SYNOPSIS

Name of Sponsor/Company: Fresenius Kabi	Individual Study Table Referring to Part of the Dossier	(For National Authority use only)
Name of Finished Product: Dipeptiven®	Volume:	
Name of Active Ingredient: Glutamine Dipeptide	Page:	
Title of Study: Efficacy and Safety of Glutamine Dipeptide (Dipeptiven®) - Supplemented Parenteral Nutrition in Critically Ill Patients : a Randomized, Multicenter study		
clinical study centre:	Hospital Universitari de Girona Dr. Josep Trueta Av Francia s/n. 17007 Girona, Spain Hospital Severo Ochoa Avda. de Orellana s/n. 28911 - Leganés (Madrid), Spain	

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Publication (reference):	Grau et al. Crit Care Med 2011;39:1263-8.
Studied period:	08/JUN/2005 first patient enrolled to 25/MAY/2007 last patient completed
Phase of development:	Phase IV
Objectives:	To assess the clinical efficacy and safety of Dipeptiven® (L-alanyl-L-glutamine 20%)-supplemented TPN in critically ill patients with an elevated Acute Physiology and Chronic Health Evaluation II (APACHE) II score (greater than 12), with either the presence of a contraindication to enteral nutrition or a proven intolerance of enteral feeding over 48h, and requiring a 5 to 9 day of total parental nutrition (TPN).
Methodology:	Prospective, controlled, randomized, double-blind and multicenter clinical study
Number of patients (planned and analysed):	146 (2 x 73) patients planned; 144 patients enrolled; 12 met exclusion criteria; 5 post-randomization loses; 127 analysed for safety (ITT) and 127 and 117 (ITT & PP) analysed for efficacy (PP).
Diagnosis and main criteria for inclusion:	Critically ill patients with an elevated APACHE II score (greater than 12), with either the presence of a contraindication to enteral nutrition or a proven intolerance of enteral feeding over 48h, and requiring a 5 to 9 day TPN
Test product, dose and mode of administration, batch number:	TPN with Ala-Gln (Dipeptiven®, test infusion) at dose of 0.5 g kg^{-1} d^{-1} plus 1.0 g kg^{-1} d^{-1} of standard aminoacid admixture (Vamin 18®).
Duration of treatment:	9 days
Reference therapy, dose and mode of administration, batch number:	TPN with a standard aminoacid admixture (Vamin 18®).

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Criteria for evaluation: <u>Efficacy:</u>	- The primary endpoint of the study was a complicated clinical outcome, defined by the occurrence of nosocomial infections. - Secondary endpoints included Sequential Organ Failure Assessment (SOFA) score, length of stay and mortality at the Intensive Care Unit (ICU), length of stay in hospital, 6-month mortality, hyperglycemia or insulin resistance.	
<u>Safety:</u>	- Laboratory variables (haematology and chemical chemistry); vital signs data (body temperature, blood pressure, heart rate and respirations); physical examination (height, weight and body mass index); caloric and nitrogen intake. - Assessment of Adverse Events.	
Statistical methods:	- A per protocol (PP) and an intention to treat (ITT) analyses was performed; efficacy variables were analysed for the ITT and PP populations; safety variables were analysed for the ITT population - Statistical analyses were performed for all available data; no imputation techniques for missing data were carried out. - Comparisons between treatment groups were carried out using a t-test or a non-parametric Wilcoxon rank sum test (if applicable) for continuous variables, whilst a Chi-square test or a Fisher exact test (if applicable, for small and/or skewed samples) were carried out to compare categorical variables between treatment groups. $P<0.05$ was considered significant.	

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SUMMARY – CONCLUSIONS:

EFFICACY RESULTS:	The incidence of nosocomial infections was similar in both groups of patients. Thus, no differences were found in the incidence of nosocomial pneumonia (x 1000 ventilator days), primary bacteraemia (x 1000 days at intensive care unit), catheter-related sepsis (x 1000 catheter days), urinary tract infections (x 1000 urinary catheter days) and surgical infections between patients receiving ALA-GLN TPN and the control group. While in the control group 7 urinary tract infections were reported, only one urinary tract infection was reported among patients receiving ALA-GLN TPN. However, there were no significant differences in the incidence of urinary tract infections between the two study groups. Similar results were found in the PP population. SOFA score for each ay were similar in both groups. ICU length of stay or hospital stay was similar in both groups and ICU and hospital mortality did not achieve significant differences. Six-month mortality was also similar in both groups. The best model for glycaemia levels along time was an autoregressive moving average model (3, 2) with a root mean-square error of 12.97. The effect of insulin dose on plasmatic glycaemia was best measured by a time series model with autocorrelation with the dose of insulin received three hours before.
SAFETY RESULTS:	In general, Dipeptiven® (L-alanyl-L-glutamine 20%) was well tolerated in this study. Overall, treatment-emergent AEs were experienced by comparable numbers of patients in each of the two

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	treatment groups. Both groups were similar with respect to the numbers of patients who had SAEs. No SAEs were considered related to study drug. There were no clinically differences between the treatment groups for any laboratory and vital signs parameter.	
Date of the report:	07/FEB/2012	