Australian Government
Department of Health
Therapeutic Goods Administration

Australian Public Assessment Report for Alanylglutamine

Proprietary Product Name: Dipeptiven

Sponsor: Fresenius Kabi Australia Pty Ltd

December 2020

TGA Health Safety Regulation

About the Therapeutic Goods Administration (TGA)

- The Therapeutic Goods Administration (TGA) is part of the Australian Government Department of Health and is responsible for regulating medicines and medical devices.
- The TGA administers the *Therapeutic Goods Act 1989* (the Act), applying a risk management approach designed to ensure therapeutic goods supplied in Australia meet acceptable standards of quality, safety and efficacy (performance) when necessary.
- The work of the TGA is based on applying scientific and clinical expertise to decision-making, to ensure that the benefits to consumers outweigh any risks associated with the use of medicines and medical devices.
- The TGA relies on the public, healthcare professionals and industry to report problems with medicines or medical devices. TGA investigates reports received by it to determine any necessary regulatory action.
- To report a problem with a medicine or medical device, please see the information on the TGA website <https://www.tga.gov.au>.

About AusPARs

- An Australian Public Assessment Report (AusPAR) provides information about the evaluation of a prescription medicine and the considerations that led the TGA to approve or not approve a prescription medicine submission.
- AusPARs are prepared and published by the TGA.
- An AusPAR is prepared for submissions that relate to new chemical entities, generic medicines, major variations and extensions of indications.
- An AusPAR is a static document; it provides information that relates to a submission at a particular point in time.
- A new AusPAR will be developed to reflect changes to indications and/or major variations to a prescription medicine subject to evaluation by the TGA.

Contents

Common abbreviations

Abbreviation	Meaning
ACM	Advisory Committee on Medicines
Ala-Gln	Alanylglutamine
APACHE	Acute Physiology And Chronic Health Evaluation
ASPEN	American Society for Parenteral and Enteral Nutrition
AusPAR	Australian Public Assessment Report
BCM	Body cell mass
BMI	Body mass index
C_{max}	Maximum plasma concentration
Cys-LT	Cysteinyl-leukotrienes
ECM	Extracellular mass
ESPEN	European Society for Clinical Nutrition and Metabolism
EU	European Union
UK	United Kingdom
USA	United States of America
GI	Gastrointestinal
GLN	Glutamine
ICU	Intensive care unit
ISS	Injury severity score
ITT	Intent to treat
IV	Intravenous
LLOQ	Lower limit of quantitation
LOS	Length of stay
MOF	Multi organ failure
PD	Pharmacodynamic(s)
PK	Pharmacokinetic(s)

Abbreviation	Meaning
PN	Parenteral nutrition
PP	Per protocol
SAPS	Simplified acute physiology score
SOFA	Sequential organ failure assessment
TGA	Therapeutic Goods Administration
TISS	Therapeutic intervention scoring system
TPN	Total parenteral nutrition

I. Introduction to product submission

Submission details

Type of submission:	New chemical entity
Product name:	Dipeptiven
Active ingredient:	Alanylglutamine
Decision:	Withdrawn
Date of withdrawal:	16 January 2020
Date of entry onto ARTG:	Not applicable
ARTG number:	Not applicable
▼ *Black Triangle Scheme:*[1]	Not applicable
Sponsor's name and address:	Fresenius Kabi Australia Pty Ltd Level 2, 2 Woodland Way, Mount Kuring-gai, NSW 2080
Dose form:	Concentrated solution
Strengths:	200 mg/mL at 50 mL and 100 mL
Container:	Vial
Pack size:	10 bottles per strength
Approved therapeutic use:	Not applicable
Route of administration:	Intravenous infusion
Proposed dosage:	0.3 to 0.5 g alanylglutamine/kg body weight
Pregnancy category:	Not applicable

[1] The **Black Triangle Scheme** provides a simple means for practitioners and patients to identify certain types of new prescription medicines, including those being used in new ways and to encourage the reporting of adverse events associated with their use. The Black Triangle does not denote that there are known safety problems, just that the TGA is encouraging adverse event reporting to help us build up the full picture of a medicine's safety profile.

Product background

This AusPAR describes the application by Fresenius Kabi Australia Pty Ltd (the sponsor) to register Dipeptiven (alanylglutamine) 200 mg/mL concentrated solution for intravenous (IV) infusion for the following proposed indication:

> *Dipeptiven is indicated as part of a clinical nutrition regimen in patients in hypercatabolic and/or hypermetabolic states. It should be given together with parenteral nutrition.*

Glutamine (GLN) is the most abundant nonessential free amino acid and is necessary to modulate the inflammatory and oxidative stress responses in patients; hence, glutamine is now commonly described as a conditionally essential amino acid, particularly in catabolic and stress states.

Systemic glutamine availability is determined by the balance of endogenous glutamine production, mainly in muscular tissue and its use by glutamine consuming organs (gut, kidney, liver and the immune system). Several studies show that in catabolic intensive care unit (ICU) patients, the endogenous production of muscular glutamine is increased to compensate for the reduction in the plasma levels of glutamine, indicating elevated glutamine needs. In addition, in catabolic states, large amounts of glutamine are released from muscle tissue as part of the body's conserved evolutionary response to stress. Recent data has revealed that following illness and injury, glutamine plays a vital role in inducing cellular protection pathways, modulation of the inflammatory response, and prevention of organ injury. These findings are the rationale for the use of glutamine supplementation in the ICU population in order to replenish the muscle pool of glutamine, attenuate the efflux of this amino acid, and provide exogenous glutamine required to meet the elevated organ needs for improvement in protein synthesis, modulation of the immune system, reduction of oxidative stress, and preservation of the gut barrier.

Regulatory status

This product is considered to be a new chemical entity for Australian regulatory purposes.

Dipeptiven was first approved in 1995 in the European Union (EU) through the mutual recognition pathway. At the time the submission was under consideration, Dipeptiven is approved in 74 countries, 29 of which are in EU, and the rest in Asia. The product was registered in the United Kingdom (UK) in 2003 and the New Zealand in 2007.

This product has not been registered in United States of America (USA) and Canada.

II. Registration timeline

The following table captures the key steps and dates for this application and which are detailed and discussed in this AusPAR.

Table 1: Timeline for Submission PM-2018-04790-1-1

Description	Date
Submission dossier accepted and first round evaluation commenced	31 January 2019
First round evaluation completed	8 August 2019
Sponsor provides responses on questions raised in first round evaluation	15 November 2019
Second round evaluation completed	15 November 2019
Delegate's Overall benefit-risk assessment and request for Advisory Committee advice	7 November 2019
Sponsor's pre-Advisory Committee response	21 November 2019
Advisory Committee meeting	6 December 2019
Withdrawal	16 January 2020
Completion of administrative activities and registration on the ARTG	Not applicable
Number of working days from submission dossier acceptance to registration decision*	Not applicable

*Statutory timeframe for standard applications is 255 working days

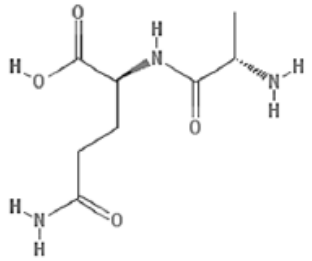
III. Submission overview and risk/benefit assessment

The submission was summarised in the following Delegate's overview and recommendations.

Quality

Analylglutamine is a dipeptide of the amino acids alanine and glutamine. The chemical structure of alanylglutamine is shown in Figure 1.

Figure 1: Chemical structure of alanylglutamine



The proposed product (Dipeptiven) is formulated as a sterile, clear and colourless concentrated solution for injection containing alanylglutamine in water for injection 200 mg/mL in two strengths, 50 mL and 100 mL.

The proposed products are supplied in pack sizes of 10 bottles for each strength. Both presentations are for single use only.

All outstanding quality issues have been addressed. There are no objections to the registration of the proposed product from a pharmaceutical chemistry perspective.

Nonclinical

The non-clinical evaluator has recommended approval.

The evaluator summarised findings as below:

- findings from nonclinical pharmacology and toxicology studies with Dipeptiven show that it is well tolerated, nutritive, and that both alanylglutamine and glycyl-tyrosine were highly bioavailable, with greater than 99% retention
- no major safety concerns based on findings from safety pharmacology studies
- no secondary pharmacodynamics (PD) studies were included in this submission
- Dipeptiven was rapidly hydrolysed to free amino acids in plasma, no pharmacokinetics (PK) interactions with alanylglutamine were anticipated.

Clinical

The clinical dossier contains five clinical pharmacology studies and eleven studies of efficacy and/or safety, categorised as follows (see Table 2). These studies were all sponsor initiated studies.

Table 2: Summary of clinical studies for Dipeptiven

Study identifier	Pharmacology	Efficacy	Safety
Studies in healthy volunteers			
94-0742-001	X[a]	–	X
94-0742-002	X[a]	–	X
AS-DP-03-DE	X[b]	–	X
93-DP-001	X[b]	–	X
Studies in adult patients			
AS-DP-01-DE	–	X	X
AS-DP-02-DE	–	X	X
AS-DP-04-DE	–	X	X
AS-AG-01-NL	–	X	X
AS-AG-02-DE	–	X	X
AS-AG-03-DE	–	X	X
AS-AG-04-DE	–	X	X
95 TPN GLN 01	–	X	X
04 TPN GLN 01	–	X	X
99-ALGL-001	–	–	X
00-ALGL-002	X[a]	–	X
FKInd200101	–	–	X

a. Study evaluated pharmacokinetic properties of Ala-Gln
b. Study evaluated pharmacokinetic and pharmacodynamic properties of Ala-Gln

Pharmacokinetics

The following is a summary taken from the clinical evaluator report:

- Alanylglutamine is rapidly hydrolysed into alanine and glutamine after infusion.
- The plasma alanine and glutamine concentrations reach steady state at 1 to 3 hours after start of infusion at a rate of 0.3 mg/kg/day.
- The concentration of alanine and glutamine at steady state ranged from 545 µmol/L to 873 µmol/L for alanine and 897 µmol/L to 1324 µmol/L for glutamine. A wide interval for steady state concentration of alanylglutamine was noted, that ranged from 33 µmol/L up to 772 µmol/L.
- The elimination half-life was between 2.4 and 3.8 minutes in healthy subjects, compared to 4.2 minutes in patients with terminal renal insufficiency.
- Dose proportionality with various infusion rates was demonstrated in a single study.
- Following glutamine infusion, there were rises in systemic levels of glutamic acid and serine.
- When patients admitted in ICU were treated with a 4 hour peripheral vein infusion of alanylglutamine 20% 2.5 mL/kg body weight (0.5 g/kg body weight), steady state was achieved soon after commencement of infusion. Median maximum plasma

concentration observed (C_{max}) was 652 µmol/L. Median half-life was 0.26 hours, rapid elimination followed cessation of infusion.

- Data from Study 94-0742-001 suggests that the infusion of Dipeptiven at a dose of 0.7 mg/kg/day may exceed the capacity for metabolising and to maintain the steady state. This might result in accumulation of Dipeptiven.

Pharmacodynamics

The Delegate commented that the lack of dose finding studies could be attributed to the time of initial registration in 1995. Due to the long history of use of this product, this issue was not considered as critical.

- Primary PD effect of alanylglutamine was to maintain systemic level of glutamine.
- No major differences were noted with studies that examined pituitary and neurological functions as secondary PD outcome measures.
- Dosage selection for pivotal studies:
  - no formal dose finding studies were included in this submission.
  - The efficacy studies used doses ranging from 0.3 to 0.5 g/kg/day.

Efficacy

Study AS-DP-01-DE

Study design: A Phase III randomised control trial (RCT), single centre, open label study.

Study period: July 1989 to December 1990.

Study location: Study centre was located in Germany.

No specific inclusion criteria were stated other than all adult patients undergoing elective gastrointestinal (GI) surgery and requiring parenteral nutrition (PN) for at least 5 days were entered into the study. 15 patients each were included in the test and control groups.

Parenteral feeding regimen was as follows, only electrolyte solutions were given on the day of surgery. From 1 to 5 post-operative days, patients received total parenteral nutrition (TPN). Amino acid dose was 1.5 g/kg/day. Treatment group received 10% dipeptide alanylglutamine solution. Infusions were administered at a constant rate over 24 hours via a central venous catheter.

Efficacy variables: urea production rate, nitrogen balance and measurement of amino acids in plasma, including alanylglutamine. No clinical outcomes were specified as efficacy variables.

Trial duration: 5 days.

Mean age of patients were around 59 and 66 years in treatment and control groups respectively. The nature and severity of surgeries were comparable across treatment groups. Serum glutamine level was not estimated at Baseline.

Results

No meaningful difference in urea production rate between treatment arms. The urea production rate varied between 450 to 550 mg urea/kg bodyweight/24 hours over the five days of the study. A relatively positive nitrogen balance was reported for the dipeptide alanylglutamine group. However, there was no significant difference between groups.

Table 3: Study AS-DP-01-DE Comparison of urea production rate

	T1	T2	T3	T4	T5
Test group	435 ± 103	486 ± 194	445 ± 86	514 ± 190	500 ± 126
Control group	456 ± 121	506 ± 130	544 ± 118	549 ± 131	510 ±140

T1 to T5 = Days 1 to 5 of the study; urea production rate given in mg/kg bodyweight/24 hours.

Table 4: Study AS-DP-01-DE Comparison of nitrogen balance

	T1	T2	T3	T4	T5
Test group	18 ± 45	10 ± 47	7 ± 46	-1 ± 57	-16 ± 58
Control group	16 ± 52	-4 ± 53	-13 ±46	-32 ± 54	-23 ± 53

T1 to T5 = Days 1 to 5 of the study; nitrogen balance given for individual days (24 hour periods) in mg/kg bodyweight/24 hours.

In spite of administration of dipeptide alanylglutamine infusion to treatment group, there was a rise in plasma glutamine levels for patients in both treatment groups. Also, there was no significant difference between treatment and control groups in the level of glutamine eliminated in urine.

No significant difference in other biochemical parameters were reported. Post-operative recovery was also comparable across groups.

Study AS-DP-02-DE

Study design: A prospective, open label, single centre RCT. The evaluator highlights that no clear method of randomisation was evident from the study report.

Single inclusion criteria was to be a patient in ICU and indicated for TPN for at least 9 days.

The study cohort was heterogeneous, the more common diagnoses including situations following acute cardiological or cerebral events, chest infections with additional complications, other infections and poisoning.

Trial duration: 9 days.

10% dipeptide alanylglutamine solution was given to the treatment group. Daily dosage of amino acid was the same as pervious study (1.5 g/kg/day).

Efficacy outcome measures were the same as previous study (Study AS-DP-01-DE), with no clinical outcomes specified. In addition, effect of glutamine supplementation on absorptive capacity of small intestine was assessed by a D-xylose absorption test;[2] that was done on Day 0 and Day 8 on a subgroup of 6 patients in each of the study groups.

Results

Urea production rate, which was measured from the total amount of urea excreted in 24 hour urine was not significantly different between groups.

[2] The D-xylose absorption test measures the level of D-xylose, a type of sugar, in a blood or urine sample.

Nitrogen balance was calculated from total nitrogen in urine and the nitrogen intake via infused amino acids. It was also corrected by the nitrogen retained as serum urea. No significant difference was observed in cumulative nitrogen balance between groups at Day 9 of study.

Plasma level of glutamine was significantly high in treatment group. Plasma amino acid levels were comparable between groups.

Study AS-DP-04-DE

Study design: A single centre, open label, Phase III, prospective RCT.

Inclusion criteria: Patients with multiple trauma and indicated for TPN for at least 7 days.

The treatment group received 10% dipeptide alanylglutamine solution via central venous catheter. The amino acid dose was 1.5 g/kg/day.

Results

No significant differences were reported for efficacy outcomes such as urea production and nitrogen balance between treatment groups.

The evaluator has highlighted the fact that the heterogeneity in the critical conditions that were treated in these studies and the various interventions that might have an effect on the efficacy outcomes made it difficult to make any conclusions regarding the efficacy of the dipeptide alanylglutamine.

The Delegate comments that these studies used 10% dipeptide alanylglutamine solution, which is different from the proposed product for marketing, which is 20% dipeptide alanylglutamine.

Study AS-AG-01-NL

Study design: A double blind, single centre, RCT.

Study duration: 10 days.

Study period: 1990 to 1992.

Inclusion criteria: Patients with various haematological malignancies indicated for TPN in an intensive care unit for at least 10 days.

15 patients were included in each arm of study. In total, twenty treatment cycles were studied across treatment groups.

Results

The evaluator has highlighted the difference in amino acid dosing in this study. The experimental (alanylglutamine) study group received 40 g of alanylglutamine in each 24 hour solution pack. The total amino acid dose was still kept the same at 1.5 g/kg/24 hour as in other studies. Overall, the majority of patients still would have received the alanylglutamine dose of 0.3 to 0.5 g/kg/day. The control group received alanylglutamine-free amino acid solution (Vamin).

Hospital length of stay was the primary efficacy variable. It was longer in the alanylglutamine group. It was attributed to two patients in that group who developed treatment related complications, which were not related to alanylglutamine.

No major differences across treatment groups were reported regarding other efficacy endpoints such as mortality, haematology results, infection rate and toxicity scores.

Study AS-AG-02-DE

Study design: A single centre RCT.

Study period: 1993 to 1995.

Treatment duration: 5 days.

Study duration: 8 days.

This study was aimed to demonstrate the role of glutamine in regaining immune competence in post-operative cases. This was measured by estimating the levels of cysteinyl-leukotrienes (Cys-LT) that reflected leukocyte function.

The single inclusion criterion was to be an adult patient with a diagnosis of rectal or colonic carcinoma planned for surgery and for TPN for 5 days post-operatively.

The treatment group received alanylglutamine at a dose of 0.3 mg/kg/24 hours and control group received Aminosteril 10% solution (without alanylglutamine).

5 patients were enrolled into each treatment groups. Blood samples for analysis were taken on the day before surgery, first day of TPN and the day after the TPN finished.

Results

Leukocyte function: There was a reduction in Cys-LT level post-surgery. On Day 5 of treatment, there was a significant difference in Cys-LT level between treatment groups. The Cys-LT level remained low in control group, meanwhile it normalised in treatment group.

No significant difference was found in measures of nitrogen balance and amino acid levels between treatment groups. Plasma level of alanylglutamine was below lower limit of quantitation (LLOQ) of 3 nmol/L.

The Delegate commented that the low number of participants in this study limits the ability to make any conclusions.

Study AS-AG-03-DE

Study design: A single centre, RCT.

Study period: 1993 to 1995.

The study design was similar to Study AS-AG-02-DE. The treatment group received standard amino acid solution with added 20% alanylglutamine, while the control group received the standard amino acid solution.

The primary efficacy variable was peripheral venous endotoxin levels. The aim was to assess the possible systemic effect of glutamine on intestinal bacterial translocation.

27 patients were each randomised to treatment and control group.

Results

No significant difference was reported for peripheral venous endotoxin levels across treatment groups.

Body compositional analysis was performed using bio-electrical impedance. No significant differences between the treatment groups was seen for the variables total body fat, total body water, extracellular mass (ECM), body cell mass (BCM), nor for ECM/BCM. However, during the treatment period, the BCM was maintained in the treatment group but declined in the control group.

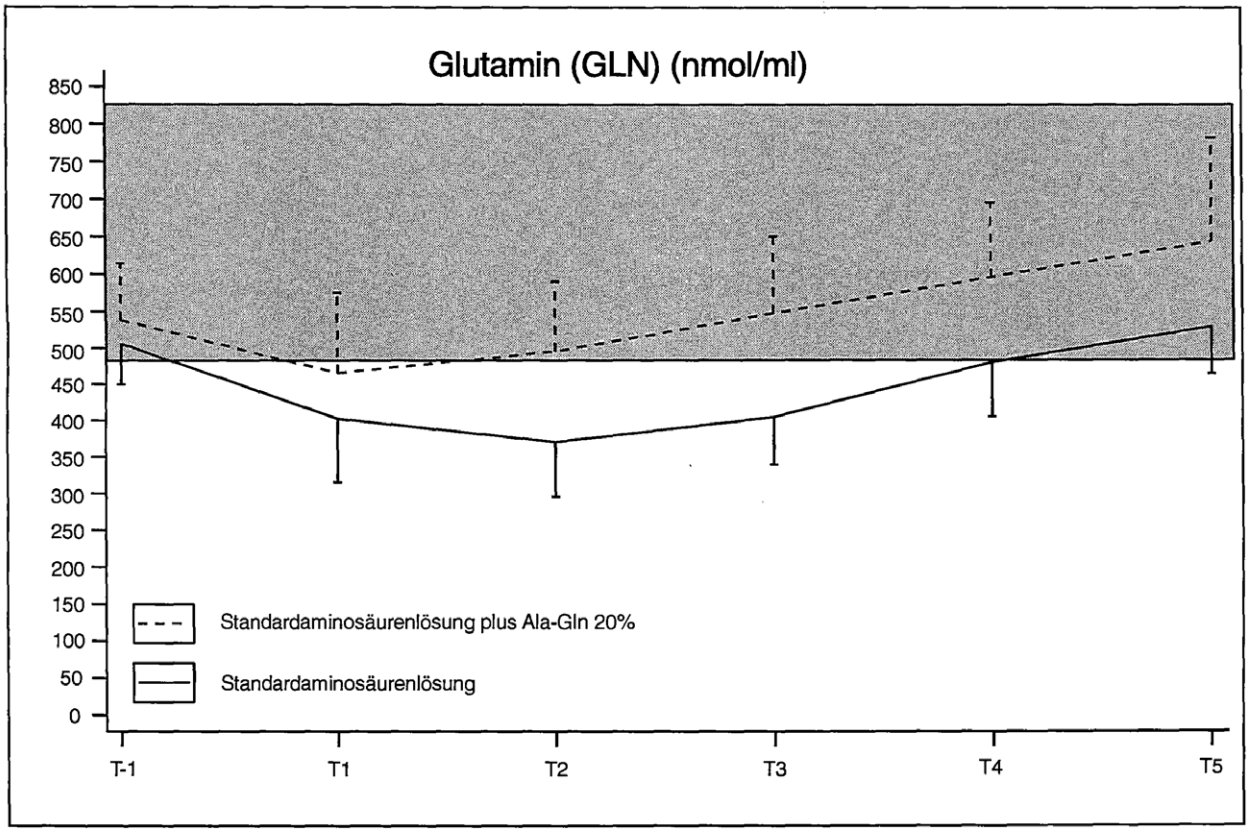
Table 5: Study AS-AG-03-DE Body cell mass change across treatment and control group

	Mean	Standard deviation	Median	Minimum	Maximum	N
Standard amino acid solution plus Ala-Gln 20%						
T-1	25.77	7.14	28	12.40	38.20	20
T4	25.47	6.84	27.15	11.20	35.40	20
Standard amino acid solution						
T-1	28.06	7.98	25.90	18.60	45.60	21
T4	26.74	7.90	24.80	14.40	42.70	21

Body cell mass (BCM) given in kg; n = number of subjects; T-1 = 1 day pre-surgery; T4 = Day 4 of PN.

During the treatment period, plasma glutamine level remained in reference range in treatment group, while it declined in the control group. However, a rise in the plasma glutamine level was noted towards the end of treatment period. Study duration was not long enough to assess the long term effect.

Figure 2: Study AS-AG-03-DE Plasma glutamine levels across treatment and control group



Dashed line represents standard amino acid solution plus Ala-Gln 20% treated group; solid line represents standard amino acid solution (control) group.

Study AS-AG-04-DE

Study design: A multicentre, double blind, parallel group, controlled RCT.

Study period: 1996 to 1997.

Treatment duration: 5 days.

Inclusion criteria: Patients having major abdominal or thoracic surgery and indicated for TPN post-operatively for at least 5 days.

The treatment group was administered with 0.5 g/kg of alanylglutamine. The control group had TPN with amino acids other than alanylglutamine.

202 patients were screened, 162 randomised and eventually, 126 patients formed the per protocol (PP) population. The mean age at Baseline was 63 to 63.5 years. 60% of patients were males. Average body mass index (BMI) was 24 kg/m^2.

Results

Primary outcome: There was no significant difference in nitrogen balance between treatment and control groups. On Day 6, the cumulative nitrogen balance was less negative, 17.9% less negative for the treatment group, compared to control group.

Table 6: Study AS-AG-04-DE Cumulative nitrogen balance in treatment and control groups

Per protocol population	Mean	Standard deviation	Minimum	Median	Maximum	N
Ala-Gln group						
Day 3	-3.5	3.5	-10	-3.1	4.3	44
Day 4	-5.1	5.3	-17.2	-6.2	6.8	44
Day 5	-10.6	7	-28.3	-11.6	4.5	44
Day 6	-14.5	9.5	-33.7	-13	4.6	44
Control group						
Day 3	-4.5	3.9	-13.5	-3.8	2.3	45
Day 4	-9.1	7.5	-35.1	-7.2	3.9	45
Day 5	-12.6	9.5	-44.9	-12	6.2	45
Day 6	-17.1	11	-52.4	-15.4	3.6	45

Cumulative nitrogen balance given in grams; N = number of subjects.

Other efficacy outcomes: Therapeutic Intervention Scoring System (TISS) scores declined to a similar extent across treatment groups.[3] .

[3] The **Therapeutic Intervention Scoring System** (**TISS**) quantifies type and number of intensive care treatments. This system, therefore, indicates the work load of intensive care and may be used for calculating costs in the ICU.

Acute Physiology And Chronic Health Evaluation II (APACHE II) scores;[4] declined to a greater degree in dipeptide alanylglutamine group, compared to control group. The treatment difference was statistically significant (p = 0.04).

Multi organ failure (MOF) scores and infection rates were comparable between treatment groups.

The length of stay (LOS) for the PP population, but not for the intent to treat (ITT) population was 14 days for treatment group and 17 days for control group. The difference was statistically significant (p = 0.013).

Plasma glutamine level was higher (572.4 µmol/L for treatment group and 494.1 µmol/L for control group. The difference was statistically significant (p = 0.0033).

Study 95-TPN-GLN-01

Study design: A multi centre, double blind, controlled RCT.

Study period: 1996 to 2000.

Treatment duration: 5 to 10 days.

Inclusion criteria: Adult ICU patients requiring TPN for 5 to 10 days. Simplified Acute Physiology II Score (SAPS II) II;[5] of > 22 accompanied by a TISS score of > 16 was used to define critically ill patients. In patients with multiple trauma, SAPS II score was replaced with injury severity score (ISS) score;[6] of > 10.

The treatment group received Dipeptiven 0.5 g/kg/day as a supplement to TPN. The total amino acid dose was 1.5 g/kg/day.

Control treatment was comparable except for a mixture of alanine and proline 0.7 g/kg/day, instead of Dipeptiven.

Study population was categorised into those having multiple trauma, complicated post-surgery recovery and acute pancreatitis. However, statistical analysis for primary and secondary endpoints were performed with the whole population.

Baseline characteristics: The ITT population had 114 patients. The average age was around 51 years. Indications for admission to ICU and TPN were comparable across treatment groups.

[4] **APACHE II** is a severity-of-disease classification system. It is applied within 24 hours of admission of a patient to an ICU: an integer score from 0 to 71 is computed based on several measurements; higher scores correspond to more severe disease and a higher risk of death.
[5] The **Simplified Acute Physiology Score II** (**SAPS II**) was designed to measure the severity of disease for patients admitted to intensive care units aged 15 or more. 24 hours after admission to ICU, the measurement has been completed and resulted in an integer point score between 0 and 163 and a predicted mortality between 0% and 100%.
[6] The **injury severity score** (**ISS**) assesses the combined effects of the multiply-injured patients and is based on an anatomical injury severity (AIS) classification, the abbreviated injury scale. ISS ranges from 1 to 75. If an injury is assigned an AIS of 6, the ISS score is automatically assigned 75.

Table 7: Study 95-TPN-GLN-01 Indication for admission to an intensive care unit and requiring total parenteral nutrition

Intention to treat analysis (N = 114)		
	Group A (Dipeptiven)	Group B (Ala,Pro)
. Multiple trauma	17	21
. Post-surgery (complicated)	34	31
- peritonitis	10	9
- resection (GI cancer)	12	16
- resection (other cause)	12	6
. Acute pancreatitis	7	4

Results

A lower proportion of patients treated with Dipeptiven experienced nosocomial infections, compared to control group (39.7% versus 57.8%). The difference was statistically significant ($p \leq 0.05$). The types of infections included surgical wound infections, septic shock, urinary tract infections and intravenous (IV) catheter infections.

The TISS score decreased in both groups, with no major between-group difference.

Table 8: Study 95-TPN-GLN-01 Primary outcome

Table 18 : Clinical outcome in overall population			
Intention to treat analysis			
	Group A, Dipeptiven (N = 58)	Group B, Ala,Pro (N = 56)	p
Complicated clinical outcome	24 (41.4 %)	34 (60.7 %)	**< 0.04***
- patients with nosocomial infections	23 (39.7 %)	32 (57.8 %)	0.06*
- episodes of nosocomial infections per patient	0.45	0.71	**< 0.05†**
- wound healing alterations	1 (1.7 %)	1 (1.8 %)	
- death during study period	2 (3.4 %)	2 (3.6 %)	
Per protocol analysis			
	Group A, Dipeptiven (N = 52)	Group B, Ala,Pro (N = 52)	p
Complicated clinical outcome	20 (38.5 %)	33 (63.5 %)	**< 0.02***
- patients with nosocomial infections	19 (36.5 %)	31 (59.6 %)	**< 0.02***
- episodes of nosocomial infections per patient	0.40	0.75	**< 0.01†**
- wound healing alterations	1 (1.9 %)	1 (1.9 %)	
- death during study period	1 (1.9 %)	2 (3.8 %)	

* = Chi-square test; t = Mann-Whitney test

Other efficacy outcomes: No major difference in length of hospital or ICU stay was observed between dipeptide alanylglutamine and control group. Median LOS was 12.5 days in ICU and 30 days in hospital for the test group and 11.5 days in ICU and 26 days in hospital for the control group. There was also no major difference in six month survival across treatment groups (72% for dipeptide alanylglutamine group versus 83% for control group, $p = 0.14$). Nitrogen balance was on average more positive in the dipeptide alanylglutamine group, but no significant difference with control group ($p = 0.63$).

Study 04-TPN-GLN-01-SP

Study design: A multicentre, controlled, double blind RCT.

Study period: 2005 to 2007.

Treatment period: 5 to 9 days.

The primary efficacy variable was the incidence of nosocomial infections. Secondary efficacy variables included sequential organ failure assessment (SOFA) score, LOS in the

ICU and the hospital, six months mortality, and the development of hyperglycaemia or insulin resistance.

Inclusion criteria: Critically ill patients in ICU indicated for TPN for at least 5 to 9 days. They needed to have an elevated APACHE II score > 12 and enteral nutrition was either contraindicated or not tolerated.

The ITT patient population consisted of 127 patients with 59 in treatment group and 68 in control group. The PP population consisted of 117 patients (53 treatment group subjects, and 64 control group subjects).

Results

The incidence of nosocomial infections was not significantly different between dipeptide alanylglutamine and control groups. A lower incidence for these infections in the dipeptide alanylglutamine group, compared to control group was noted.

Table 9: Study 04-TPN-GLN-01-SP Incidence of nosocomial infections (per protocol population)

Nosocomial Infections						
per protocol						
	Yes		No		case no.	
	N	%	N	%	N	%
Ala-Gln Group	21	39.6	32	60.4	53	100.0
Control group	30	46.9	34	53.1	64	100.0
P-value chi-square test	0.4310					
Relative risk [95% CI]	0.85 [0.56 - 1.28]					

No significant differences between treatment groups were reported for SOFA scores, length of stay in ICU or hospital, mortality in ICU and 6 month mortality.

Literature-based component of the submission

The submission also included 31 published studies, identified by a literature search. The efficacy outcomes of those studies are summarised under the following headings:

- *Incidence of nosocomial infections*: there was conflicting evidence in terms of reduction in infection control in the dipeptide alanylglutamine group, compared to control group. Data from 9 out of 31 studies indicate a reduction in infection rate, meanwhile other study results indicating that no difference for this outcome.
- *Nitrogen balance*: 8 out of 31 published study results indicate an improved nitrogen retention or reduction in negative balance.
- *ICU and hospital length of stay:* conflicting evidence related to this outcome is evident from the published study data. 9 studies reported shorter length of hospital stay, meanwhile 14 study results indicate no difference between treatment groups. Length of stay in ICU was shorter in dipeptide alanylglutamine group in 3 studies, with significant difference in one study.
- *Mortality*: overall, no significant difference between treatment groups were reported in terms of in hospital mortality.

- Data from studies by Heyland et al;[7] and Sykorova et al;[8]indicated an increased mortality rate in dipeptide alanylglutamine treated patients.

Study by Heyland et al;[7] was a blinded 2 by 2 factorial multicentre RCT. 1223 patients were randomised to four treatment arms to receive supplements of glutamine, antioxidants, both, or placebo. Around 30% of patients had renal dysfunction and majority of patients had multiple organ failure at Baseline.

Supplements were started within 24 hours after admission to the ICU and were provided both intravenously and enterally. patients received high doses of study nutrients administered separate from artificial nutrition IV glutamine supplementation (0.35 g/kg/day) parenterally provided as 0.50 g/kg/day of the dipeptide alanylglutamine and an additional 30 g/day of glutamine enterally, provided as 42.5 g alanylglutamine and glycine-glutamine dipeptides.

The primary outcome was the 28 day mortality. the primary analysis demonstrated no clinical benefit of these nutrition interventions and identified a trend toward increased mortality at 28 days (32.4% versus 27.2%; adjusted odds ratio, 1.28; 95% confidence interval (CI), 1.00 to 1.64; p = 0.049) and a significant increase in hospital and 6 months mortality among patients who received glutamine compared with those who did not receive glutamine.

In a post hoc subgroup analysis, both glutamine and antioxidants appeared harmful (increase mortality) in all patients treated with alanylglutamine, with statistically significant rate of mortality effect in patients with baseline renal dysfunction. No subgroups suggested reduced mortality with supplements.

The adverse effects of glutamine observed in the REDOXS trial;[7] were partially attributed to the high dose of study supplements provided to these patients. It also needs to be considered that the duration of treatment was 28 days which is much longer than the proposed duration of treatment of 10 days.

In the study by Sykorova et al;[8] 44 adult autologous transplant patients with haematological malignancies were randomised to parenteral nutrition either prophylactically or ad hoc. In each group, they were further randomised to receive standard PN or PN with 0.5 g/kg of glutamine as alanylglutamine. Glutamine supplementation was found to be associated with worse outcome, with a significantly lower proportion of patients having disease free survival rate (35% versus 77%, p = 0.03), compared to PN group. Event free survival rate was also shorter in patients treated with glutamine supplement (33% versus 65%).

Pooled data and meta analyses

8 metanalyses, 3 systematic reviews and a Cochrane review was also included in this submssion.

The majority of analyses reported a reduction in infections. The Cochrane review;[9] reported a risk ratio of 0.79 with reduction in infections that was statically significant ($p \leq 0.00001$).

[7] Heyland, Daren K et al. REducing Deaths due to OXidative Stress (The REDOXS Study): Rationale and study design for a randomized trial of glutamine and antioxidant supplementation in critically-ill patients. *The Proceedings of the Nutrition Society* vol. 65,3 (2006): 250-63.
[8] Sykorova, A et al. A randomized, double blind comparative study of prophylactic parenteral nutritional support with or without glutamine in autologous stem cell transplantation for hematological malignancies -- three years' follow-up. Neoplasma vol. 52,6 (2005): 476-82.
[9] Information extract from cochrance.org.

Safety

The majority of the sponsor conducted studies in the 1990s did not have a safety population. Also, number of patients were not adequate enough to assess safety.

No major treatment related safety issues were noted in the published studies that randomised large patient population. Most of the events were in line with the nature and severity of underlying illness in patients treated in ICU setting.

Risk management plan

There was no requirement for a risk management plan evaluation for a submission of this type.[10]

Risk-benefit analysis

Delegate's considerations

The proposed indication is Dipeptiven is indicated as part of a clinical nutrition regimen in patients in hypercatabolic and/or hypermetabolic states. It should be given together with parenteral nutrition.

Both hypercatabolism and hyperanabolism are fundamental physiological changes that happen in almost all of the critical illnesses. It would include a large patient population with a variety of critical conditions. The clinical practice guidelines, including those of the American Society for Parenteral and Enteral Nutrition (ASPEN) and the European Society for Clinical Nutrition and Metabolism (ESPEN) do not recommend glutamine supplementation for general use in critical care setting. The Delegate was unable to access the Australasian Society for Parenteral Nutrition (AusPEN) guidelines, as its access is restricted to members. The part of the indication that states as Dipeptiven to be administered only along with TPN reassures that this product will only be used in intensive care setting. The Delegate's concerns for a broad indication for this product are illustrated in the discussion below.

Based on the findings from the studies included in this submission and the evolving evidence related to role of parenteral glutamine in critical care nutrition since it was last approved in New Zealand in 2007, there is conflicting evidence in terms of treatment benefits for patients. Moreover, there is evidence of harm, when administered to the broader ICU patient population, from a higher systemic/supraphysiologic levels of glutamine.[7] The single centre trials that the sponsor has conducted with small patient population in the early nineties did not show major benefit in terms of nitrogen balance, urea production, mortality and infection rate. Multicentre trials with large patient population conducted after the year 2000 provide conflicting evidence for patient benefits such as reduction in infection, length of hospital/ICU stay and mortality. The SIGNET study;[11] randomised 502 ICU patients to receive parenteral glutamine (20 g/day) along with TPN and the treatment effects were compared to patients receiving TPN without added glutamine. There was no significant treatment benefit in terms of incidence of new infections, mortality rate, length of stay, days of antibiotic use and modified SOFA score.

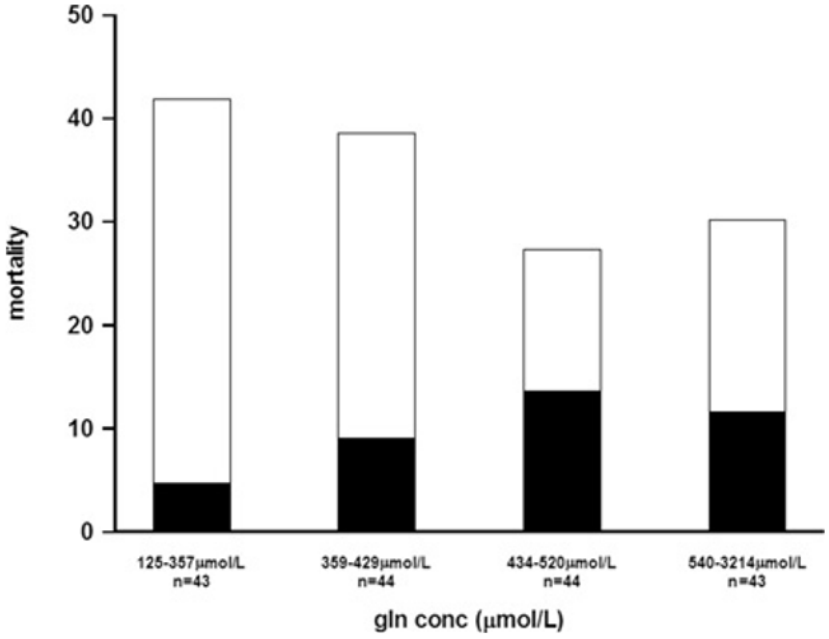
In healthy individuals, serum glutamine level is maintained at 600 to 900 μmol/L. Baseline serum levels of glutamine are found to be low in patient populations like burn injuries,

[10] The sponsor must still comply with routine product vigilance and risk minimisation requirements.
[11] Andrews, Peter J D et al. Randomised trial of glutamine, selenium, or both, to supplement parenteral nutrition for critically ill patients. BMJ (Clinical research ed.) vol. 342 d1542. 17 Mar. 2011, doi:10.1136/bmj.d1542

trauma, post-surgery patients and patients with pancreatitis. There is moderate evidence to suggest treatment benefit with parenteral glutamine in post-operative patients, especially those who underwent GI surgery. A recent Cochrane review;[9] concluded that patients treated with glutamine infusion benefitted with reduced infection rate (moderate quality of evidence), length of hospital stay (low quality evidence) and no effect on mortality rate and length of ICU stay.

The Delegate has noted that in all the studies included in this submission, the interventions to supplement glutamine were irrespective of the baseline serum levels in patients. Not many studies have estimated serum level of glutamine at Baseline. In a sub-sample of REDOXS study;[7] only 31% of patients were glutamine deficient (< 420 µmol/L) while 15 % had supra-normal levels (> 930 µmol/L) at Baseline.[12] Moreover, a U-shaped curve represents the association between glutamine and mortality, where both low (< 420 µmol/L) and high (> 930 µmol/L) levels were associated with a higher mortality risk.[13] These findings suggest that a targeted approach to replenish systemic level of glutamine would be beneficial.

Figure 3: All cause 6 month mortality and intensive care unit mortality of consecutive patients admitted to general intensive care at Karolinska Huddinge.



All-cause 6-month mortality (open bars) and ICU mortality (filled bars) of consecutive patients admitted to the general ICU (n = 174) at Karolinska University Hospital, Huddinge, Sweden, divided into quartiles according to the admittance plasma glutamine concentration Mortality is different in between the quartiles, where the two lower quartiles are different from the two higher (P = 0.037). Adapted from Rodas, P.C., et al., Glutamine and glutathione at ICU admission in relation to outcome*. Clin Sci (Lond),* 2012. 122(12): p. 591-7.

The Delegate has considered the fact that the total daily dose of glutamine (parenteral plus enteral) administered in REDOXS study;[7] (0.7 g/kg) was higher than the recommended dose in the proposed Product Information (PI) (0.3 to 0.5 g/kg). For this reason, findings of REDOXS study;[7] that are related to mortality rates cannot be fully extrapolated to the current submission. However, the study findings indicate that high systemic levels of

[12] Oudemans-van Straaten, H.M., et al., Plasma glutamine depletion and patient outcome in acute ICU admissions. *Intensive Care Med*, 2001. 27(1): p. 84-90.
[13] Rodas, P.C., et al., Glutamine and glutathione at ICU admission in relation to outcome. *Clin Sci (Lond)*, 2012. 122(12): p. 591-7.

glutamine can cause more harm than benefits. If glutamine is administered at the recommended dose to all patients in 'hypercatabolic and/or hypermetabolic states', irrespective of the basal systemic level of glutamine, then it is likely to result in high systemic level of glutamine in a large proportion of patients. Based on evidence from REDOXS study;[7] this practice could be harmful for patients.

The REDOXS study data found that majority of patients did not have glutamine deficiency in early stage of illness.[7] In addition, recent data from REDOXS study;[7] and other trials suggest that parenteral glutamine should not be given to all patients early in the acute phase of critical illness, in patients with multiple organ failure or in patients with un-resuscitated shock requiring significant vasopressor support. In the proposed PI, severe renal and hepatic insufficiency and severe metabolic acidosis are stated as contraindications. This appears to exclude the patient population for whom Dipeptiven infusion could cause harm, rather than benefit. However, it doesn't help to identify the patient population who might benefit the most with Dipeptiven infusion.

The Delegate appreciates that the product was first registered many years ago. However, the evidence in critical care nutrition that is related to glutamine supplementation has been constantly evolving during this period. Data from recently published studies suggest conflicting evidence regarding efficacy and provide safety concerns related to mortality with high systemic glutamine levels.

To conclude, the critically ill population is a heterogeneous one. It is unknown whether glutamine kinetics always have the same pattern or if it varies with the underlying pathological situation. Hence, from a clinical perspective, it is important to identify the patient group who will benefit the most with supplemental parenteral glutamine.

Request for sponsor

- ***The sponsor is required to provide periodic safety reports from the UK since Dipeptiven was first registered.***

Sponsor response

The most recent periodic safety update report (PSUR) covering 73 countries, which includes the UK, for the interval 25 July 2017 to 31 May 2019 was provided by the sponsor. In addition, PSURs from 1995 until 2013 are also provided. PSURs from 2012 until 2017 were provided with the initial application.

Request for Advisory Committee on Medicines advice

The Delegate has requested advice from Advisory Committee on Medicine.

The Delegate has requested the following advice from Advisory Committee on Medicine.

1. Do all patients of the heterogeneous ICU population have the same needs in terms of parenteral glutamine supplementation, or are there specific needs for specific sub-populations?
2. What is the best approach to identify the patient population who will have maximum treatment benefit with parenteral glutamine?
3. The Delegate suggests that the commencement of glutamine infusion in TPN to be guided by the baseline serum glutamine level. The ACM's comments will be appreciated.
4. Based on the evaluated data, the duration of most of the studies ranged from 5 to 10 days. The Delegate suggests that continuation of treatment with Dipeptiven beyond 10 days should be at the discretion of the treating physician. The ACM's comments will be appreciated.

5. Are the contraindications specified in the proposed PI adequate enough to exclude patient population who might be at risk with parenteral glutamine supplementation?
6. Based on the REDOXS study;[7] findings that fatality occurred mostly in patients with multi-organ failure, the Delegate believes it will be worthwhile to include multi-organ failure as a contraindication. The ACM's comments will be appreciated.

Advisory Committee considerations[14]

Specific advice

The ACM advised the following in response to the Delegate's specific request for advice.

1. Do all patients of the heterogeneous ICU population have the same needs in terms of parenteral glutamine supplementation, or are there specific needs for specific sub-populations?

The ACM was of the view that it is unknown whether all ICU patients have the same needs in terms of parenteral glutamine supplementation and that there is insufficient evidence available to support the needs of any particular sub-group.

2. What is the best approach to identify the patient population who will have maximum treatment benefit with parenteral glutamine?

The ACM considered that the best evidence for the use of parenteral glutamine is in previously well patients in critical care for burns and trauma treatment may benefit from treatment with alanylglutamine. However, the ACM was of the view that there is insufficient evidence to suggest an appropriate dosage regimen for alanylglutamine in this setting. In addition, there is lack of evidence to support this usage, based on clinical studies that are designed specifically to examine the efficacy and safety of alanylglutamine in this patient population. The ACM was of the opinion that there is lack of evidence to strongly support benefit from the use of parenteral glutamine in any patient population.

3. The Delegate suggests that the commencement of glutamine infusion in TPN to be guided by the baseline serum glutamine level. The ACM's comments will be appreciated.

The ACM advised that relying on measurement of serum glutamine levels to guide clinical decision making is not practical, as testing for this is only available in specialist metabolic pathology labs, of which there are only five in Australia, and has a minimum turnaround timeframe of two days, often longer.

4. Based on the evaluated data, the duration of most of the studies ranged from 5 to 10 days. The Delegate suggests that continuation of treatment with Dipeptiven beyond 10 days should be at the discretion of the treating physician. The ACM's comments will be appreciated.

The ACM was of the view that treatment beyond 10 days should not be recommended unless there is clear evidence of glutamine deficiency despite having appropriate protein supplementation in their TPN.

[14] The ACM provides independent medical and scientific advice to the Minister for Health and the Therapeutic Goods Administration (TGA) on issues relating to the safety, quality and efficacy of medicines supplied in Australia including issues relating to pre-market and post-market functions for medicines.
The Committee is established under Regulation 35 of the *Therapeutic Goods Regulations 1990*. Members are appointed by the Minister. The ACM was established in January 2017 replacing Advisory Committee on Prescription Medicines (ACPM) which was formed in January 2010. ACM encompass pre and post-market advice for medicines, following the consolidation of the previous functions of the Advisory Committee on Prescription Medicines (ACPM), the Advisory Committee on the Safety of Medicines (ACSOM) and the Advisory Committee on Non-Prescription Medicines (ACNM). Membership comprises of professionals with specific scientific, medical or clinical expertise, as well as appropriate consumer health issues relating to medicines.

5. ***Are the contraindications specified in the proposed PI adequate enough to exclude patient population who might be at risk with parenteral glutamine supplementation?***

The ACM was of the view that the contraindications proposed in the PI do not adequately exclude patient populations who might be at risk with parenteral glutamine supplementation. In particular, the ACM noted that while the PI recommends that 'possible symptoms of hyperammonaemia should be controlled', the PI does not suggest monitoring ammonia levels and clinical symptoms of hyperammmonaemia can overlap with other pathology. The ACM advised that as high glutamine levels lead to high ammonia levels, at a minimum the PI should be amended to exclude the use of glutamine in patients with abnormal levels. However, the ACM expressed concern that there is evidence (for example Takahashi et al;[15]) to suggest that high glutamine levels in themselves may lead to cerebral oedema, irrespective of serum ammonia levels, and that as a result, artificially elevating serum glutamine levels may have unintended negative consequences.

6. ***Based on the REDOXS study;[7] findings that fatality occurred mostly in patients with multi-organ failure, the Delegate believes it will be worthwhile to include multi-organ failure as a contraindication. The ACM's comments will be appreciated.***

The ACM considered the Delegate's suggestion that multi-organ failure could be included as a contraindication to parenteral glutamine use, based on outcomes of the REDOXS study.[7] While the ACM agreed with the Delegate that glutamine should not be used in such patients, the ACM noted that this would exclude most patients within an ICU setting.

ACM recommendation

The Advisory Committee on Medicines (ACM), having considered the evaluations and the Delegate's overview, as well as the sponsor's response to these documents, advised the following:

The proposed indication considered by the ACM was:

> *Proposed indication:*
>
> *Dipeptiven is indicated as part of a clinical nutrition regimen in patients in hypercatabolic and/or hypermetabolic states. It should be given together with parenteral nutrition.*
>
> *Delegate's revised indication:*
>
> *Dipeptiven is indicated as part of a clinical nutrition regimen in patients in hypercatabolic and/or hypermetabolic states with low level of basal serum glutamine. It should be given together with parenteral nutrition.*

The ACM agreed that Dipeptiven had an overall negative benefit-risk profile for the proposed indication as the evidence submitted did not satisfactorily establish the efficacy and safety of the product

Outcome

The sponsor withdrew their submission on 16 January 2020 before a decision had been made by the TGA.

[15] Takahashi H et al., Glutamine Synthetase Inhibition Prevents Cerebral Oedema During Hyperammonemia. In: Reulen HJ et al., *Brain Edema VIII. Acta Neurochirurgica*, 1990 (51) Springer, Vienna.

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