SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Dipeptiven
concentrate for solution for infusion

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

1 ml contains:

Active substance	**Quantity**
N(2)-L-alanyl-L-glutamine	200 mg (= 82.0 mg L-alanine, 134.6 mg L-glutamine)

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

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Concentrate for solution for infusion. A clear colourless solution.

4. CLINICAL PARTICULARS

4.1 Therapeutic 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.
In patients in extreme cases of hypercatabolic stage such as major abdominal surgery, BMT, diffuse injury of GI mucous.

4.2 Posology and method of administration

Solution for infusion after mixture with 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 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.

Dipeptiven is an infusion solution concentrate which is not designed for direct administration.

Patients with total parenteral nutrition
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 should be mixed with a compatible amino acid carrier solution or an amino acid containing infusion regimen prior to administration.

Duration of administration
The duration of use should not exceed 3 weeks.

Paediatric population
Safety and efficacy in children have not been established.

4.3 Contraindications

Dipeptiven should not be administered to patients with severe renal insufficiency (creatinine clearance < 25 ml/minute), severe hepatic insufficiency, circulatory shock, hypoxia, multiple organ failure, severe metabolic acidosis or known hypersensitivity to the active substances or to any of the excipients listed in section 6.1.

4.4 Special warnings and precautions for use

For a safe administration the maximum dose of Dipeptiven should not exceed 2.0 ml (corresponding to 0.4 g N(2)-L-alanyl-L-glutamine) per kg body weight per day (see section 4.2, 4.9 and 5.1).

Dipeptiven should only be used as part of clinical nutrition, and its dosage is limited by the amount of protein/amino acids provided by nutrition (see section 4.2). Whenever the clinical condition does not allow nutrition (e.g., circulatory shock, hypoxia, unstable critically ill patients, severe metabolic acidosis) Dipeptiven should not be administered.

Oral/enteral intake of glutamine-supplemented formulas in combination with parenteral nutrition should be taken into consideration for calculation of the prescribed dose of Dipeptiven.

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, creatinine clearance, urea, as well as liver function tests (alkaline phospatase, ALT, AST), and 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 generally 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.

4.5 Interaction with other medicinal products and other forms of interaction

No interactions are known to date.

4.6 Fertility, pregnancy and lactation

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

4.7 Effects on ability to drive and use machines

Not applicable

4.8 Undesirable effects

None known when correctly administered.

Reporting suspected adverse reactions after authorization of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Any suspected adverse reactions should be reported to the Ministry of Health according to the National Regulation by using an online form https://sideeffects.health.gov.il/ and emailed to the Registration Holder's Patient Safety Unit at: drugsafety@neopharmgroup.com

4.9 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.

Experience from a study in critically ill patients with at least two organ failures at admission, receiving the maximum approved daily intravenous infusion of Dipeptiven (0.5 g alanyl-glutamine/kg/day) together with a high dose of enteral glutamine (30 g) provided as a mixture of alanyl-glutamine and glycyl-glutamine and without appropriate clinical nutrition, has shown an increase in serious side effects.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Amino acids – concentrate for solution for parenteral nutrition, ATC code: B05X B02

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.

A large multicenter study in critically ill patients with at least two organ failures at admission has shown a trend towards higher mortality in patients who received a very high total dose of glutamine-dipeptides (see section 4.9). This may exceed the patient's ability to metabolize glutamine (see also section 4.4).

5.2 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.

5.3 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 body weight 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 body weight of a 10% solution (5 g N(2)-L-alanyl-L-glutamine/kg body weight) 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 body weight per day i.v. over 13 weeks and with 4.5 g N(2)-L-alanyl-L-glutamine/kg body weight 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* tests 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 body weight 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 body weight 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, intra-arterial, paravenous and intramuscular administration gave no indications of unusual intolerance reactions with incorrect administration.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

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

The expiry date of the product is indicated on the packaging materials

To be used immediately after the bottle is opened.

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

6.4 Special precautions for storage

Do not store above 25C.

Store in the original package.

6.5 Nature and content of container

Glass bottles

1 x 50 ml, 10 x 50 ml

1 x 100 ml, 10 x 100 ml

Type II, colourless glass.

Rubber closure.

Not all pack sizes may be marketed

6.6 Special precautions for disposal and other 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 containers. For single use only.
The addition of the concentrate to the 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. For details see section 4.2.

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.

Manufacturer: Fresenius Kabi Austria GmbH, Graz, Austria

Licence number : 136-14-31269

Registration Holder: Cure Medical & Technical Supply, P.O.B 3340, Petach-Tikva.

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