRATION

2.1 Important Administration Information

NOURESS is for *intravenous infusion after dilution and admixing use* only. Prior to administration, NOURESS *must be diluted and used as an admixture* in parenteral nutrition solutions.

The resulting solution is for intravenous infusion 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 (5.2)]*.

2.2 Preparation and Administration Information

- Prior to administration, NOURESS *must be diluted and used as an admixture* in parenteral nutrition solutions.
- NOURESS is to be prepared only in a suitable work area such as a laminar flow hood (or an equivalent clean air compounding area). The key factor in the preparation is careful aseptic technique to avoid inadvertent touch contamination during mixing of solutions and addition of other nutrients.
- NOURESS is for addition to amino acid solutions prior to further admixing with dextrose injection using a parenteral nutrition container.
- 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)]*.
- Use a dedicated line for parenteral nutrition solutions.
- Intravenous lipid emulsions can be infused concurrently into the same vein as NOURESS-containing amino acid and dextrose solutions by a Y-connector located near the infusion site; flow rates of each solution should be controlled separately by infusion pumps.
- For administration, use a 0.22 micron in-line filter.
- To prevent air embolism, use a non-vented infusion set or close the vent on a vented set, avoid multiple connections, do not connect flexible containers in series, fully evacuate residual gas in the container prior to administration, do not pressurize the flexible

container to increase flow rates, and if administration is controlled by a pumping device, turn off pump before the container runs dry.

- Visually inspect the diluted parenteral nutrition solution containing NOURESS for particulate matter and discoloration before admixing, after admixing, after removal from refrigeration, and prior to administration. The solution should be clear and there should be no precipitates. A slight yellow color does not alter the quality and efficacy of this product.

2.3 Preparation Instructions for Admixing Using a Parenteral Nutrition Container

- Remove NOURESS vial from the carton and inspect for particulate matter.
- Transfer the required amount of NOURESS to an amino acid solution using strict aseptic techniques to avoid microbial contamination.
- The amino acid solution containing NOURESS can then be used to prepare admixtures in the parenteral nutrition container using strict aseptic techniques.
- Amino acids solution containing NOURESS may be mixed with dextrose injection. The following proper mixing sequence must be followed to minimize pH related problems:
    1. Transfer dextrose injection to the parental nutrition pooling container
    2. Transfer phosphate salt
    3. Transfer NOURESS-containing amino acid solution
    4. Transfer electrolytes
    5. Transfer trace elements
- Use gentle agitation during admixing to minimize localized concentration effects; shake containers gently after each addition.
- For automated compounding, refer to Instructions for Use of the applicable compounder.
- Because additives may be incompatible, evaluate all additions to the parenteral nutrition container for compatibility and stability of the resulting preparation. Consult with pharmacist, if available. Questions about compatibility may be directed to Avadel Pharmaceuticals. If it is deemed advisable to introduce additives to the parenteral nutrition container, use aseptic technique.
- Inspect the final parenteral nutrition solution containing NOURESS to ensure that precipitates have not formed during mixing or on addition of additives. Discard if any precipitates are observed.

Stability and Storage

- For single use only. Discard unused portion of the vial of NOURESS.
- Use parenteral nutrition solution containing NOURESS promptly after mixing. Any storage of the admixture should be under refrigeration at 2ºC to 8ºC (36ºF to 46ºF) and limited to a brief period of time, no longer than 24 hours. After removal from

refrigeration, inspect for precipitates, use promptly, and complete the infusion within 24 hours. Discard if any precipitates are observed.

- Discard any remaining admixture.
- Protect parenteral nutrition solution from light.

2.4 Dosing Considerations

The dosage of the final parenteral nutrition solution containing NOURESS must be based on the concentrations of all components in the solution and the recommended nutritional requirements *[see Dosage and Administration (2.5)]*. Consult the prescribing information of all added components to determine the recommended nutritional requirements.

The dosage of NOURESS should be individualized based on the patient's clinical condition (ability to adequately metabolize amino acids), body weight and nutritional/fluid requirements, as well as additional energy given orally/enterally to the patient. Prior to initiating parenteral nutrition, 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, and complete blood count.

Prior to administration of parenteral nutrition solution containing NOURESS, correct severe fluid, electrolyte and acid-base disorders.

2.5 Recommended Dosage for Neonates

The recommended dosage and volume of NOURESS is based upon the recommended daily protein (amino acid) requirements.

Table 1. Recommended Daily Dosage of NOURESS in Neonates (Preterm and Term Infants Less Than One Month of Age)

Dosage	Protein[a] Requirement (g Amino Acids/kg/day)[1]	Dosage (mg NOURESS/g Amino Acids)	Volume (mL NOURESS/g Amino Acids)
Neonates	3 to 4	22	0.44

[a] Protein is provided as amino acids.

NOURESS contains 50 mg/mL of cysteine hydrochloride (equivalent to 34.5 mg/mL of cysteine). Therefore, the recommended dosage of NOURESS provides 15 mg cysteine/gram of amino acids for neonates.

3 DOSAGE FORMS AND STRENGTHS

Injection: 500 mg/10 mL (50 mg/mL) cysteine hydrochloride, USP as a clear, colorless, sterile solution in a single-dose vial.

4 CONTRAINDICATIONS

NOURESS is contraindicated in:

- Patients with known hypersensitivity to one or more amino acids.
- Patients with inborn errors of amino acid metabolism due to risk of severe metabolic or 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 fatal cases, pulmonary embolism occurred as a result of calcium phosphate precipitates. 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 parenteral nutrition infusion and initiate a medical evaluation. In addition to inspection of the solution *[see Dosage and Administration (2.1, 2.2)]*, the infusion set and catheter should also periodically be checked for precipitates.

5.2 Vein Damage and Thrombosis

NOURESS must be diluted and used as an admixture in parenteral nutrition solutions. Solutions with an osmolarity of 900 mOsm/L or greater must be infused through a central catheter *[see Dosage and Administration (2.1)]*. The infusion of hypertonic nutrient injections into a peripheral vein may result in vein irritation, vein damage, and/or thrombosis. 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.

5.3 Increased Blood Urea Nitrogen (BUN)

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

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

5.4 Acid-Base Imbalance

Administration of NOURESS may result in metabolic acidosis in neonates.

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

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