Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Glamin, solution for infusion

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

1000 ml of the infusion solution contains:

Active ingredients	Quantity	
Alanine	16.00	g
Arginine	11.30	g
Aspartic acid	3.40	g
Glutamic acid	5.60	g
Glycyl-Glutamine H_2O	30.27	g
(corresp.to Glycine 10.27 g corresp.to Glutamine 20.0 g)		
Glycyl-Tyrosine 2 H_2O	3.45	g
(corresp.to Glycine 0.94 g corresp.to Tyrosine 2.28 g)		
Histidine	6.80	g
Isoleucine	5.60	g
Leucine	7.90	g
Lysine-Acetate	12.70	g
(corresp.to Lysine 9.0 g)		
Methionine	5.60	g
Phenylalanine	5.85	g
Proline	6.80	g
Serine	4.50	g
Threonine	5.60	g
Tryptophan	1.90	g
Valine	7.30	g

For a full list of excipients, see section 6.1.

Amino acids/dipeptides	134.00	g/l
Total nitrogen	22.40	g/l
Energy content	2300 kJ	(540 kcal)/l
Density	1.0414	g/cm^3

3 PHARMACEUTICAL FORM

Solution for infusion.
Clear, colourless to slightly yellow solution

4 CLINICAL PARTICULARS

4.1 Therapeutic 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.

In parenteral nutrition regimens amino acid solutions should always be administered in combination with appropriate energy-supplying infusion solutions.

4.2 Posology and method of administration

The dosage depends on the amino acid requirements.

Generally, 1-2 g amino acids/dipeptides (corresp. to 0.17-0.34 g N) per kg body weight per day are recommended. This corresponds to 7-14 ml Glamin/kg body weight/day or to 500-1000 ml Glamin/day for a patient weighing 70 kg.

Recommended infusion rate: 0.6-0.7 ml (corresp. to 0.08-0.09 g amino acids/dipeptides)/kg body weight/hour. This corresponds to 500 ml in 10-12 hours or 1000 ml in 20-24 hours for a patient weighing 70 kg.

Dosage to be adjusted individually for patients with renal or liver diseases.

Glamin is not recommended for use in children *(see 4.4)*.

Method and duration of administration:

Intravenous infusion. Glamin should be administered by the central venous route due to its osmolarity above 800 mosm/l.

Infusion may be continued for as long as required by the patient's clinical condition. No experience is available so far for administration over more than 2 weeks.

4.3 Contraindications

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, hyponatremia, hypokalemia, hyperlactatemia, increased serum osmolarity, pulmonary oedema, decompensated cardiac insufficiency and hypersensitivity to the active substances or to any of the excipients.

4.4 Special warnings and precautions for use

Monitoring advice:
Serum electrolytes, serum osmolarity, water balance, acid-base status as well as liver function tests (alkaline phosphatase, GPT, GOT) should be monitored.

Use in pediatric patients:
Glamin is not indicated for use in children below the age of 2 years since its composition is not adapted to the requirements of these patients. For older children experience is lacking, the use of Glamin can therefore not be recommended.

See also section 6.2 and 6.6.

4.5 Interaction with other medicinal products and other forms of interaction

Not investigated, however, no interactions are known to date.

4.6 Fertility, pregnancy and lactation

No human data are available on the use of Glamin during pregnancy and lactation. The use of Glamin during pregnancy and lactation should be subject to a benefit-risk evaluation.

However, an evaluation of experimental animal studies (embryotoxicity study in rabbit) does not indicate direct or indirect harmful effects with respect to reproduction.

4.7 Effects on ability to drive and use machines

Not relevant.

4.8 Undesirable effects

Not to be expected, if used as directed.

See 4.2 and 4.4.

4.9 Overdose

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

Therapy if symptoms of overdose occur: Reduce infusion rate or, if necessary, interrupt infusion.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Solution with amino acids and dipeptides for parenteral nutrition.
ATC code: B05BA01.

Glamin is an infusion solution for parenteral nutrition containing 18 essential and non-essential amino acids, three 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 utilization 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. Both dipeptides, glycyl-glutamine and glycyl-tyrosine, are included to improve availability of glutamine and tyrosine and to stimulate protein synthesis. The dipeptides are not expected to exert other specific pharmacodynamic effects than those of the corresponding free amino acids. Only in rats it has been shown that glutamine decreases clearance of methotrexate.

5.2 Pharmacokinetic properties

The two dipeptides glycyl-glutamine and glycyl-tyrosine are rapidly and quantitatively hydrolyzed 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 plasma.

5.3 Preclinical safety data

a.) Local tolerance

Due to the osmolarity of 1040 mosm/l, Glamin should be administered by the central-venous route. Peripheral-venous infusion of Glamin in the dog for 28 days (6 hours daily) induced no macroscopic or microscopic changes at the infusion site.
In clinical phase I studies no regional vascular complications were observed during peripheral-venous infusion.

b.) Single dose toxicity

No evidence of toxicity was apparent in rats or mice after a bolus injection of Glamin at a dosage corresponding to 2-3 times the daily recommended dose for patients to be infused over 10-20 hours.
Nor were any signs of toxicity observed in rats when the individual dipeptide glycyl-glutamine or glycyl-tyrosine was infused for 8 hours at a dosage of 5.1 and 5.9 g/kg, respectively.

c.) Repeated dose toxicity

Subchronic toxicity studies with Glamin in rats and dogs for 28 days revealed no drug-related changes in the clinical observations, laboratory investigations or postmortem examinations.

d.) Mutagenic potential

No mutagenic potential was demonstrated for the individual dipeptides.

e.) Oncogenic/carcinogenic potential

For the intended indication conventional carcinogenicity studies are not considered mandatory. The lack of mutagenic activity of the dipeptides would not imply any carcinogenic potential. Moreover, the dipeptides are rapidly hydrolyzed to their constituent amino acids and there are many years of experience for amino acids as physiological substrates.

f.) Reproduction toxicity

No embryotoxic or teratogenic effects were observed in rabbits infused with the maximum tolerable volume of 24 ml of Glamin/kg (4 hours daily).
Additional studies are not considered necessary in view of the clinical use, the pharmacokinetic properties and the lack of adverse reproductive effects in the rabbit as well as of changes in repro-ductive organs in the subchronic toxicity studies.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Citric acid (pH adjustment).
Water for injection.

6.2 Incompatibilities

This medicinal product must not be mixed with other medicinal products except those mentioned in section 6.6.

6.3 Shelf life

Shelf life of the medicinal product as packaged for sale:
Infusion bag: 1 year

Shelf life after first opening of the container:
Glamin should be used immediately after opening of the container.

6.4 Special precautions for storage

Infusion bag
Do not store above 25°C.
Store in overpouch.

6.5 Nature and contents of container

Infusion bags consisting of an inner bag and an overpouch. The inner bag is made of polypropylene-based polymer. An oxygen absorber is placed between inner bag and overpouch.

Bag sizes: 250 ml, 10 x 250 ml
500 ml, 12 x 500 ml
750 ml, 8 x 750 ml
1000 ml, 6 x 1000 ml

Not all pack sizes may be marketed.

6.6 Special precautions for disposal of a used medicinal product or waste materials derived from such medicinal product and other handling of the product

Instructions for use.

Use only clear solutions in intact containers.

To achieve a complete parenteral nutrition regimen, Glamin should be administered in combination with carbohydrates and/or fat as well as electrolytes, trace elements and vitamins.

Compatibility

For the following mixture with Glamin compatibility is documented:
1000 ml Glamin with 20 % fat emulsion (up to 1000 ml Intralipid 20%*), up to 1000 ml glucose 40 %, 80 mmol NaCl, 5 mmol $CaCl_2$, 60 mmol KCl, 3.5 mmol Mg-L-hydrogen-glutamate, phosphate supplement (15 ml Addiphos*), trace elements (10 ml Addamel N*/Addel N*/Additrace*), fat soluble vitamins (10 ml Vitalipid N Adult*) and water soluble vitamins (1 vial Soluvit N*/Solivito N*).

(*) used for compatibility testing

Additions should be performed aseptically immediately before the start of the infusion.
For single use only. Any unused product or waste material should be disposed of in accordance with local requirements.

7 MARKETING AUTHORISATION HOLDER

Fresenius Kabi Limited
Cestrian Court
Eastgate Way
Manor Park
Runcorn
Cheshire WA7 1NT
United Kingdom

8 MARKETING AUTHORISATION NUMBER

PA 566/6/4

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 09 January 2004

Date of last renewal: 29 May 2010

10 DATE OF REVISION OF THE TEXT

June 2011