GREENOR 20%
w/v SOLUTION
FOR INFUSION
50ml vial

DATA SHEET

NAME OF BRAND
GREENOR (N(2)-l-alanyl-l-glutamine 200 mg/mL) Concentrate for Solution for Infusion

PRESENTATION
GREENOR is a clear, colourless concentrate for solution for infusion.

Content
50 mL contains:
10 g N(2)-L-alanyl-L-glutamine (= 4.10 g L-alanine, 6.73 g L-glutamine) Water for Injections

Theoretical osmolarity	921 mosmol/L
Titration acidity	90 – 105 mmol NaOH/L
pH value	5.4 - 6.0

USES
Actions
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.

Pharmacokinetics
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 (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-glutamine under constant infusion is below 5 % and thus the same as that of infused amino acids.

INDICATIONS
GREENOR is indicated as part of a clinical nutrition regimen in patients in hypercatabolic and/or hypermetabolic states. It should be given together with parenteral or enteral nutrition or a combination of both.

DOSAGE AND 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

GREENOR is administered parallel with parenteral nutrition or enteral nutrition or a combination of both. Dosage depends on the severity of the catabolic state and on amino acids/protein requirement.

A maximum daily dosage of 2 g amino acids/or protein per kg bodyweight should not be exceeded in parenteral/enteral nutrition. The supply of alanine and glutamine via GREENOR should be taken into consideration in the calculation. The proportion of the amino acids supplied through GREENOR should not exceed approx. 30% of the total amino acids/protein supply.

Daily dose
1.5 - 2.5 mL of GREENOR 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 GREENOR 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 GREENOR 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 at least 1.0 g amino acids/protein per kg body weight per day. With amino acids from GREENOR included, this results in a daily dosage of at least 1.5 g amino acids/protein per kg body weight.

The following adjustments are examples for the supply with GREENOR and amino acids through the parenteral nutrition solution, and/or protein through enteral nutrition formula:

Amino acids/protein requirement 1.2 g/kg body weight per day:
0.8 g amino acids/protein + 0.4 g N(2)-L-glutamine per kg body weight

Amino acids/protein requirement 1.5 g/kg body weight per day:
1.0 g amino acids/protein + 0.5 g N(2)-L-alanyl-L-glutamine per kg body weight

Amino acids/protein requirement 2 g/kg body weight per day:
1.5 g amino acids/protein + 0.5 g N(2)-L-alanyl-L-glutamine per kg body weight.

GREENOR 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.
GREENOR should be mixed with a compatible amino acid carrier solution or an amino acid containing infusion regimen prior to administration.

Patients with total enteral nutrition
GREENOR is continuously infused over 20-24 hours per day. For peripheral venous infusion, dilute Dipeptiven to an osmolarity ≤ 800 mosmol/L (e.g. 50 mL Dipeptiven +50 ml saline).

Patients with combined enteral and parenteral nutrition
The full daily dosage of GREENOR should be administered with the parenteral nutrition, i.e. mixed with a compatible amino acid solution or an amino acid contained in infusion regimen prior to administration.

The rate of infusion depends on that of the carrier solution and should be adjusted according to the proportions or parenteral and enteral nutrition.

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

Children
Safety and efficacy in children have not been established.

CONTRAINDICATIONS
GREENOR should not be administered to patients with severe renal insufficiency (creatinine clearance < 25 mL/min), severe hepatic insufficiency, severe metabolic acidosis or known hypersensitivity to the active substances or to any of the excipients.

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

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 mosm/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 GREENOR for longer periods than nine days is limited.

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.

GREENOR is presumed to be safe or unlikely to produce an effect on the ability to drive or use machinery

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

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.

ADVERSE REACTIONS
None known when correctly administered.

INTERACTIONS
No interactions are known to date.

OVERDOSAGE
As with other infusion solutions, chills, nausea and vomiting can occur, when the infusion rate of GREENOR is exceeded. Infusion shall be stopped immediately in this case.

PHARMACEUTICAL PRECAUTIONS
Instructions for use

GREENOR 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 carrier solution prior to application should take place under aseptic conditions. Thorough mixing and compatibility must be ensured. Unused solution should be disposed of.

GREENOR is infused with the carrier solution. For details see *Dosage and Administration* section.

STORAGE
Store below 25°C.
Shelf life: 24 months
Do not use after the expiry date stated on the label.
Any remaining solution from the opened container must be discarded.

MEDICINES CLASSIFICATION
General Sale Medicine

PACKAGE QUANTITIES
Glass bottles of 50mL (available), 100mL(NA) and 250 mL (NA).

FURTHER INFORMATION
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-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 (8h/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 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.

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, necrosis) 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, intraarterial, paravenous and intramuscular administration gave no indications of unusual intolerance reactions with incorrect administration.