

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Synthamin 14, 8.5% Amino Acid Intravenous Infusion without Electrolytes.

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

L-Leucine	Ph. Eur.	0.620 w/v
L-Isoleucine	Ph. Eur.	0.510% w/v
L-Lysine (as hydrochloride salt)	Ph. Eur.	0.493% w/v
L-Valine	Ph. Eur.	0.493% w/v
L-Phenylalanine	Ph. Eur.	0.476% w/v
L-Histidine	Ph. Eur.	0.408% w/v
L-Threonine	Ph. Eur.	0.357% w/v
L-Methionine	Ph. Eur.	0.340% w/v
L-Tryptophan	Ph. Eur.	0.153% w/v
L-Alanine	Ph. Eur.	1.760% w/v
L-Arginine	Ph. Eur.	0.978% w/v
Amino acetic acid	Ph. Eur.	0.876% w/v
L-Proline	Ph. Eur.	0.578% w/v
L-Serine	Ph. Eur.	0.425% w/v
L-Tyrosine	Ph. Eur.	0.034% w/v

3. PHARMACEUTICAL FORM

The product is a clear, or slightly coloured sterile non-pyrogenic solution of amino acids for intravenous infusion to human beings.

4. CLINICAL PARTICULARS

4.1. Therapeutic indications

Synthamin 14, 8.5% Amino Acid Intravenous Infusion without Electrolytes provides a biologically available source of nitrogen (L-amino acids) for amino acids synthesis. When administered with an adequate source of energy such as concentrated carbohydrate solutions, minerals and vitamins, the mixture provides (with the exception of essential fatty acids) sufficient parenteral nutrition for patients unable to absorb adequate oral nutrition.

4.2. Posology and method of administration

The solution is for administration by intravenous infusion through a central venous catheter with the tip located in the central vena cava.

The total daily dose of the solution depends upon the patient's metabolic requirement and clinical response. The determination of nitrogen balance and accurate daily body weights, corrected for fluid balance, are probably the best means of assessing individual nitrogen requirements.

In addition to meeting nitrogen needs, the rate of administration is governed, especially during the first few days of therapy, by the patient's ability to tolerate glucose. Daily intake of amino acids, electrolytes and glucose should be increased gradually to the maximum required dose as indicated by frequent determination of urine and blood sugar levels.

Recommended daily dietary allowances for protein range from 2.2g/kg of body weight for infants to 56g of protein per day for adults weighing 70kg. An associated source of non-protein energy should be administered in a quantity not less than 0.75 megajoules (180 kcal) per gram of nitrogen. In the initial treatment of severe trauma or in the presence of marked malnutrition, higher doses of amino acids with correspondingly larger quantities of carbohydrate will be necessary to promote adequate patient response to therapy. The degree of negative nitrogen balance being treated is the primary consideration in determining replacement therapy.

Electrolyte supplementation may be indicated according to the clinical needs of the patient (see Section 6.2).

Fat emulsion co-administration should be considered when prolonged parenteral nutrition is required in order to prevent essential fatty acid deficiency (EFAD).

As indicated on an individual basis, vitamins and trace elements and other components (including glucose and lipids) can be added to the parenteral nutrition regimen to meet nutrient needs and prevent deficiencies and complications from developing (see Section 6.2).

The osmolarity of a specific infusion solution must be taken into account when peripheral administration is considered.

Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration.

The flow rate should be increased gradually during the first hour.

The flow rate must be adjusted taking into account the dose being administered, the daily volume intake, and the duration of the infusion.

Use of a final filter is recommended during administration of all parenteral nutrition solutions.

Paediatric population

In children, the dosage of parenteral nutrition should be individually tailored to the amino acid, electrolyte and energy requirements of the patient.

When used in neonates and children below 2 years, the solution (in containers and administration sets) should be protected from light exposure after admixture through administration (Section 4.4 and 6.6).

4.3. Contraindications

Synthamin is contraindicated in patients with:

- Known hypersensitivity to any of the active substances or excipients, or to components of the container
- Congenital abnormality of amino acid metabolism

4.4 Special warnings and precautions for use

WARNINGS

Anaphylactic/anaphylactoid reactions and other hypersensitivity/infusion reactions have been reported with Synthamin administered as a component of parenteral nutrition (see Section 4.8). The infusion must be stopped immediately if any signs or symptoms of a reaction develop.

Pulmonary vascular precipitates causing pulmonary vascular emboli and pulmonary distress have been reported in patients receiving parenteral nutrition. In some cases, fatal outcomes have occurred. 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 distal to the in-line filter and suspected in vivo precipitate formation has also been reported.

Pulmonary vascular precipitates have also been reported with Synthamin (see Section 4.8).

If signs of pulmonary distress occur, the infusion should be stopped and medical evaluation initiated.

In addition to inspection of the solution, the infusion set and catheter should also periodically be checked for precipitates.

Infection and sepsis may occur as a result of the use of intravenous catheters to administer parenteral formulations, poor maintenance of catheters or contaminated solutions.

Immunosuppression and other factors such as hyperglycaemia, malnutrition and/or their underlying disease state may predispose patients to infectious complications.

Careful symptomatic and laboratory monitoring for fever/chills, leukocytosis, technical complications with the access device, and hyperglycaemia can help recognize early infections.

The occurrence of septic complications can be decreased with heightened emphasis on aseptic technique in catheter placement, maintenance, as well as aseptic technique in nutritional formula preparation.

Refeeding severely undernourished patients may result in the refeeding syndrome that is characterized by the shift of potassium, phosphorus, and magnesium intracellularly as the patient becomes anabolic. Thiamine deficiency and fluid retention may also develop. Careful monitoring and slowly increasing nutrient intakes while avoiding overfeeding can prevent these complications.

Hypertonic infusion solutions may cause irritation of the vein when administered into a peripheral vein (see Section 4.8).

PRECAUTIONS

Monitoring should be appropriate to the patient's clinical situation and condition, and should include determinations of water and electrolyte balance, serum osmolarity, acid/base balance, blood glucose, liver and kidney function.

Metabolic complications may occur if the nutrient intake is not adapted to the patient's requirements, or the metabolic capacity of any given dietary component is not accurately assessed. Adverse metabolic effects may arise from administration of inadequate or excessive nutrients or from inappropriate composition of an admixture for a particular patient's needs.

Amino acid solutions should be used with caution in patients with preexisting liver disease or liver insufficiency.

Liver function parameters should be closely monitored in these patients, and they should be monitored for possible symptoms of hyperammonemia (see below).

Patients on parenteral nutrition may experience hepatic complications (including cholestasis, hepatic steatosis, fibrosis and cirrhosis, possibly leading to hepatic failure, as well as cholecystitis and cholelithiasis) and should be monitored accordingly. The etiology of these disorders is thought to be multifactorial and may differ between patients. Patients developing abnormal laboratory parameters or other signs of hepatobiliary disorders should be assessed by a clinician knowledgeable in liver diseases in order to identify possible causative and contributory factors, and possible therapeutic and prophylactic interventions.

Increase in blood ammonia levels and hyperammonemia may occur in patients receiving amino acid solutions. In some patients this may indicate the presence of a congenital disorder of amino acid metabolism (see Section 4.3) or hepatic insufficiency.

Blood ammonia should be measured frequently in newborns and infants to detect hyperammonemia, which may indicate the presence of a congenital abnormality of amino acid metabolism.

Depending on extent and etiology, hyperammonemia may require immediate intervention. Should symptoms of hyperammonemia develop, administration should be discontinued and the patient's clinical status re-evaluated.

Azotemia has been reported with parenteral administration of solutions containing amino acids, and may occur in particular in the presence of renal impairment.

Use with caution in patients with pulmonary oedema or heart failure. Fluid status should be closely monitored.

Use with caution in patients with renal insufficiency. Fluid and electrolyte status should be closely monitored in these patients.

Severe water and electrolyte disorders, severe fluid overload states, and severe metabolic disorders should be corrected before starting the infusion.

Mixtures containing amino acids may precipitate acute folate deficiency and folic acid should be administered daily.

It is essential to provide an adequate source of non-protein energy concurrently if parenterally administered amino acids are to be retained by the body and utilised for protein synthesis. Concentrated glucose solutions are an effective source of such energy.

The infusion of Synthamin with highly concentrated glucose solutions may result in hyperglycaemia, glycosuria and hyperosmolar syndrome. Blood and urine glucose should be monitored on a routine basis in patients receiving this treatment.

Paediatric use

There have been no studies performed by Baxter Healthcare Corporation in the paediatric population. See above regarding monitoring for hyperammonemia in paediatric patients.

Light exposure of solutions for intravenous parenteral nutrition, especially after admixture with trace elements and/or vitamins, may have adverse effects on clinical outcome in neonates, due to generation of peroxides and other degradation products. When used in neonates and children below 2 years, Synthamin should be protected from ambient light until administration is completed (see sections 4.2, 6.3 and 6.6).

Geriatric use

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

4.5. Interaction with other medicinal products and other forms of interaction

No interaction studies have been performed by Baxter Healthcare Corporation with Synthamin.

4.6. Fertility, pregnancy and lactation

There are no adequate data from the use of Synthamin in pregnant or lactating women. Healthcare Professionals should carefully consider the potential risks and benefits for each specific patient before administering Synthamin.

4.7. Effects on ability to drive and use machines

There is no information of the effects of Synthamin on the ability to operate a vehicle or other heavy machinery.

4.8. Undesirable effects

The following adverse reactions have been reported in the post-marketing experience.

Frequency is defined as very common ($\geq 1/10$); common ($\geq 1/100$ to $< 1/10$); uncommon ($\geq 1/1000$ to $< 1/100$); rare ($\geq 1/10,000$ to $< 1/1000$); very rare ($< 1/10,000$); and not known (cannot be estimated from the available data). Other adverse reactions reported with parenteral amino acid products include:

Tabulated list of adverse reactions

System Organ Class	Preferred MedDRA Term	Frequency
Immune system disorders	Anaphylactic/anaphylactoid reactions*	Not known
	Hypersensitivity**	Not known
Vascular disorders	Pulmonary vascular precipitate	Not known

*Including: skin, gastrointestinal and severe circulatory (shock) and respiratory manifestations

**Includes the following manifestations: Pyrexia, Chills, Hypotension, Hypertension, Arthralgia, Myalgia, Urticaria, Rash, Pruritus, Erythema, Headache.

Other adverse reactions reported with parenteral amino acid products include:

- Azotemia, Hyperammonemia

Adverse reactions reported with parenteral nutrition to which the amino acid component may play a causal or contributory role include:

- Hepatic failure, Hepatic cirrhosis, Hepatic fibrosis, Cholestasis, Hepatic steatosis, Blood bilirubin increased, Hepatic enzyme increased; Cholecystitis, Cholelithiasis

- Infusion site thrombophlebitis; venous irritation (infusion site phlebitis, pain, erythema, warmth, swelling, induration).

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the Yellow Card Scheme at:

Website: www.mhra.gov.uk/yellowcard

4.9. Overdose

In the event of inappropriate administration (overdose, and/or infusion rate higher than recommended), hypervolemia, electrolyte disturbances, acidosis and/or azotemia may occur. In such situations, the infusion must be stopped immediately. If medically appropriate, further intervention may be indicated to prevent clinical complications.

There is no specific antidote for overdose. Emergency procedures should include appropriate corrective measures.

5. PHARMACOLOGICAL PROPERTIES

5.1. Pharmacodynamic properties

None stated.

5.2. Pharmacokinetic properties

None stated.

5.3. Preclinical safety data

No data is presented as amino acids are basic and widespread elements in mammalian metabolism. Therefore conventional animal safety testing is not appropriate.

6. PHARMACEUTICAL PARTICULARS

6.1. List of excipients

Water for Injections	Ph. Eur.	QS to 100%
Glacial acetic acid	Ph. Eur.	QS (for pH adjustment)
Sodium acetate	Ph. Eur.	QS (for pH adjustment)

6.2. Incompatibilities

Additives may be incompatible.

Do not add other medicinal products or substances without first confirming their compatibility and the stability of the resulting preparation.

Excessive addition of calcium and phosphate increases the risk of the formation of calcium phosphate precipitates (see Section 4.4).

6.3. Shelf life

The shelf life is 24 months providing the unit has not been opened.

When used in neonates and children below 2 years, the solution (in bags and administration sets) should be protected from light exposure until administration is completed (see sections 4.2, 4.4 and 6.6).

6.4. Special precautions for storage

Storage temperature should not exceed 25°C.

Product supplied in a clear overpouch should be protected from light during storage.

6.5. Nature and contents of container

The products are supplied in poly (vinyl chloride) Viaflex® containers which are sealed in a plastic laminated overpouch, or in dual bag containers sealed in a plastic laminated overpouch.

The container is sealed with a closure made from poly (vinyl chloride).

The solutions are supplied in 250ml, 500ml, 1000ml, 2000ml and 3000ml fill volumes.

6.6. Special precautions for disposal and other handling

2 litre and 3 litre containers are bulk source containers for pharmacy use and should not be used for direct intravenous infusion.

Do not administer unless the solution is clear and colourless or slightly yellow, and the container undamaged.

To open

Do not remove from overpouch until ready to use.

Remove the protective overpouch.

Check bag for leaks.

If additions to the bag are made

Aseptic conditions must be observed.

Ensure stability and compatibility of additives.

Prepare the injection site of the bag.

Puncture the injection site and inject the additives using an injection needle or a reconstitution device.

Mix content of the bag and the additives thoroughly.

Inspect final solution for discoloration and particulate matter.

Check bag for leaks.

Ensure proper storage requirements of additives are followed.

Administration of the infusion

Do not be administered simultaneously with, before or after an administration of blood through the same infusion equipment, because of the possibility of pseudo-agglutination.

Do not connect bags in series in order to avoid air embolism due to possible residual air contained in the primary bag.

For single use only.

Discard all equipment after use.

Discard any unused portion.

Do not reconnect partially used bags.

When used in neonates and children below 2 years, protect from light exposure, until administration is completed. Exposure of Synthamin to ambient light, especially after admixture with trace elements and/ or vitamins, generates peroxides and other degradation products that can be reduced by protection from light exposure (see sections 4.2, 4.4 and 6.3).

7. MARKETING AUTHORISATION HOLDER

Baxter Healthcare Ltd.,
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Thetford,
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IP24 3SE

8. MARKETING AUTHORISATION NUMBER

PL 0116/0295

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

1st December 1997 / 25th July 2002

10. DATE OF REVISION OF THE TEXT

April 2020