Package Insert M0xxxxx/xx
Dipeptiven®

Size	315 x 148 mm
Code	4115
EAN-Code:	-

Colours
● Black

1. Korrektur: 30.05.2008 | 10:28 uhr
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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-alanine-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.

Shelf-life
24 months.
To be used immediately after the bottle is opened.
Dipeptiven® is not to be stored after addition of other components.

Special precautions for storage
Do not store above 25°C.
Store in the original package.

Nature and content of container
50 ml glass bottle
100 ml glass bottle
250 ml glass bottle

Fresenius Kabi

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Instructions for use and handling
Dipeptiven® is an infusion solution concentrate which is not designed for direct administration.
The container and the solution should be inspected visually prior to use. Use only clear, particle-free solution and undamaged container. For single use only.
The addition of the concentrate to the amino acid carrier solution prior to application should take place under aseptic conditions ensuring that the concentrate is well dispensed. Thorough mixing and compatibility must be ensured. 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 authorisation holder
Fresenius Kabi Deutschland GmbH
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Germany

Manufactured by
Fresenius Kabi Austria GmbH
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Date of revision
April 2006

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M0xxxxx/xx

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 for injections

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

Pharmaceutical form
Concentrate for solution for infusion

Therapeutical indication
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.
Adults
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 amino acid supplied through Dipeptiven should not exceed approx. 30% of the total amino acid supply.
Daily dose
1.5 - 2.5 ml of Dipeptiven per kg body weight (equivalent to 0.3 - 0.5 g N(2)-L-alanyl-L-glutamine per kg body weight). This equates to 100 to 175 ml Dipeptiven for a patient of 70 kg body weight.

Maximum daily dose: 2.5 ml equivalent to 0.5 g N(2)-L-alanyl-L-glutamine of Dipeptiven® per kg body weight.
The maximum daily dose of 0.5 g N(2)-L-alanyl-L-glutamine per kg body weight should be administered in combination with a compatible amino acid solution providing at least 1.0 g amino acids per kg body weight and day. This results in a daily dosage of at least 1.5 g amino acids per kg body weight.
The following adjustments are examples for the supply with Dipeptiven and other amino acids through the carrier solution:
Amino acid requirement 1.2 g/kg body weight per day: 0.8 g amino acids + 0.4 g N(2)-L-alanyl-L-glutamine per kg body weight.
Amino acid requirement 1.5 g/kg body weight per day: 1.0 g Amino acids + 0.5 g N(2)-L-alanyl-L-glutamine per kg body weight.
Amino acid requirement 2 g/kg body weight per day: 1.5 g amino acids + 0.5 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.

Children
Safety and efficacy in children have not been established.

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 the active substances or to any of the excipients.

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 phospatase, 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 general 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 medicinal products 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 machines
Not applicable

Undesirable effects
None known when correctly administered.

Overdose
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 4h/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 (8h/day) and in rats (6h/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, vomiting occurred. 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.