

PRODUCT INFORMATION

NAME OF MEDICINE

GLAMIN®

Amino acid / dipeptide 13.4% Solution for intravenous infusion.

DESCRIPTION

Glamin is an amino acid solution which contains glutamine and tyrosine as glycyl dipeptides for total parenteral intravenous nutrition.

Content (per 1000mL):

Active ingredients

Alanine	16.00g
Arginine	11.30g
Aspartic acid	3.40g
Glutamic acid	5.60g
Glycyl-L-glutamine monohydrate (Equivalent to glycine 10.27g & glutamine 20.0g)	30.27g
Glycyl-L-tyrosine dihydrate (Equivalent to glycine 0.94g & tyrosine 2.28g)	3.45g
Histidine	6.80g
Isoleucine	5.60g
Leucine	7.90g
Lysine-Acetate (equiv to lysine 9.0g)	12.70g
Methionine	5.60g
Phenylalanine	5.85g
Proline	6.80g
Serine	4.50g
Threonine	5.60g
Tryptophan	1.90g
Valine	7.30g

Inactive ingredients

Citric acid-anhydrous	2.53g
Water for injections to	1000ml

1000mL of Glamin supplies :

Amino acids and dipeptides	134g
Total Nitrogen	22.4g
Energy content	2300kJ (540kcal)
Theoretical osmolarity	1040 mOsm
Theoretical osmolality	1140 mOsm/kg water
Density	1.0414 g/cm ³
pH	approximately 5.8.

PHARMACOLOGY

Glamin is an infusion solution for parenteral nutrition containing 18 essential and non-essential amino acids, two of which are in the form of the dipeptides glycyl-glutamine and glycyl-tyrosine.

The solution is suitable to support protein synthesis and to improve nitrogen balance during intravenous nutrition. In order to ensure optimal utilisation of the infused amino acids and dipeptides, the patient's requirements of energy (carbohydrates, fat), electrolytes, trace elements and vitamins should be covered.

Pharmacological effects, except nutritive ones, are not expected from amino acid solutions as long as they are infused according to the recommended dosage for parenteral nutrition.

Pharmacokinetics of dipeptides

The two dipeptides glycyl-glutamine and glycyl-tyrosine are rapidly and quantitatively hydrolysed to their constituent amino acids when infused intravenously in animals and humans. Several tissues participate in the hydrolysis of the dipeptides, but the kidneys play the quantitatively most important role. The liver, skeletal muscle and intestine also participate in the clearance of the dipeptides. Finally, hydrolysis of the dipeptides also takes place in the plasma.

The half-life of the dipeptides is short with a value of less than 30 minutes for glycyl-glutamine and less than 10 minutes for glycyl-tyrosine. For glycyl-glutamine, the volume of distribution approximated that of the blood volume and mean clearance was 91 mL/min. Less than 2% of the dipeptides were excreted unchanged in the urine.

CLINICAL TRIALS

Clinical trials carried out to date have compared Glamin to Vamin 18EF (an amino acid solution containing 11.4% amino acids, but no dipeptides). A series of 13 clinical trials involving a total of 374 patients, 189 of whom were treated with Glamin have shown that Glamin is as well tolerated as Vamin 18EF. The findings also demonstrate that Glamin is as efficacious as Vamin 18EF when given to patients after moderate to major abdominal surgery. Even though the results are strictly valid only for the studied patient groups, they can most likely be extended to other groups requiring intravenous nutrition and support of protein metabolism.

In the studies, plasma amino acid concentrations showed small to moderate changes during infusion of Glamin or Vamin 18EF. The combined data of all the clinical trials indicated a slightly higher concentration of glutamine in the Glamin group. However, all plasma amino acid concentrations were well within the normal range in both study groups and there was no accumulation of amino acids in plasma during the study period. The urinary excretion of both amino acids and dipeptides was also low, in the case of glycyl-glutamine it amounted to 3-4% of the administered amount and the corresponding value for glycyl-tyrosine was 2-3%. Taken together, the combined data indicates that the dipeptides of Glamin are rapidly hydrolysed, and the amino acids are efficiently utilised in a manner similar to that for Vamin 18EF.

The short life proteins of the liver, primarily prealbumin, were chosen as efficacy variables. No differences were observed between the two study groups with regard to changes in these variables during the post-operative period. Urea, nitrogen excretion and cumulative nitrogen balance were also measured. The results were similar for both groups.

The incidence of clinical adverse events was similar in both groups of patients. The majority of the observed adverse events were most likely related to the patients' basic disorder or to the surgical procedure (fever, dyspnoea, rupture of the wound, insufficiency of intestinal anastomosis, etc). The appearance of clinical symptoms such as nausea, vomiting, dizziness, etc may possibly be related to the infusion of amino acid solutions besides being a frequent occurrence in the post-operative period, but the incidence of these events was not different in the two groups.

INDICATIONS

Glamin provides amino acids as part of parenteral nutrition therapy, when oral or enteral nutrition is impossible, insufficient or contraindicated especially in patients with a moderate to severe catabolic status.

CONTRAINDICATIONS

Glamin is contraindicated in patients with inborn errors of amino acid metabolism (e.g. phenylketonuria), severe liver failure and severe renal failure.

General contraindications of parenteral nutrition are: unstable life-threatening circulatory conditions (shock), metabolic acidosis, insufficient cellular oxygen supply, hyperhydration, hyponatraemia, hypokalaemia, hyperlactataemia, increased serum osmolarity, pulmonary oedema, decompensated cardiac insufficiency and known hypersensitivity to any of the ingredients.

PRECAUTIONS

Amino acids solutions should not be used as carrier solutions for drugs. Glamin may only be mixed with other solutions where compatibility is documented.

Only clear solutions in intact containers should be used.

Caloric requirements

It is essential to provide for appropriate caloric supply concurrently if parenterally administered amino acids are to be retained by the body and utilised maximally for protein synthesis. Concentrated glucose solutions or fat emulsions are effective sources of such calories.

Monitoring

Frequent clinical evaluation and laboratory testing are necessary for proper monitoring during administration. Electrolytes, osmolarity, glucose, fluid balance, acid-base status, renal and liver function and full blood count should all be monitored.

Impaired hepatic and renal function

There is no clinical trial experience with the use of Glamin in patients with mild or moderate impairment of hepatic or renal function. Administration of amino acid solutions to patients with hepatic insufficiency may result in serum amino acid imbalances, hyperammonaemia, stupor and coma. Glamin should be used with caution in these patient populations. Glamin is contraindicated in patients with renal failure (if dialysis or hemofiltration is not available) or severe liver failure.

Carcinogenesis, Mutagenesis, Impairment of Fertility

The carcinogenic potential of Glamin or the individual dipeptides has not been investigated in animal studies. The genotoxic potential of the dipeptides has not been investigated *in*

vivo, however, assays of the dipeptides for gene mutations and chromosomal damage *in vitro* were negative. The genotoxic potential of Glamin has not been investigated.

The effect of Glamin on fertility has not been investigated in animal or clinical studies.

Use in pregnancy (Category : Exempt)

There were no abnormalities or embryotoxic effects in rabbits when the animals were dosed during embryo-foetal development with Glamin at intravenous dose levels similar (1.2 times) to the maximum recommended clinical doses (14 mL/kg/day), based on body surface area. The effect of Glamin on peri and postnatal development has not been investigated.

There are no adequate and well-controlled studies in pregnant women. As animal studies are not always predictive of human response, Glamin should only be used during pregnancy if the benefit to the mother outweighs the risks to the foetus.

Use in lactation

No data on the effects of Glamin during lactation are available. Caution should be exercised when Glamin is administered to a nursing woman and should only be used if clearly needed.

Use in children

There is no experience with the use of Glamin solution in patients less than 18 years of age and it therefore cannot be recommended for use in children.

Interaction with other drugs

In rats it has been shown that glutamine decreases the clearance of methotrexate. However, in humans there are no known drug interactions.

ADVERSE EFFECTS

A meta-analysis for a combined 12 trials of Glamin versus Vamin 18 EF showed the number of patients with clinical adverse events was 28.6% (50/175) versus 32.0% (55/172), respectively. Clinical adverse events regardless of causal relationship for the entire sample of 12 studies grouped according to organ classes are presented in the following table:

	Glamin % n=175	Vamin 18 EF % n=172
General (body as a whole)	12.0	15.1
Gastrointestinal system	9.1	11.0
Nervous system/psychiatric	3.4	6.4
Respiratory system	5.1	2.9
(Cardio)vascular	2.3	4.1
Resistance mechanism	1.1	1.7
Skin and appendages	1.7	0.6
Urinary system	0.6	0.6
Platelet, bleeding or clotting	1.1	-

The most common adverse events based on the 12 clinical studies with Glamin sorted by CIOMS III categories of frequency and COSTART (5th Edition, 1995) body system and terms (not assessed as being necessarily related to Glamin) are as follows:

Incidence of frequency $\geq 1\% < 10\%$

Fever, chills or hot flushes.

Incidence of frequency $\geq 0.1\% < 1\%$

Nausea or vomiting, confusion, agitation or hallucination, hiccups, dyspnoea, pneumonia, hypertension or hypertonia, anastomosis insufficiency, gastrooesophageal reflux, dizziness or vertigo, pulmonary complication, headache or migraine.

Laboratory parameters

Incidence of frequency $\geq 1\% < 10\%$

Increases of gamma-GT, ALAT, AP, ASAT, glucose, bilirubin, urea, decreases of leucocytes, cholinesterase, haemoglobin.

Incidence of frequency $\geq 0.1\% < 1\%$

Increases of ESR, uric acid, triglyceride, creatinine, decreases of albumin, sodium, potassium, leucocytes, total protein, RBP, haematocrit/PCV, calcium, chloride, prealbumin, phosphate; urinary glucose, urinary blood and urinary protein.

DOSAGE AND ADMINISTRATION

The dosage of Glamin will depend on the patient's amino acid requirements. Generally, 1-2g amino acids/dipeptides (corresponding to 0.17-0.34g N) per kg body weight per day are recommended. This corresponds to 7-14ml Glamin per kg body weight per day or to 500-1000mL Glamin per day for a patient weighing 70kg.

The recommended infusion rate is 0.6-0.7mL (corresponding to 0.08-0.09g amino acids/dipeptides) per kg body weight per hour. This corresponds to 500mL in 10-12 hours or 1000mL in 20-24 hours for a patient weighing 70kg.

In patients with mild to moderate hepatic or renal impairment, dosage should be adjusted individually (see Precautions).

Glamin should be administered by the central venous route due to its osmolarity above 800 mOsm/L.

Use only clear solutions in intact containers.

The safety and efficacy of using Glamin for periods greater than two weeks has not been established.

Compatibility

Compatibility with Glamin 1000mL has been documented for the following:

- 20% fat emulsion (up to 1000mL Intralipid 20%*)
- glucose 40% (up to 1000mL)
- 80 mmol NaCl
- 5 mmol CaCl₂
- 60 mmol KCl
- 3.5 mmol Mg-L-hydrogen-glutamate
- fat soluble vitamins (10mL Vitalipid N Adult*)
- water soluble vitamins (1 vial Soluvit N*)

(* These have been used for compatibility testing)

Addition of individual supplements, e.g. phosphate supplements or trace elements, is possible but requires compatibility testing in each case.

Additions should be performed aseptically immediately before the start of the infusion. Discard any residual contents. All steps of admixing must be performed under strictly aseptic conditions, e.g. using laminar air flow technique, by professionally trained personnel according to individual hospital policy.

Recommended admixing sequence

1. Add trace elements and phosphate-free electrolyte solutions to Glamin.
2. Add phosphate-containing electrolytes to the glucose solution.
3. Transfer the solutions produced in steps 1 and 2 into the ethylvinylacetate (EVA) bag.
4. Reconstitute Soluvit N with Vitalipid N and add to Intralipid.
5. Transfer Intralipid/vitamin mixture to the EVA bag.
6. Mix the contents of the bag by gentle agitation.

Note: Glucose solutions should not be added directly to Intralipid, but should be mixed with Glamin first. Electrolytes should never be added directly to Intralipid, but should be diluted in Glamin and glucose solution before being mixed with the emulsion.

When a mixture must be stored in the refrigerator for up to 24 hours before use, the vitamins and trace elements should be added just prior to administration.

The use of EVA bags for compounding should follow the manufacturer's instructions under strictly aseptic conditions.

OVERDOSAGE

When infusion rates exceed the recommended maximum rate, signs of intolerance may occur such as nausea, vomiting, flushing and sweating in combination with renal excretion of amino acids and dipeptides.

If symptoms of overdose occur, therapy includes reduction of the infusion rate or, if necessary, interruption of the infusion.

PRESENTATION AND STORAGE CONDITIONS

Glamin is an electrolyte free, clear, and colourless to slightly yellow solution available in glass bottles of 250mL, 500mL and 1000mL.

Store below 25°C.

NAME AND ADDRESS OF THE SPONSOR

Fresenius Kabi Australia Pty Limited

964 Pacific Highway

Pymble NSW 2073

Australia

Telephone: (02) 9391 5555

Fresenius Kabi New Zealand Limited

60 Pavilion Drive

Airport Oaks, Auckland 2022

New Zealand

Freecall: 0800 144 892

POISON SCHEDULE

Australia : Not scheduled

New Zealand : General Sale Medicine

DATE OF TGA APPROVAL:

13th March, 2002

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22nd February, 2010