INSTRUCTIONS FOR USE

Trade name of the medicinal product

Dipeptiven®

Active substance: N(2)-L-alanyl-L-glutamine

Qualitative and quantitative composition

100 ml contains:

20 g N(2)-L-alanyl-L-glutamine
(= 8.20 g L-alanine, 13.46 g L-glutamine)

Water

theoretical osmolarity	921 mosmol/l
titration acidity	90–105 mmol NaOH/l
pH value	5.4–6.0

Pharmaceutical form

concentrated solution for infusion

Therapeutical indications

Dipeptiven® is indicated as part of an intravenous parenteral nutrition regimen as a supplement to amino acid solutions or an amino acid containing infusion regimen, e.g. in patients in hypercatabolic and/or hypermetabolic states.

Posology and method of administration

For central venous infusion after addition to a compatible infusion solution.

Solutions of mixtures with an osmolarity above 800 mosmol/l should be infused by the central venous route.

Dosage depends on the severity of the catabolic state and on amino acid requirement. A maximum daily dosage of 2 g amino acids/kg body weight should not be exceeded in parenteral nutrition. The supply of alanine and glutamine via Dipeptiven® should be taken into consideration in the calculation; the proportion of the ami-

no acids supplied through Dipeptiven® should not exceed approx. 20% of the total supply.

Daily dose

1.5–2.0 ml of Dipeptiven® per kg body weight (equivalent to 0.3–0.4 g N(2)-L-alanyl-L-glutamine per kg body weight). This equates to 100 to 140 ml Dipeptiven® for a patient of 70 kg body weight.

Maximum daily dose: 2.0 ml equivalent to 0.4 g N(2)-L-alanyl-L-glutamine of Dipeptiven® per kg body weight.

The following adjustments thus result for the amino acid supply through the carrier solution:

Amino acid requirement 1.5 g/kg body weight per day: 1.2 g amino acids + 0.3 g N(2)-L-alanyl-L-glutamine per kg body weight.

Amino acid requirement 2 g/kg body weight per day: 1.6 g amino acids + 0.4 g N(2)-L-alanyl-L-glutamine per kg body weight.

The rate of Infusion depends on that of the carrier solution and should not exceed 0.1 g amino acids/kg body weight per hour.

Dipeptiven® is an infusion solution concentrate which is not designed for direct administration. It should be mixed with a compatible amino acid carrier solution or an amino acid containing infusion regimen prior to administration.

One volume part Dipeptiven® is to be mixed with at least 5 volume parts carrier solution (e.g. 100 ml Dipeptiven® + at least 500 ml amino acid solution).

3.5% of the active ingredient should be the maximum concentration during therapy.

The duration of use should not exceed 3 weeks.

Contra-Indications Dipeptiven® should not be administered to patients with severe renal insufficiency (creatinine

clearance < 25 ml/minute), severe hepatic insufficiency, severe metabolic acidosis or known hypersensitivity to any of the ingrediets.

Special warnings and precautions for use

It is advisable to regularly monitor liver function parameters in patients with compensated hepatic insufficiency.

As there is currently insufficient data on administration of Dipeptiven® to pregnant women, nursing mothers and children, administration of the preparation in these patient groups is not recommended.

Serum electrolytes, serum osmolarity, water balance, acid-base status as well as liver function tests (alkaline phosphatase, ALT, AST), possible symptoms of hyperammonaemia should be controlled.

The enzymes alkaline phosphatase, GPT, GOT, bilirubin level and the acid-base status should be monitored.

The choice of a peripheral or central vein depends on the final osmolarity of the mixture. The general accepted limit for peripheral infusion is about 800 mosmol/l but it varies considerably with the age and gneral condition of the patient and the characteristics of the peripheral veins.

Experience with the use of Dipeptiven® for longer periods than nine days is limited.

Interaction with other medications and other forms of interaction

No interactions are known to date.

Use during pregnancy and lactation

Due to lack of experience, Dipeptiven® should not be administered during pregnancy and lactation.

Effects on ability to drive and use maschines	Not applicable
Undesirable effects	None known when correctly administered.
Overdose (symptoms, emergency procedure, antidotes)	As with other infusion solutions, chills, nausea and vomiting can occur, when the infusion rate of Dipeptiven® is exceeded. Infusion shall be stopped immediately in this case.
Pharmacodynamic properties	The dipeptide N(2)-L-alanyl-L-glutamine is endogenously split into the amino acids glutamine and alanine hereby supplying glutamine with infusion solutions for parenteral nutrition. The released amino acids flow as nutrients into their respective body pools and are metabolised according to the needs of the organism. Many disease conditions, in which parenteral nutrition is indicated, are accompanied by a glutamine depletion, which glutamine containing infusion regimens counteract.
Pharmacokinetic properties	N(2)-L-alanyl-L-glutamine is rapidly split into alanine and glutamine after infusion. In man, half-lives of between 2.4 and 3.8 min (in terminal renal insufficiency 4.2 min) and a plasma clearance of between 1.6 and 2.7 l/min were determined. The disappearance of the dipeptide was accompanied by an equimolar increase of the corresponding free amino acids. Hydrolysis probably takes place exclusively in the extracellular space. Renal elimination of N(2)-L-alanyl-L-glutamine under constant infusion is below 5% and thus the same as that of infused amino acids.
Preclinical safety data	Acute and subchronic toxicity: A matrix of dosage finding tests were conducted on rats and

dogs over 1 to 7 days. In the rats, infusion of 50 ml/kg b.w. of a 10%, 15%, 20% and 30% solution of N(2)-L-alanyl-L-glutamine over 4 h/day led to tonic spasms, increased respiratory rate and exitus. Infusion of 50 ml/kg b.w. of a 10% solution (5 g N(2)-L-alanyl-L-glutamine/kg b.w.) resulted in necrotic areas at the infusion site, reduced body weight and yellowing of the kidneys in the rats (6 h/day), and a temporary increase in heart rate in the dog (8 h/day).

Investigations were carried out in dogs (8 h/day) and in rats (6 h/day) with 0.5 and 1.5 g N(2)-L-alanyl-L-glutamine/kg b.w. per day i.v. over 13 weeks and with 4.5 g N(2)-L-alanyl-L-glutamine/kg b.w. per day i.v. over 6 weeks.

In the dogs, vomitting occured. With the high dose tonic or tonic-clonic cramps, increased salivation, ataxia, sedation, and lateral position were observed.

Mutagenic and tumorigenic potential: In vitro and in vivo test gave no indications of mutagenic potential.

Studies investigating the tumorigenic potential were not carried out. Carcinogenic effects are not to be expected.

Reproduction toxicity: In animal trials, no indications of teratogenic or other embryotoxic and peripostnatal injuries could be observed up to a dosage of 1.6 g N(2)-L-alanyl-L-glutamine/kg b.w. per day.

Local tolerance: Following repeated i.v. infusion of N(2)-L-alanyl-L-glutamine (5 and 10% solution) over 13 weeks, intolerance reactions occurred at the infusion sites (swellings, discolourations, necroses) in the rats and dogs from 0.5 g/kg b.w. onwards. Histopathologically, substance-induced inflammatory reactions with mild to fully developed dermatitis purulenta

necroticans and osteomalacia of the tail vertebrae, thrombophlebitis and periphlebitis, were observed in the rats. In the dog, perivascular inflammatory reactions and, occasionally, vessel blockage were observed.

The tests conducted on the dog on local tolerance after a single, intraarterial, paravenous and intramuscular administration gave no indications of unusual intolerance reactions with incorrect administration.

List of excipients

Water for injection.

Incompatibilities (major)

When mixed with a carrier solution, it is imperative to ensure injection, under hygienic conditions, thorough mixing and compatibility.

Further drugs should not be added to the mixture.

Dipeptiven® is not to be stored after addition of other components.

Shelf-life

36 months in original package.

To be used immediately after the bottle is opened.

Special precautions for storage

Store at room temperature (15 – 25 °C).

Nature and contents of containers

50 ml glass bottle
100 ml glass bottle
250 ml glass bottle

Instruction for use and handling

Dipeptiven® is an infusion solution concentrate which is not designed for direct administration. The addition of the concentrate to the amino acid solution prior to application should take place under aseptic conditions ensuring that the

concentrate is well dispensed. Unused solution should be disposed of.

Dipeptiven® is infused with the carrier solution. One volume part Dipeptiven® is to be mixed with at least 5 volume parts carrier solution (e. g. 100 ml Dipeptiven® + at least 500 ml amino acid solution).

3.5% of N(2)-L-alanyl-L-glutamine should be the maximum concentration during therapy.

Marketing authorization holder

Fresenius Kabi Deutschland GmbH
D-61346 Bad Homburg v. d. H.
Germany

Manufactured by
Fresenius Kabi Austria GmbH
A-8055 Graz, Austria

Date of revision

June 2000