CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

200656Orig1s000

MEDICAL REVIEW(S)

CLINICAL REVIEW

Application Type	NDA Class 2 Re-submission
Application Number(s)	200656
Priority or Standard	Standard
Submit Date(s)	November 25, 2013
Received Date(s)	November 25, 2013
PDUFA Goal Date	Original date May 25, 2014; extended 3 months to August 25, 2014 due to new data
Division / Office	DGIEP/ODE 3
Reviewer Name(s)	Karyn L. Berry, MD, MPH
Review Completion Date	August 13, 2014
Established Name	Amino acids, electrolytes, and dextrose in lipid injectable emulsion
Trade Name	Kabiven (amino acids, electrolytes, and dextrose in lipid injectable emulsion) for intravenous use Perikabiven (amino acids, electrolytes, and dextrose in lipid injectable emulsion) for intravenous use

Therapeutic Class	Solutions for Parenteral Nutrition
Applicant	Fresenius Kabi, USA, LLC
Formulation(s)	Intravenous Supplied as: Kabiven 2566 mL, 2053 mL, 1540 mL and 1026 mL Perikabiven 2400 mL, 1920 mL, 1440 mL
Dosing Regimen	Kabiven The dose should be individualized and is dependent on the patient's clinical condition, body weight and nutritional requirements. • Adult dosage: 19 to 38 mL/kg/day (0.63 to 1.26 g/kg/day of amino acids, 0.74 to 1.48 g/kg/day of fat, 1.85 to 3.71 g/kg/day of dextrose) • The maximum infusion rate is 2.6 mL/kg/hour (corresponding to 0.25 g/kg/hour of dextrose, the limiting factor, 0.09 g/kg/h of amino acids, and 0.1 g/kg/hour of fat). Recommended infusion period is 12 to 24 hours Perikabiven The dose should be individualized and is dependent on the patient's clinical condition, body weight and nutritional requirements. • Adult dosage: 27 to 40 mL/kg/day (0.64 to 0.94g/kg/day of amino acids, 0.95 to 1.4 g/kg/day of fat, 1.83 to 2.71 g/kg/day of dextrose) • The maximum infusion rate is 3.7

mL/kg/hour (corresponding to 0.25 g/kg/hour of dextrose, the limiting factor, 0.09 g/kg/h of amino acids, 0.13 g/kg/h fat). The recommended infusion period is 12 to 24 hours

Indication(s)

Kabiven

For intravenous infusion into a central vein as a source of calories, protein and essential fatty acids for adult patients requiring parenteral nutrition (b) (4) prevention of essential fatty acid deficiency (b) (4) or treatment of negative nitrogen balance (b) (4)

(b) (4)

Perikabiven

For intravenous infusion into a peripheral or central vein as a source of calories, protein and essential fatty acids for adult patients requiring parenteral nutrition (b) (4) prevention of essential fatty acid deficiency (b) (4) or treatment of negative nitrogen balance (b) (4)

(b) (4)

Intended Population(s)

Adults

Template Version: March 6, 2009

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1 Recommendations/Risk Benefit Assessment

The Applicant, Fresenius Kabi, submitted this Class 2 re-submission 505(b)(2) application for Kabiven and Perikabiven in response to the Complete Response (CR) letter dated November 21, 2011. In this re-submission, the Applicant provided responses to the deficiencies listed in the CR letter. The deficiencies cited in the CR letter were numerous and crossed multiple discipline reviews (i.e. Clinical, Chemistry, Pediatrics and Maternal Health, Division of Medication Error Prevention and Analysis and the Center for Devices and Radiological Health).

These deficiencies included:

Clinical

- Insufficient data to [redacted] (b) (4), including no submitted pediatric study plan

Product Quality

- Insufficient data on the amount of heavy metals in each compartment of the three chamber bag
- Inadequate controls for the levels of heavy metals in each compartment
- Revised proposed product expiration date
- Deficiencies with DMF # [redacted] (b) (4)
- Insufficient data for the [redacted] (b) (4) container system related to [redacted] (b) (4) and [redacted] (b) (4) and manufacturing facilities deficiencies,

Device Performance

- Demonstrate pressure at which [redacted] (b) (4) bag burst
- [redacted] (b) (4)
- Clarify whether the injection point could be penetrated multiple times and test bag for leakage after multiple punctures
- Test injection point leakage after the septum is punctured with a 19 or 21 gauge needle

Human Factors Assessment

- Perform an assessment to identify potential use-related hazards are no different than the usual hazards that clinicians face when delivering drug product through other intravenous (IV) bags.

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Labeling

- Submit revised content of labeling and draft container labels that incorporate the proprietary name, Perikabiven, and the established name, lipid injectable emulsion with amino acids and electrolytes and dextrose.

Facility Inspections

- Satisfactory resolution of deficiencies identified during recent inspections of manufacturing facilities.

Drug Product Indications:

Kabiven
For intravenous infusion into a central vein as a source of calories, protein and essential fatty acids for patients requiring parenteral nutrition (b) (4) prevention of essential fatty acid deficiency (b) (4) or treatment of negative nitrogen balance (b) (4)

(b) (4)

Perikabiven
For intravenous infusion into a peripheral or central vein as a source of calories, protein and essential fatty acids for patients requiring parenteral nutrition (b) (4) prevention of essential fatty acid deficiency (b) (4) or treatment of negative nitrogen balance (b) (4)

(b) (4)

Kabiven and Perikabiven are new combination products that propose to provide parenteral nutrition (PN) in a three (3) chamber plastic bag. The individual chambers in Kabiven and Perikabiven contain: Glucose (b) (4) % [Kabiven] and Glucose (b) (4) %

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[Perikabiven] (Chamber 1); Amino acids ([redacted] (b) (4)) including electrolytes (Chamber 2), and Intralipid 20% (Chamber 3).

The Applicant references prior findings by the FDA of safety and efficacy for Intralipid 20% (NDA 018449 and NDA 020248), Novamine 11.4% (NDA 017957) and two (2)-chamber bag (CB) products Aminosyn II with electrolytes in dextrose with calcium (NDA 019683) and CliniMix E sulfite free with electrolytes in dextrose with calcium (NDA 20678).

1.1 Recommendation on Regulatory Action

From the clinical standpoint, the submitted clinical data are adequate to suggest that Kabiven and Perikabiven could be considered effective and safe at the proposed dosage as a source of calories, protein and essential fatty acids in adults. This recommendation is based on data submitted to address the safety issues that were identified by this reviewer and other disciplines during the first review cycle.

[redacted] (b) (4) (b) (4). This reviewer therefore, recommends [redacted] inserting the statement that efficacy and safety have not been established in the pediatric population.

In this resubmission, the Applicant has requested [redacted] (b) (4) and a [redacted] (b) (4) The Applicant has also proposed [redacted] (b) (4)

Based on nutritional calculations using age and weights submitted by the Applicant, Kabiven and Perikabiven may not provide adequate nutrition for patients < 2 years of age. Therefore, a partial waiver for pediatric patients less than 2 years of age may be appropriate on the grounds that the product fails to represent a meaningful therapeutic benefit over existing therapies for pediatric patients **and** is unlikely to be used in a substantial number of all pediatric age groups or the pediatric age group(s).

A deferral for safety studies in pediatric patients from ages 2 to 16 years is reasonable. The Applicant's basis for a deferral request is *"the drug or biological product is ready for approval for use in adults before pediatric studies are complete (FD&C Act, section 505B(a)(3)(A)(i)),"* is acceptable. Kabiven and Perikabiven are fixed combination products for parenteral nutrition. [redacted] (b) (4)

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[redacted] (b) (4) Since the Applicant proposes to only conduct one trial, all age groups will need to be adequately represented in this trial.

1.2 Risk Benefit Assessment

The applicant has adequately addressed all discipline deficiencies, including clinical deficiencies, listed in the CR letter.

Since the original review of NDA 200656, the Division has become aware of an unexpected serious risk of liver injury in pediatric and neonatal patients who receive parenteral nutrition. Liver injury may be related to the presence of phytosterols. Phytosterols are impurities present in intravenous fat emulsion (IVFE) products and have been implicated as a causative factor of parenteral nutrition associated liver disease (PNALD). The Division considers this information to be "new safety information" as defined in section 505-1(b)(3) of the FDCA. [redacted] (b) (4), (b) (5)

Regarding pediatric issues, since Kabiven and Perikabiven are combination products they qualify as new active ingredients and the Pediatric Research Equity Act (PREA) applies. The Applicant therefore must include a pediatric assessment that is adequate to assess the safety and effectiveness of the product and to support dosing and administration for all relevant pediatric populations, unless the requirement is waived, deferred, or inapplicable

As previously noted, in the first review cycle the applicant requested [redacted] (b) (4) This request was denied. The applicant was informed that they would need to submit the following: [redacted] (b) (4)

In this complete response re-submission, the Applicant requested [redacted] (b) (4) and a [redacted] (b) (4) (b) (4)

Pediatric nutritional needs vary based on the age and weight of the patient. Therefore, the Applicant performed nutritional calculations to determine the utility of the various components of these products at different patient weights to assess if patients will receive current acceptable and adequate ratios of amino acids, fat and dextrose., Based on these calculations it was determined that Kabiven and Perikabiven, fixed dose combination products, may not be appropriate to meet the nutritional needs of pediatric patients below a certain weight or age. Therefore, a partial waiver for pediatric patients less than 2 years of age or 12 kg for Perikabiven and 10 kg for Kabiven is appropriate on the grounds that the product fails to represent a meaningful therapeutic benefit over existing therapies for pediatric patients **and** is unlikely to be used in a substantial number of all pediatric age groups or the pediatric age group(s).

A deferral of safety studies in pediatric patients from ages 2 to 16 years is reasonable. Clinical trials are needed in the pediatric population ≥ 2 years of age to assess safe and effective doses of Kabiven and Perikabiven in this population. These trials will assist in identifying any adverse events and to establish the safety of recommended doses for pediatric patients. If the Applicant only conducts one trial, they will need to ensure that adequate numbers of each age group are represented in the trial.

The partial waiver and deferral plans were presented to the PeRC PREA Subcommittee on June 18, 2014. The PeRC agreed with the Division to grant a partial waiver in patients < 2 years of age and deferral of trials in patients ≥ 2 years of age. The PeRC also agreed with the Division's plan to have the Applicant study Kabiven first because it is a centrally administered product. If there are no new safety or efficacy issues identified with Kabiven then the PeRC agreed that studies in Perikabiven would not be needed.

1.3 Recommendations for Postmarket Risk Evaluation and Mitigation Strategies

No postmarket risk evaluation and mitigation are recommended.

1.4 Recommendations for Postmarket Requirements and Commitments

A postmarketing requirement (PMR) safety trial is needed to assess a safe and effective dose of Kabiven in pediatric patients aged 2 to 16 years. Adequate numbers of each

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age group must be represented in the trial. The proposed pediatric trial is, *"Safety and tolerance of Kabiven in pediatric patients ages 2 to 16 years requiring parenteral nutrition: A prospective, controlled, randomized, open-label study."*

Schedule milestones:

Final Protocol Submission:	02/2015
Study/Trial Completion:	08/2017
Final Report Submission:	08/2018

This reviewer recommends initially studying Kabiven since it is a centrally administered product. PMRs would be required for Perikabiven if new safety or efficacy issues are identified in the Kabiven trial.

2 Introduction and Regulatory Background

The Applicant, Fresenius Kabi, resubmitted this 505(b)(2) application for Kabiven and Perikabiven in response to the Complete Response (CR) letter dated November 21, 2011.

Kabiven and Perikabiven are new combination products that propose to provide parenteral nutrition (PN) in a three (3) chamber plastic bag. These solutions are stored in separate compartments of the multichamber bag, which is manufactured using a [redacted] (b) (4) The compartments are separated by breakable seals, which on opening result in a standardized "all in one" admixture. The individual chambers in Kabiven and Perikabiven contain: Glucose [redacted] (b) (4) % [Kabiven] and Glucose [redacted] (b) (4) % [Perikabiven] (Chamber 1); Amino acids ([redacted] (b) (4)) including electrolytes (Chamber 2), and Intralipid 20% (Chamber 3).

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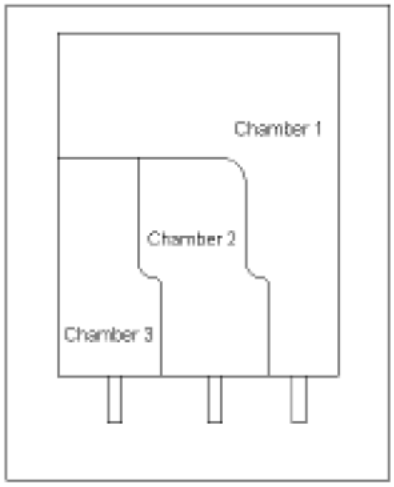
Figure 1: 3 chamber bag



The smallest chamber (chamber 3) always contains lipid emulsion, the middle chamber (chamber 2) contain the amino acid solution and the chamber next to the handle (chamber 1) contains the glucose solution.

The Applicant references prior findings by the FDA of safety and efficacy for Intralipid 20% (NDA 018449 and NDA 020248), Novamine 11.4% (NDA 017957) and two (2)-chamber bag (CB) products Aminosyn II with electrolytes in dextrose with calcium (NDA 019683) and CliniMix E sulfite free with electrolytes in dextrose with calcium (NDA 20678).

This review is an addendum to the 1st cycle Clinical Review and will only present information and data that is either new to the 2nd review cycle, is interpreted differently or is necessary for context so that this review may be used as a stand-alone document.

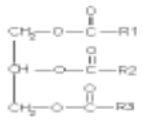
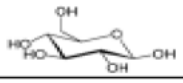
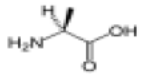
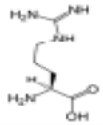
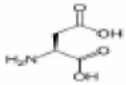
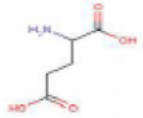
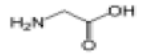
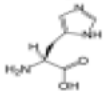
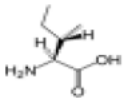
2.1 Product Information

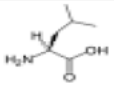
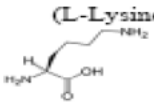
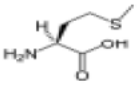
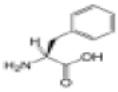
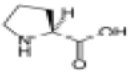
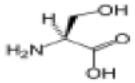
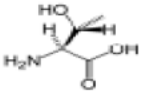
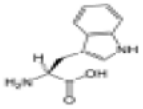
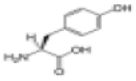
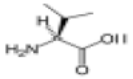
The individual referenced products of Kabiven and Perikabiven have been approved in the United States as components of PN. The IVFE, Intralipid 20%, a Fresenius Kabi product, is a soybean oil based lipid emulsion that provides essential and non-essential long chain fatty acids. In PN it is also an energy source.

The amino acid component is [redacted] (b) (4). According to the applicant it [redacted] (b) (4) to Hospira's Novamine 11.4% (NDA 017957). [redacted] (b) (4). The difference between [redacted] (b) (4) and Novamine 11.4% is the [redacted] (b) (4) versus [redacted] (b) (4) in Novamine 11.4%.

Kabiven and Perikabiven electrolyte solution contain sodium glycerophosphate, an organic form of phosphate, which is not approved in the US, and the following electrolytes: sodium acetate trihydrate, potassium chloride, magnesium [redacted] (b) (4) heptahydrate and calcium chloride dihydrate. Sodium glycerophosphate is manufactured by [redacted] (b) (4)

Table 1: Chemical Name and Structure

Name	Molecular Formula	Structure
Lipids		
Soybean oil	Triacylglycerol with fatty acid chains mainly C16:0, C18:1, C18:2	 R=Fatty Acid Chains
Carbohydrate		
Glucose monohydrate (Dextrose)	$C_6H_{12}O_2.H_2O$	
Amino Acids		
L-Alanine	$C_3H_7NO_2$	
L-Arginine	$C_6H_{14}N_4O_2$	
L-Aspartic acid	$C_4H_6NO_4$	
L-Glutamic acid	$C_5H_8NO_4$	
Glycine	$C_2H_5NO_2$	
L-Histidine	$C_6H_9N3O_2$	
L-Isoleucine	$C_6H_{13}NO_2$	

Name	Molecular Formula	Structure
L-Leucine	$C_6H_{13}NO_2$	
L-Lysine hydrochloride	$C_6H_{14}N_2O_2.HCl$	(L-Lysine) 
L-Methionine	$C_5H_{11}NO_2S$	
L-Phenylalanine	$C_9H_{11}NO_2$	
L-Proline	$C_5H_9NO_2$	
L-Serine	$C_3H_7NO_3$	
L-Threonine	$C_4H_9NO_3$	
L-Tryptophan	$C_{11}H_{12}N_2O_2$	
L-Tyrosine	$C_9H_{11}NO_3$	
L-Valine	$C_5H_{11}NO_2$	
Electrolytes		
Calcium chloride dihydrate	$CaCl_2.2H_2O$	-
Sodium glycerophosphate	$C_3H_5(OH)_2PO_4Na_2.xH_2O$	-
Magnesium [redacted] (b) (4) heptahydrate	$MgSO_4.7H_2O$	-
Potassium chloride	KCl	-
Sodium acetate trihydrate	$CH_3COONa.3H_2O$	-

Proposed indication for Kabiven:
For intravenous infusion into a central vein as a source of calories, protein and essential fatty acids for patients requiring parenteral nutrition [redacted] (b) (4) [redacted] prevention of essential fatty acid deficiency [redacted] (b) (4) or treatment of negative nitrogen balance [redacted] (b) (4)

[redacted] (b) (4)

(b) (4)

Proposed indication for Perikabiven
For intravenous infusion into a peripheral or central vein as a source of calories, protein and essential fatty acids for patients requiring parenteral nutrition (b) (4) prevention of essential fatty acid deficiency (b) (4) or treatment of negative nitrogen balance (b) (4)

(b) (4)

Dosing and Administration Kabiven and Perikabiven:
The ability to eliminate fat and to metabolize dextrose should govern the dosage and infusion rate of Kabiven and Perikabiven. The dosage should be made with regard to the patient's clinical condition, body weight and nutritional requirement. Kabiven is produced in 4 sizes for patients with high, moderately increased, basal or low nutritional requirements. The four sizes of Kabiven bags proposed are: 1026 ml, 1540 ml, 2053 ml and 2566 ml. The components of Kabiven are Intralipid 20%, (b) (4) with electrolytes and Glucose (b) (4)%.

Table 2: Proposed Dosing Information for Kabiven

Mode of Administration	Central vein
Energy requirement	Dependent on clinical condition; usually (b) (4) kcal/kg of body weight/day
Dosing	(b) (4)

(b) (4)	Maximum daily dose: 40 mL/kg/day. (b) (4) (b) (4)
Infusion Rate	Not more than 2.6mL/kg bw/hr (corresponding to 0.25g dextrose, 0.09g amino acid and 0.1g (b) (4)/kg bw)
Recommended Infusion Period	12 to 24 hours

Applicant's table

Perikabiven is produced in 3 sized for patients with moderately increased, basal or low nutritional requirements. The three sizes of Perikabiven bags proposed are 1440 ml, 1920 ml and 2400 ml. The components of Perikabiven are Intralipid 20%, (b) (4) with electrolytes and Glucose (b) (4)%.

Table 3: Proposed Dosing Information for Perikabiven

Mode of Administration	Peripheral or Central vein
Energy requirement	Dependent on clinical condition; often 20 to 30 kcal/kg of body weight/day
Dosing	(b) (4) (b) (4)

	(b) (4)
Infusion Rate	Not more than 3.7 mL/kg/hr (corresponding to 0.25 g/kg dextrose, 0.09g/kg amino acid and 0.13 g/kg (b) (4))
Recommended Infusion Period	12 to 24 hours

Applicant's table

2.2 Tables of Currently Available Treatments for Proposed Indications

There are a number of products currently available that are components of parenteral nutrition. These include: intravenous lipid emulsions (IVLE), amino acids, electrolytes, dextrose, trace elements and vitamins.

Refer to the 1st cycle review.

2.3 Availability of Proposed Active Ingredient in the United States

Sodium glycerophosphate, an active ingredient, is not currently marketed in the US. Various formulations of IV fat emulsions, amino acids, electrolytes and dextrose are marketed in the US.

Refer to the 1st cycle review.

2.4 Important Safety Issues With Consideration to Related Drugs

The individual components of the 3 chamber bag: IVFE, dextrose, and amino acids with electrolytes have widespread distribution and a generally good safety profile. However, there are potential safety issues/complications associated with PN products. These include 1) the risk of heavy metal contamination of these products during the manufacturing process, 2) the risk of metabolic complications such as hyper/hypoglycemia, refeeding syndrome, electrolyte imbalances, lipid abnormalities, acid-base disturbance, hepatobiliary disorders and bone disease and 3) the risk of mechanical and septic complications such as central vascular access complications, mechanical complications, catheter related infections and catheter occlusion and thrombosis.

Refer to the 1st cycle review for information on labeled adverse events for various products.

2.5 Summary of Presubmission Regulatory Activity Related to Submission

The following is a summary of submission regulatory activities related to this current submission that occurred from the date of the CR letter to re-submission.

November 25, 2013
The Division received the Applicant's resubmission to their NDA. A complete class 2 response to our November 21, 2011 action letter.

October 25, 2013 (Type C Meeting)
Discussion with Applicant regarding its attempt to mitigate errors observed in the previous Human Factor study and its efforts to enhance usability of the 3 chamber bag to ensure patient safety. The Applicant agreed to conduct human factor/usability studies with homecare nurses, since it is likely that this product will be used in the homecare setting. The Applicant also agreed to submit the protocol for review prior to study initiation. Also during this meeting, the Division discussed with the Applicant that the (b) (4) bag leachables data would need to be addressed in the complete response resubmission. The Applicant was also informed that the Agency had identified a new safety concern related to the possible presence of (b) (4) as a leachable in the 1 chamber (b) (4) bag that they would need to provide additional information/data to address.

December 11, 2012 (Type C Meeting)
The results of the summative human factors/usability study were discussed.

September 14, 2012 (Advice Letter)
The Agency provided recommendations and comments to the Applicant on the revised Human Factors/Usability Study protocol that was submitted on August 24, 2012.

July 31, 2012 (General Advice Letter)
Letter form ONDQA acknowledging telephone conferences with Applicant on November 4, 2011 and July 20, 2012 on data to support expiration dating period. The Applicant was informed that the data they provided only supported a (b) (4) month expiration dating period. The Applicant was informed what additional data would be required to grant a longer expiration dating period.

July 26, 2012 (General Advice Letter)
The Agency provided comments and recommendations to the Applicant on their Human Factors/Usability Study protocol. The Agency also provided the Applicant with comments and recommendations on the device performance data submitted.

July 20, 2012 (Acknowledge Incomplete Response)

Upon further review of the applicant's June 1, 2012 submission, the response to the Human Factors Assessment deficiency (deficiency #10 of the November 21, 2011 Complete Response (CR) letter) was found to be incomplete. Specifically, the applicant did not conduct a usability study on the final design of their instructions for use as communicated in the November 21, 2011 action letter.

A teleconference was held with the Applicant on July 20, 2012 to discuss the deficiencies associated with the Human Factors Assessment and the Applicant was informed that the June 1, 2012 response to the November 21, 2011 action letter was incomplete.

During the teleconference, the Agency recommended that the Applicant delay starting the Summative Human Factors Study until they can review and incorporate FDA recommendations into the study. FDA requested that the testing be conducted on the commercial-equivalent product and that the Applicant submit testing results as part of their complete response.

July 11, 2012
The Applicant contacted the Agency to request comments from the Division of Medication Error Prevention (DMEPA) regarding the summative study submitted on June 1, 2012. In an email dated July 11, 2012, the applicant indicated that the summative study) "is planned to be performed to validate the labeling changes from the previous study, in which a nursing arm has been added as per DMEPA's recommendations." The applicant further indicated that the study start date was planned for July 23, 2012.

June 12, 2012
The Division issued an acknowledgement letter indicating the submission was a class 2 resubmission

June 1, 2012
The Applicant submitted their complete response to the November 21, 2011 action letter.

2.6 Other Relevant Background Information

During the first review cycle, requests were submitted by sponsors of two of the RLDs to withdraw their applications. Hospira Inc., the sponsor of Novamine Amino Acids Injections (NDA 17957), submitted a request on [redacted] (b) (4) to withdraw the application for this product. The sponsor stated that the product is not currently marketed and the withdrawal is not associated with any safety or efficacy issues.

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Hospira, also the sponsor of Aminosyn II with Electrolytes in Dextrose Injection with Calcium (NDA 19683) submitted a request on [redacted] (b) (4) to withdraw the application for this product. The sponsor stated that the product is not currently marketed and the withdrawal is not associated with any safety or efficacy issues.

Novamine Amino Acids Injection (NDA 17957)
Annual reports from 12/01/2005-12/01/2009 were reviewed. The sponsor stated that the product was not currently marketed. No clinical adverse event data was reported.

Aminosyn II with Electrolytes in Dextrose Injection with Calcium (NDA 19683)
Annual reports from 10/01/2005 to 10/01/2009 and safety reports from 10/01/2008 through 10/01/2010 were reviewed. No clinical adverse event data was reported.

Medical Reviewer's comments: Based on a review of available annual reports, safety reports and the literature, this reviewer concludes that withdrawal of NDA 17957 and NDA 19683 was not because of safety or efficacy issues.

3 Ethics and Good Clinical Practices

Refer to the 1st cycle review

3.1 Submission Quality and Integrity

3.2 Compliance with Good Clinical Practices

3.3 Financial Disclosures

4 Significant Efficacy/Safety Issues Related to Other Review Disciplines

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4.1 Chemistry Manufacturing and Controls

Dr. Tarun Mehta, the CMC reviewer, has determined that the Applicant provided sufficient information to assure the identity, strength, purity and quality of the drug product. All CMC deficiencies cited in the CR letter were adequately addressed. Dr. Tarun also notes that the Office of Compliance has issued an "Acceptable" recommendation for this application.

The following is a summary of the resolution of deficiencies noted in the CR letter (11/21/2011) and issues noted in the General Advice Letter (07/26/2012 and 07/31/2012) and Type C Meeting Minutes (10/25/2013) as per Dr. Mehta's review.

1. The applicant revised the specification of the drug product in line with recommendation of ICH Q3D with validation of analytical method L73 (ICP-SFMS), for the determination of arsenic (As), cadmimum (Cd), chromium (Cr), copper (Cu), mercury (Hg), manganese (Mn), lead (Pb), selenium (Se) and zinc (Zn) in mixed fat emulsion product by ICP-SFMS.

   Analytical data showed the amount of each specified heavy metal is well below the acceptance criterion. Also submitted information is the total volume of emulsion after three chambers are opened and mixed, which will help to determine the total amount of heavy metals to be exposed to the patients.

2. The particulate matter problem caused by (b) (4) from the stopper on the bag has been rectified. Specification for the stopper has been established with a limit of <(b) (4) ppm. A new batch for Kabiven and Perikabiven was manufactured with the new stopper, and particulate matters were monitored for up to 18 months at a long term condition. Data showed no more particulate matters were found.

   Therefore, the expiration dating period for both products can be extended to 24 months.

3. The deficiency noted for the DMF # (b) (4) (for the drug substance, (b) (4)), was corrected and it is now deemed adequate to support this NDA.

4. (b) (4) which are used in the inner layer of the bag are (b) (4) safe food contact materials.

The leachable study was performed on [redacted] (b) (4) and the data submitted in [redacted] (b) (4) for the NDA 17,643 for Intralipid. After further research on [redacted] (b) (4) exposure, the non-clinical pharmacology reviewer has determined that this is not a safety concern.

5. A new supplier for [redacted] (b) (4) was proposed for Kabiven and Perikabiven, and based on the review for DMF [redacted] (b) (4), it is deemed adequate for these drug products.

Kabiven and Perikabiven contain sodium glycerophosphate, an organic form of phosphate, which is not approved in the US. Sodium glycerophosphate is manufactured by [redacted] (b) (4). This application was the first use of this material in the US as an active ingredient in a pharmaceutical preparation, therefore in the first review cycle it was considered a new molecular entity (NME).

Egg phospholipids have been extensively used as an excipient ([redacted] (b) (4)) in parenteral lipid products, but in the current products it also functions as an active ingredient since it contributes to the labeled phosphorous content of the product, along with the glycerophosphate. Since this was the first use of egg phospholipid as an active ingredient, the CMC reviewer classified egg phospholipids as an NME.

On May 13, 2014, the CMC precedence committee met and decided that there are no NMEs used in this application. The committee though did determine that sodium glycerophosphate is used as an active ingredient to supply phosphate and is therefore considered a new active ingredient.

Please refer to Dr. Tarun's review dated May 21, 2014.

4.2 Clinical Microbiology

No new data was submitted.

4.3 Preclinical Pharmacology/Toxicology

There were no non-clinical deficiencies identified in the CR letter. However, in subsequent communications with the Applicant, they were informed that in addition to deficiencies listed in the CR letter, they needed to submit a safety assessment of the extractables and leachables from the 3-CB [redacted] (b) (4) packaging system in the resubmission.

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In the resubmission, the Applicant submitted a complete safety assessment of leachables/extractables from the 3-CB (b) (4) packaging system. In his review, Dr. B. Emmanuel Akinshola, the Non-clinical reviewer, found that the calculated maximum potential exposure to the leachables/migrants under the worst case scenario was lower than or at least, equal to the PDE (permitted daily exposure) calculated from the available nonclinical data for each component of the (b) (4) 3-CB packaging system. There is a clear separation between the estimated maximum patient exposure to the migrants (or their degradation products) and the exposures considered to be safe based on animal data. Based on his review of the submitted data, Dr. Akinshola concluded that there are no safety concerns for the potential leachables/extractables from the (b) (4) 3-CB packaging system into Kabiven/Perikabiven intravenous products.

Please refer to Dr. Akinshola's review dated May 13, 2014.

4.4 Clinical Pharmacology

No outstanding issues for Clinical Pharmacology. The original pharmacology review concluded that the NDA was acceptable from a pharmacology standpoint.

See 1st cycle Clinical Pharmacology review.

4.4.1 Mechanism of Action

4.4.2 Pharmacodynamics

4.4.3 Pharmacokinetics

4.5 Office of Medication Error Prevention and Risk Management

The Applicant submitted correspondence on November 22, 2013 requesting review of their proposed proprietary names, Kabiven (for the central formulation) and Perikabiven (for the central/peripheral formulation). OMEPM reviewed this request and found the proposed proprietary names of Kabiven and Perikabiven acceptable.

4.6 Center for Devices and Radiological Health

A consult was requested from CDRH to re-evaluate the device constituent of this combination product. The review focused on resolving device engineering deficiencies that were identified in the CR letter, i.e. leaking, burst, dropping and infusion port leaking. CDR Alan Stevens, the CDRH reviewer, determined that the engineering deficiencies that were identified in the CR letter were adequately addressed and resolved. CDR Stevens noted that no additional device engineering deficiencies remain.

Please refer to CDR Stevens review dated December 6, 2013.

4.7 Division of Medication Error Prevention and Analysis (DMEPA)

A review was requested of DMEPA to evaluate the Human Factor/Usability Study results, revised prescribing information and container labels provided by the Applicant in the re-submission.

The applicant submitted the results of a supplemental summative study involving trained pharmacists and pharmacy technicians as requested by the Agency. DMEPA found the study design acceptable and no use errors or close call were observed during the study. DMEPA concluded that the Applicant adequately addressed the failures cited in the previous review (OSE review #2012-937 dated July 20, 2012). Dr. Denise Baugh, the DMEPA reviewer also noted that though it is unlikely that all pharmacy staff will receive the same training as that in the study, it is also unlikely that new PN products would be introduced into this clinical setting without staff having access to the necessary training to support safe use.

Dr. Baugh also reviewed submitted results of a summative study involving self-trained home care nurses as it is recognized that the home is a setting where this product may be used. One participant in this study did not fully activate the bag (i.e., parts of the vertical seal between the lipid and amino acid chambers remained closed) and this error was attributed to the user. The Applicant states that the participant did not appear to read the IFU, the illustrated user guide, and was distracted while the training video was playing. Please refer to DMEPA full review dated April 14, 2014.

The Applicant noted that no further revisions to the container label or prescribing information are necessary in light of the results from the 2 studies. DMEPA agree with the Applicant and noted that the IFU provides detailed diagrams appropriately located (e.g., adjacent to the narrative), use of bold and large font sizes to increase the prominence of important statements on the bag label, and appropriate use of

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redundancy (e.g., identical information in the section titled “Read This” on the over pouch labeling and the bag label). DMEPA found the proposed container label and prescribing information acceptable.

Dr. Baugh determined that the Applicant adequately addressed and resolved the Human Factors Assessment deficiencies in the CR letter.

Please refer to Dr. Baugh’s review dated April 14, 2014.

4.8 CDRH Human Factors Review

CDRH Human Factors was requested to review two human factors validation study reports submitted by the Applicant. Dr. QuynhNhu Nguyen, CDRH Human Factors reviewer, found the results of the studies acceptable. She noted that human factors training validation study showed that training was an effective mitigation to reduce use errors associated with your 3-chamber parenteral nutritional bag. The human factors study with homecare nurses underscored the effectiveness of this mitigation. Dr. Nguyen recommended that the applicant specify training as a requirement in their Instructions for Use and other device labeling, and ensure that the in-service training guide will be used consistently in the training program.

Dr. Nguyen determined that the Applicant adequately addressed and resolved the Human Factors Assessment deficiencies in the CR letter.

Please refer to Dr. Nguyen’s review dated April 22, 2014.

5 Sources of Clinical Data

5.1 Tables of Studies/Clinical Trials

No new clinical trials were submitted to evaluate safety and efficacy of the drug products.

See 1st review cycle clinical review

5.2 Review Strategy

NA

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5.3 Discussion of Individual Studies/Clinical Trials

NA

6 Review of Efficacy

Efficacy Summary

During the first review cycle, efficacy of this application was assessed by a clinical pharmacology study. The Applicant submitted a relative bioavailability study (Study Glyc-001-CP1) to provide pharmacokinetic bridging of the phosphate moiety in order to justify the change from inorganic phosphate to sodium glycerophosphate (novel organic phosphate source) that is proposed for use in both Kabiven and Perikabiven.

The results of Study Glyc-001-CP1 demonstrated comparability of phosphate provision from the new organic sodium glycerophosphate to that of equimolar doses of the approved inorganic phosphate. The relative bioavailability results supported incorporation of sodium glycerophosphate as a source of phosphate provision into the proposed PN products.

The Applicant submitted eleven supportive Kabiven and Perikabiven clinical trials. None of the clinical trials had clinical efficacy endpoints, but three of the Kabiven trials had laboratory efficacy assessments.

The reader is referred to the first cycle review for additional information.

No new efficacy data was submitted during this review cycle.

6.1 Indication

KABIVEN™ is indicated for intravenous infusion into a central vein as a source of calories, protein and essential fatty acids for

- Patients requiring parenteral nutrition
- Prevention of essential fatty acid deficiency (b) (4)
- (b) (4) or treatment of negative nitrogen balance

PERIKABIVEN™ is indicated for intravenous infusion into a peripheral or central vein as a source of calories, protein and essential fatty acids for

- Patients requiring parenteral nutrition
- Prevention of essential fatty acid deficiency (b) (4)
- (b) (4) or treatment of negative nitrogen balance

6.1.1 Methods

NA

6.1.2 Demographics

NA

6.1.3 Subject Disposition

NA

6.1.4 Analysis of Primary Endpoint(s)

NA

6.1.5 Analysis of Secondary Endpoints(s)

NA

6.1.6 Other Endpoints

NA

6.1.7 Subpopulations

NA

6.1.8 Analysis of Clinical Information Relevant to Dosing Recommendations

NA

6.1.9 Discussion of Persistence of Efficacy and/or Tolerance Effects

NA

6.1.10 Additional Efficacy Issues/Analyses

NA

7 Review of Safety

Safety Summary

The safety issues related to this application include the need for pediatric safety studies to assess safe and effective dosing of these products in this population and the presence of phytosterols in IVFE component of these products and their safety implications.

Because nutritional needs vary based on the age and weight of the patient, and because Kabiven and Perikabiven are fixed dose combinations, these products are not appropriate or adequate to meet the nutritional needs of pediatric patients below a certain weight or age. Therefore, a partial waiver for pediatric patients less than 2 years of age is appropriate on the grounds that the products fail to represent a meaningful therapeutic benefit over existing therapies for pediatric patients **and** is unlikely to be used in a substantial number of all pediatric age groups or the pediatric age group(s). A deferral of studies in pediatric patients ages 2 to 16 years is acceptable.

Phytosterols are impurities present in IVFE products and their presence is a potential safety issue. Phytosterols have been implicated as a causative factor of parenteral nutrition associated liver disease (PNALD), especially in pediatric and neonatal patients. As a potential safety issue, there is a clinical need to assess/characterize the sterols found in these products. (b) (4), (b) (5)

The Applicant reported that no additional clinical studies/trials have been conducted with Kabiven or Perikabiven since the filing of the NDA. Therefore, no updated safety information related to studies/clinical trials is available for this sub-mission.

The Applicant did submit Periodic Safety Update Report (PSUR) 009/01 (FEB 2011 to JAN 2013). Based on the current safety data for Kabiven and Perikabiven, the safety profile has not altered. This current PSUR submitted by the Applicant did not identify any new safety hazards.

Kabiven is registered in 61 countries and Perikabiven is registered in 67 countries. The Applicant reported no changes in foreign labeling. During the period covered by the report, no actions related to safety have been taken by regulatory authorities. The Applicant reported that a review of the literature revealed no new or yet unknown risks

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in relation to the administration of Kabiven and Perikabiven, which would require a change of the risk-benefit-ratio.

7.1 Methods

NA

7.1.1 Studies/Clinical Trials Used to Evaluate Safety

NA

7.1.2 Categorization of Adverse Events

NA

7.1.3 Pooling of Data Across Studies/Clinical Trials to Estimate and Compare Incidence

NA

7.2 Adequacy of Safety Assessments

NA

7.2.1 Overall Exposure at Appropriate Doses/Durations and Demographics of Target Populations

NA

7.2.2 Explorations for Dose Response

NA

7.2.3 Special Animal and/or In Vitro Testing

NA

7.2.4 Routine Clinical Testing

NA

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7.2.5 Metabolic, Clearance, and Interaction Workup

NA

7.2.6 Evaluation for Potential Adverse Events for Similar Drugs in Drug Class

NA

7.3 Major Safety Results

Please refer to 1st cycle review

7.3.1 Deaths

7.3.2 Nonfatal Serious Adverse Events

7.3.3 Dropouts and/or Discontinuations

7.3.4 Significant Adverse Events

7.3.5 Submission Specific Primary Safety Concerns

7.4 Supportive Safety Results

Please refer to 1st cycle review

7.4.1 Common Adverse Events

7.4.2 Laboratory Findings

7.4.3 Vital Signs

7.4.4 Electrocardiograms (ECGs)

7.4.5 Special Safety Studies/Clinical Trials

7.4.6 Immunogenicity

7.5 Other Safety Explorations

Since the original review of NDA 200656, the Division has become aware of an unexpected serious risk of liver injury in pediatric and neonatal patients, which may be related to the presence of phytosterols. Phytosterols have been implicated as a causative factor of parenteral nutrition associated liver disease (PNALD). PNALD is believed to occur in stages starting with parenteral nutrition associated cholestasis (PNAC), the predominant presentation in infants. As PNAC progresses to PNALD, the process can lead to a high incidence of morbidity and mortality. The Division considers this information to be "new safety information" as defined in section 505-1(b)(3) of the FDCA.

Phytosterols are an impurity present in IVFE products and their presence is a potential safety issue. As a potential safety issue, there is a clinical need to assess/characterize the sterols found in these products. (b) (4), (b) (5)

(b) (4)

(b) (4)

Also refer to 1st cycle review.

Medical Reviewer's comments: (b) (4) .

7.5.1 Dose Dependency for Adverse Events

7.5.2 Time Dependency for Adverse Events

7.5.3 Drug-Demographic Interactions

7.5.4 Drug-Disease Interactions

7.5.5 Drug-Drug Interactions

7.6 Additional Safety Evaluations

Refer to 1st cycle review

7.6.1 Human Carcinogenicity

7.6.2 Human Reproduction and Pregnancy Data

7.6.3 Pediatrics and Assessment of Effects on Growth

In the US, RLDs have various pediatric approvals. Intralipid is approved for all pediatric age groups. Aminosyn II is not recommended for use in infants but may be used in older pediatric populations; however pediatric studies are not included in labeling. Both Novamine and Clinimix E include general recommendations for pediatric use down to

birth, but labeling states that the safety and effectiveness of the products in pediatric patients have not been established by adequate and well-controlled studies.

Per the Applicant, Kabiven and Perikabiven are labeled in the European Union for use in pediatric patients 2 years of age and older and carry a contraindication for use in pediatric patients under the age of 2 years of age because the product does not contain the amino acids cysteine and taurine which are considered to be essential in neonates and young infants.

Under the Pediatric Research Equity Act (PREA), all applications for a new active ingredient, new indication, new dosage form, new dosing regimen, or new route of administration must include a pediatric assessment that is adequate to assess the safety and effectiveness of the product and to support dosing and administration for all relevant pediatric populations, unless requirement is waived, deferred, or inapplicable. As combination products, Kabiven and Perikabiven qualify as a new active ingredient.

In the first review cycle, the Applicant submitted a request (b) (4)

(b) (4)

During the 1st review cycle, a consult was obtained from Pediatric Maternal Health Staff to assess the Applicant's proposal. At that time the PMHS reviewer, recommended that (b) (4)

The applicant's request [redacted] (b) (4) was denied by the Division. In the CR letter, the Applicant was informed that they would need to submit the following:

[redacted] (b) (4)

In this complete response re-submission the Applicant requested [redacted] (b) (4) and a deferral of trials in pediatric patients ages 2 to 16 years. (b) (4) [redacted] The Applicant also proposed [redacted] (b) (4) The Applicant's proposed [redacted] (b) (4) [redacted]

The criteria for a full or partial waiver under PREA are the following:

1. Necessary studies are impossible or highly impracticable (because, for example, the number of patients is so small or the patients are geographically dispersed).

2. The product would be ineffective or unsafe in one or more of the pediatric group(s) for which a waiver is being requested. Note: If this is the reason the studies are being waived, this information must be included in labeling.
3. The product fails to represent a meaningful therapeutic benefit over existing therapies for pediatric patients **and** is unlikely to be used in a substantial number of all pediatric age groups or the pediatric age group(s) for which a waiver is being requested.

In addition, a partial waiver can be granted if the applicant can demonstrate that reasonable attempts to produce a pediatric formulation necessary for that age group have failed.

The Applicant requested a waiver for pediatric patients less than 2 years of age based on criteria [redacted] (b) (4) #3 above.

In the re-submission pediatric plan the Applicant proposes to conduct one safety study in pediatric patients aged 2 to 16 years. Previously, the Applicant proposed (b) (4)

On May 9, 2014, the Applicant submitted a revised and updated proposed timelines for the proposed trial. The proposed timelines are:

- Protocol Submission: Final clinical study protocol submission to FDA will be made within (b) (4)
- Study initiation (first patient in): (b) (4) months after submission of the protocol. Expected date for initiation: (b) (4)
- Study completion (last patient out): approximately 24 months from the first subject in date. Expected date of completion: (b) (4)
- Submission of final clinical study report: approximately 6 - 12 months after study end (last patient last visit). Expected date of completion: (b) (4)

In this re-submission a PMHS consult was again requested to review and advice on the Applicant's proposed waiver and deferral of pediatric studies for Kabiven and Perikabiven under PREA and pediatric sections of labeling. In her consult review, Dr. Donna Snyder, PMHS reviewer, determined that the Applicant did not (b) (4) additional data is needed to support the waiver request under criteria #3.

(b) (4)

(b) (4) However, PMHS suggests that a statement regarding the absence of cysteine and taurine be included in the pediatric use section.

The product fails to represent a meaningful therapeutic benefit over existing therapies for pediatric patients **and** is unlikely to be used in a substantial number of all pediatric age groups or the pediatric age group(s) for which a waiver is being requested.
Dr. Snyder stated that the applicant submitted an argument that the Kabiven and Perikabiven do not provide a meaningful benefit over other available products on the market and has requested a waiver for pediatric patients less than 2 years of age. According to the applicant, there are 76 approved amino acid solutions, some of which are especially formulated for pediatric patients that may be a better choice for these patients.

Kabiven and Perikabiven contain lipid, protein (amino acids), and carbohydrates, and the requirements for these components differ by weight, Dr. Snyder therefore performed calculations to determine the utility of the products at several patient weights. Dr. Snyder stated that because use of these products in the younger and lower weight pediatric patients (less than 2 years of age or less than 12 kg for Perikabiven and 10 kg for Kabiven) would require the supplementation of protein (amino acids) **and** glucose in order to meet the nutritional needs of the patient, use of these products below these weights may be unlikely and may not provide a benefit over use of individual lipid, amino acid and electrolyte solutions. A partial waiver for this rationale may be reasonable.

PMHS recommended that the Division request that the applicant provide additional information to support a waiver for this rationale. Because nutritional needs vary based on the age and weight of the patient, and because Kabiven and Perikabiven are fixed dose combinations, these products may not be appropriate to meet the nutritional needs of pediatric patients below a certain weight or age. PMHS also agrees that additional safety studies are warranted (b) (4) .
On May 30, 2014, as a result of an Information Request (IR) the Applicant provided age and weight nutritional calculations based on American Academy of Pediatrics (AAP) and A.S.P.E.N. recommendations for the fixed combination products Kabiven and Perikabiven. Pediatric patients < 2 years of age generally require specific, individually compounded PN.

Based on the nutritional calculations provided, the PMHS review team and the Division agreed that Kabiven and Perikabiven may not provide adequate nutrition for patients < 2 years of age. Therefore, a partial waiver for pediatric patients less than 2 years of age is appropriate on the grounds that the product fails to represent a meaningful

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therapeutic benefit over existing therapies for pediatric patients **and** is unlikely to be used in a substantial number of all pediatric age groups or the pediatric age group(s).

The Applicant's basis for deferral request is "the drug or biological product is ready for approval for use in adults before pediatric studies are complete (FD&C Act, section 505B(a)(3)(A)(i))," Kabiven and Perikabiven are fixed combination products for parenteral nutrition. (b) (4)

The partial waiver and deferral plans were presented to the PeRC PREA Subcommittee on June 18, 2014. The PeRC agreed with the Division to grant a partial waiver in patients < 2 years of age and deferral of trials in patients ≥ 2 years of age. The proposed pediatric trial, *"Safety and tolerance of Kabiven in pediatric patients ages 2 to 16 years requiring parenteral nutrition: A prospective, controlled, randomized, open-label study."* The PeRC also agreed with the Division's plan to study Kabiven first because it is a centrally administered product. If there are no new safety or efficacy issues identified with Kabiven then the PeRC agreed that studies in Perikabiven would not be needed.

Please refer to Dr. Snyder's complete review dated May 21, 2014.

Medical Reviewer's comments: The Division, PMHS and PeRC all agree to grant a partial waiver in patients < 2 years of age and deferral of trials in patients ≥ 2 years of age. The Applicant's basis for deferral of clinical trials is acceptable. The Applicant's proposed trial must include adequate representation of all pediatric age groups.

Since the course of the disease, inadequate nutritional state when other forms of nutrition are inadequate or contraindicated, and the effects of the drugs are sufficiently similar in adults and pediatric patients, this reviewer agrees that a determination of efficacy of these products as a source of nutrition in the pediatric population could be based on data from the adult trials.

7.6.4 Overdose, Drug Abuse Potential, Withdrawal and Rebound

NA

7.7 Additional Submissions / Safety Issues

NA

8 Postmarket Experience

Kabiven is registered in (b) (4) countries and Perikabiven is registered in (b) (4) countries. The Applicant reported for no changes in foreign labeling. During the period covered by the report, no actions relating to safety have been taken by regulatory authorities.

The Applicant reported that a review of the literature revealed no new or yet unknown risks in relation to the administration of Kabiven / Perikabiven, which would require a change of the risk-benefit-ratio.

Approximately, (b) (4) patients have been treated with Kabiven and Perikabiven from February 2011 to January 2013 based on the calculation with average treatment duration of 5 days with patients receiving an average dose of one unit of Kabiven / Perikabiven per day. During the period from February 1, 2011 to January 31, 2013, sixteen Individual Case Safety Reports (ICSRs) were reported in relation to drug administration. The Applicant reported that causality is unlikely in these cases.

Medical Reviewer's comments: After review of the case safety reports provided by the Applicant of these spontaneous reports, each case had multiple confounding factors. This reviewer though agrees with the Applicant's interpretation that causality is unlikely due to the drug.

9 Appendices

9.1 Literature Review/References

None

9.2 Labeling Recommendations

The Kabiven and Perikabiven draft labels were reviewed by multiple disciplines and offices.

The Office of Prescription Drug Promotion recommended including information regarding serious warning and precautions regarding sepsis (section 5.3 in the label)

and metabolic effects (section 5.4 in the label) in the Highlights sections for completeness (see memo in DARRTS dated April 30, 2014).

The Maternal Health Staff was consulted to review the label, specifically subsections 8.1 and 8.3. Dr. Carrie Ceresa, the MHS reviewer, concluded that A Pregnancy Category C classification is appropriate for both Kabiven and Perikabiven labeling based on the lack of adequate and well controlled studies in pregnant women and a lack of animal reproduction studies. In her review, Dr. Ceresa notes that the pregnancy subsection of the labeling was structured in the spirit of the proposed PLLR, while complying with current labeling regulations. The nursing mothers subsection of labeling was revised to comply with current labeling recommendations (see memo in DARRTS dated May 13, 2014).

Dr. Baugh, the DMEPA reviewer, found the proposed container label and prescribing information acceptable (see section. (see section 4.7)

Dr. QuynhNhu Nguyen, CDRH Human Factors reviewer, recommended that the applicant specify training as a requirement in their Instructions for Use and other device labeling, and ensure that the in-service training guide will be used consistently in the training program (see section 4.8).

Dr. Donna Snyder, PMHS reviewer, recommended that the Pediatric Use subsection describe what is known and unknown about use of the drug in the pediatric population, including limitations of use, and must highlight any differences in efficacy or safety in the pediatric population versus the adult population. PMHS supplied labeling recommendations based on recently reviewed lipid and parenteral nutrition products. Intravenous fat emulsions (Intralipid) include a boxed warning for a risk of death in neonates related to intravascular fat accumulation in the lungs. Intravenous fat emulsions also contain a warning for Parenteral Nutrition Associated Liver Disease. Dextrose bundles labeling recommends close monitoring in newborns, particularly premature and low birth weight infants, to avoid the risk of hypo or hyperglycemia. Because Kabiven and Perikabiven will not be approved for use in pediatric patients, information otherwise should be limited to Section 8.4, Pediatric Use with appropriate cross-references to Warnings and Precautions for the specific risks identified for pediatric patients.

Medical Reviewer's comments: This reviewer agrees with the recommendations of the various disciplines regarding the label. These recommendations will be incorporated into the label and negotiated with the Applicant.

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9.3 Advisory Committee Meeting

None

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/s/

KARYN L BERRY
08/13/2014

RUYI HE
08/13/2014

FDA CENTER FOR DRUG EVALUATION AND RESEARCH

MEMORANDUM

DATE: November 20, 2011

TO: NDA 200656
Kabiven and Perikabiven (lipid injectable emulsion with amino acids and electrolytes and dextrose)
APP Pharmaceuticals, LLC (a Fresenius Kabi company)

FROM: Julie Beitz, M.D.
Director, Office of Drug Evaluation III

RE: Complete Response Action

Kabiven and Perikabiven (lipid injectable emulsion with amino acids and electrolytes and dextrose) are total parenteral nutrition systems. The products are a source of calories, protein and essential fatty acids for patients requiring parenteral nutrition a (b) (4) the prevention of essential fatty acid deficiency (b) (4) or treat negative nitrogen balance (b) (4) (b) (4)

Kabiven and Perikabiven are designed to provide sterile solutions using innovative 3-chamber bag technology. Kabiven is administered by central vein only, whereas Perikabiven may be administered by either central or peripheral vein. The applicant proposes tha (b) (4) .

This memorandum documents my concurrence with a complete response action for the Kabiven and Perikabiven products.

Before this application may be approved, the applicant will need to address several deficiencies. The applicant has not provided sufficient information to (b) (4) To address this deficiency, the

applicant must submit [redacted] (b) (4)

The applicant will need to address deficiencies regarding device performance. Use-related hazards will need to be identified and mitigated; appropriate human factors studies will be needed to address any specific hazards that are identified.

Information submitted did not delineate the levels of selected heavy metals that may be present in each chamber of the 3-chamber bag. The applicant will need to submit this information and develop specifications and acceptance criteria to control the levels of these heavy metals in each chamber.

The applicant must confirm that the primary container/closure system (i.e., [redacted] (b) (4) .

Discussions regarding product labeling and postmarketing study requirements or commitments remain unresolved. Satisfactory resolution of deficiencies identified during the inspection of the [redacted] (b) (4) manufacturing facilities in [redacted] (b) (4), and the Fresenius Kabi manufacturing facility in Sweden is required before the application may be approved.

In addition, in the complete response letter, the applicant will be notified that deficiencies involving DMF # [redacted] (b) (4) were conveyed by the Agency on August 31, 2011 to the DMF holder, [redacted] (b) (4) These deficiencies will need to be addressed before the application may be approved.[1]

Product Description

Kabiven and Perikabiven are sterile parenteral nutrition products, each comprised of [redacted] (b) (4) drug substances representing seventeen amino acids, [redacted] (b) (4) electrolytes, glucose monohydrate, and purified soybean oil. The products are designed so that the dextrose solution, the amino acid and electrolyte solutions, and the fat emulsion are each contained between the chambers are broken and their contents are admixed. An additive port provides flexibility to include vitamins and other ingredients. Kabiven is manufactured in four packaging sizes delivering a total of 1026, 1540, 2053, or 2566 mL; Perikabiven is manufactured in three sizes: 1440, 1920 and 2400 mL.

There are currently no 3-chamber bag products approved in the US that provide an all-in-one source of total parenteral nutrition. Individually approved 1-chamber or 2-chamber bag products are co-administered to provide the necessary nutritional requirements.

Regulatory Considerations

Kabiven and Perikabiven are manufactured by Fresenius Kabi and have been approved in Sweden since 1999 for adults and pediatric patients 2 years of age and above. Kabiven

[1] These deficiencies involve controls for impurities in the [redacted] (b) (4) drug substance. *See* **Product Quality**.

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and Perikabiven have been registered in 58 and 53 countries, respectively.

On January 28, 2011, APP Pharmaceuticals, LLC, a subsidiary of Fresenius Kabi, submitted NDA 200656 for Kabiven and Perikabiven. In accordance with previous Agency advice, the application was submitted as a 505(b)(2), and referenced the Agency's findings of safety and effectiveness for the following products:

1. Intralipid 20% Injection, NDA 018449 (Fresenius Kabi Deutschland Gmbh)
2. Intralipid 20% Injection, NDA 020248 (Fresenius Kabi Deutschland Gmbh)
2. Novamine 11.4% Injection, NDA 017957 (Hospira, Inc.)
3. Aminosyn II 3.5%, with electrolytes in dextrose injection with calcium, NDA 019683 (Hospira, Inc.)
4. Clinimix E 2.75/10 Injection, sulfite-free with electrolytes, NDA 020678 (Baxter Healthcare Corp.)

The intravenous fat emulsion component of Kabiven and Perikabiven is identical to that of approved Intralipid 20%. The amino acid component, (b) (4) (b) (4) approved Novamine 11.4% (e.g., (b) (4) , whereas Novamine contains (b) (4)). The dextrose component differs between the two products, as Kabiven and Perikabiven contain (b) (4)% and (b) (4)% dextrose, respectively. The electrolyte components of Kabiven and Perikabiven do not exactly correspond to that of Aminosyn II 3.5% or Clinimix E; in particular, Kabiven and Perikabiven contain sodium glycerophosphate, an organic form of phosphate. Sodium glycerophosphate is hydrolyzed *in vivo* by nonspecific phosphatases to release phosphate. The applicant contends that this organic form of phosphate (b) (4) a potentially life-threatening complication that can be associated with inorganic phosphate. Although sodium glycerophosphate is commercially available under monograph, this is the first use as an active ingredient in a drug product, and is, therefore, considered a new molecular entity.

Sodium glycerophosphate provides for (b) (4)% of the phosphate in Kabiven and Perikabiven. The remaining (b) (4)% is derived from egg phospholipid, used as an (b) (4) in the Intralipid component. Because of the relatively large amount of phosphate that is contributed by egg phospholipid, it is considered to be an active ingredient rather than an excipient. As this is the first use of egg phospholipid as an active ingredient in a drug product, it is also considered a new molecular entity.

This application was not referred to the Gastrointestinal Drugs Advisory Committee for discussion because the application did not raise significant safety or efficacy issues, the application did not raise significant public health questions on the role of the products in the diagnosis, cure, mitigation, treatment or prevention of a disease, and outside expertise was not necessary.

Hospira, Inc. submitted a request to withdraw NDA 019683 for Aminosyn II 3.5% Injection on (b) (4), and on (b) (4), a request to withdraw NDA 017957 for Novamine 11.4% Injection. Hospira stated that the products were not currently marketed and the withdrawal requests were not associated with any safety or

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efficacy concerns. This application refers to these listed drugs. Before this application may be approved, the Agency will need to determine whether Aminosyn II 3.5% Injection and Novamine 11.4% Injection were withdrawn for reasons of safety or effectiveness. Since the application will not be approved during this review cycle, the Agency's determination will be deferred to the next review cycle.

On November 4, 2011, the Agency informed the applicant in writing that deficiencies in the application preclude discussion of product labeling and postmarketing commitments or requirements.

The applicant, APP Pharmaceuticals, LLC, a wholly owned subsidiary of Fresenius Kabi, submitted a letter from Fresenius Kabi dated November 11, 2011 granting right of reference to NDA 018449. Therefore, APP no longer needs to rely upon the Agency's finding of safety and effectiveness for Intralipid 20% because they can now reference the data in NDA 018449 directly.

Clinical Pharmacology

Formal pharmacokinetic bridging for all active components was not deemed necessary. However, to support the inclusion of sodium glycerophosphate, a new molecular entity, in the Kabiven and Perikabiven products, the applicant submitted the results of two relative bioavailability studies. Study Glyc-001-CP1 compared phosphate provision from equimolar doses (a total of 80 mmol infused over 4 hours) of two different phosphate sources (IPhosphate, Hospira, Inc. vs. Glycophos, Fresenius Kabi) in 24 healthy volunteers, ages 18-45 years. The products were infused via peripheral vein. The phosphate content of meals and water was standardized. The pharmacokinetic profile of the two different phosphate sources was found to be similar, though not strictly bioequivalent on all parameters.

Study KABI-003-CP1 explored the relative bioavailability of phosphate provision from organic sodium glycerophosphate administered alone compared to administration as a component of Perikabiven in 10 healthy volunteers, ages 18-45 years. Equimolar amounts of phosphate were provided as either Perikabiven (0.101 mmol phosphate/13.3 mL Perikabiven/kg body weight) or as Glycophos (0.101 mmol Glycophos/13.3 mL NaCl/kg body weight). The products were infused over 8 hours. No significant differences in serum phosphate levels were observed when sodium glycerophosphate was given alone or as a component of Perikabiven. Results from this study however were not considered supportive due to confounding by the contribution of phosphate from food sources that exceeded study drug doses.

Efficacy

Results from ten randomized and one open-label clinical trial conducted in adult patients requiring parenteral nutrition were submitted in support of the efficacy of Kabiven and Perikabiven. These trials were of short duration (7 days) with the exception of one trial which was 4 weeks in duration. None of the Perikabiven trials administered the product via central vein. None of the active comparator products in these trials have been approved for use in the US, and only three trials were designed with pre-defined analyses of efficacy. Nonetheless, laboratory assessments in patients receiving Kabiven products

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or comparators produced similar results, including assessments of: serum amino acid and fatty acid patterns, serum levels of pre-albumin, insulin, triglycerides, urea, creatinine, and C-reactive protein, and urinary excretion of amino acids, nitrogen, urea and creatinine.

Safety

Parenteral nutrition products are associated with a number of well-recognized safety concerns. These include the risk of 1) clinical toxicity from heavy metal contamination of product components during their manufacture (e.g., chromium and manganese toxicities), 2) metabolic complications such as hyperglycemia or hypoglycemia, refeeding syndrome, electrolyte imbalances, lipid abnormalities, acid-base disturbance, hepatobiliary disorders and bone disease, and 3) complications related to vascular access, including catheter occlusion and thrombosis, and catheter-related infection and sepsis.

A total of 145 subjects have received Kabiven and 93 have received Perikabiven in clinical trials. The mean age of subjects treated with Kabiven was 59 years, and the mean body mass index (BMI) was 24 kg/m^2. The mean age of subjects treated with Perikabiven was 57 years and the mean BMI was 22 kg/m^2. There were no treatment-related deaths or serious adverse events. Treatment-emergent adverse events considered to be related to Kabiven or Perikabiven occurred in 21% and 15% of subjects, respectively. The most common adverse events reported in Kabiven-treated subjects were nausea (15%), pyrexia (9%), and hypertension (8%); hyperglycemia was reported in 2% and hypokalemia in 4%. The most common adverse events reported in Perikabiven-treated subjects were hyperglycemia (5%), hypokalemia (4%), and pyrexia (4%); nausea was noted in only 2%.

Injection site reactions were assessed using the modified Maddox score in Perikabiven-treated subjects receiving the product via peripheral vein. Six subjects developed a palpable venous cord greater than 3 inches above the IV site, and one subject experienced frank vein thrombosis.

Kabiven and Perikabiven contain soybean oil and egg phospholipid which may rarely cause allergic reactions. Cross-allergic reactions have been reported between soybean and peanut oil. For these reasons, foreign regulatory authorities have required that the product labels carry a contraindication for patients with hypersensitivity to egg, soy or peanut protein.

Device Considerations

The Center for Devices and Radiologic Health (CDRH), General Hospital Devices Branch, was consulted to evaluate device performance, biocompatibility and human factors.

Kabiven and Perikabiven are delivered using bags produced from [redacted] (b) (4) There were no deficiencies noted with regard to biocompatibility.

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The following deficiencies, identified with regard to device performance and human factors, will need to be addressed before this application may be approved.

- **Device performance**

1. The applicant performed a test to demonstrate the resistance of the (b) (4) packaging to temperature, pressure and leakage, however it is unclear whether altitude was accounted for as part of the testing regimen. CDRH believes that it is more relevant to demonstrate the pressure at which the (b) (4) bag bursts. If the burst pressure significantly exceeds (for example, by a factor of 2) the typical atmospheric pressures expected with higher altitudes, then concerns of the bag bursting at these altitudes will have been mitigated. The applicant should repeat the testing regimen to determine burst pressure and utilize appropriate statistical methods to determine sample size and to interpret the test results.

(b) (4)

3. The applicant performed a test to demonstrate that the injection point does not leak when it is punctured by a 23 gauge needle. It appears that the septum at the injection point was punctured only once before subjecting the bag to a 20 kPa pressure. However, from the device description provided, it appears that one of the points is utilized to spike the bag with medication after the contents are mixed. It is conceivable that this septum would be penetrated multiple times prior to beginning the infusion. Also, it is unclear whether the 23 gauge needle will adequately test the non-coring nature of the septum at the injection point. Therefore the applicant should a) clarify whether the injection point could be penetrated multiple times, and if so, modify the test to account for multiple punctures, prior to testing the bag for leakage, and b) test the injection point leakage after the septum is punctured with a 19 or 21 gauge needle, needle gauges that are more representative of an extreme needle size for penetrating the injection point septum.

- **Human factors assessment**

Although the (b) (4) bag will only be utilized by health care providers, after evaluating the packaging sample provided, CDRH reviewers found it very cumbersome to manipulate. Thus, to ensure that use-related hazards associated with using the (b) (4) bag have been successfully identified and mitigated, the applicant should perform an assessment to identify potential use-related hazards and demonstrate that these hazards are no different than the usual hazards that clinicians face when delivering drug products through other IV bags. Based on this assessment, the applicant can then determine what human factors studies should be conducted, as outlined in CDRH's *Guidance for Industry and FDA Premarket and Design Control Reviewers, Medical Device Use-Safety: Incorporating Human Factors Engineering into Risk Management*, dated July 18, 2000.

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When developing the appropriate human factors studies, consideration should be given to the following:

a. Devices and Labeling Used and Training Provided

The (b) (4) bags used in human factors studies should represent the final design and include instructions for use or any other labeling materials. The training provided to study participants should approximate the training that actual end users will receive. Participants should assess the clarity of the instructions for use and the applicant should assess the extent to which the instructions support safe and effective use of the (b) (4) bag. Study results demonstrating effectiveness of the training provided and instructions for use should be analyzed separately from the results of use performance.

b. User Tasks

The rationale for which user tasks will be included should be provided, and how many trials each participant would need to complete to adequately assess user performance. The tasks should be prioritized to reflect the relative magnitude and severity of the potential impact of inadequate task performance on the safety of the device and the user.

c. Use Environment and Conditions

Human factors studies should be conducted in an environment that includes or simulates all key aspects of the real-world environments in which (b) (4) bags would be used. Identification of potentially challenging use conditions should be anticipated, and use of the bags under such conditions should be evaluated. The applicant should describe the testing environment and realism of the simulated use and justify their appropriateness for use in human factors studies.

d. Study Participants

For devices that are intended to be marketed in the US, human factors studies should be conducted in the US with (American) English speaking participants. A minimum of 15 participants from each major user group should be tested. Participants should be representative of the intended end-user populations. If users with distinctly different characteristics (e.g., skill sets or experience levels) will use the bags, you should include 15 from each distinct group. A rationale that supports that these groups are representative of the overall population of users for the device should be provided. Participants should not be the applicant's own employees, or those that have been exposed to the device prior to the testing.

e. Data Collection

Data collected and analyzed in human factors studies should be described in terms of how they support the claim that the device can be used safely and effectively by the indicated users. Both empirical and qualitative data will be needed.

Empirical Data. Participants should be given an opportunity to use the device independently and in as realistic a manner as possible, without guidance, coaching, praise

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or critique from the test faciltator/moderator. Data regarding the successful or failed performance of key tasks should be measured directly rather than by soliciting participant opinions. Observation of participant behavior during the study will also permit assessment of participants' adherence to protocol and proper technique, and of any errors or problems that occur.

Qualitative Data. At the conclusion of the study, participants should be asked open-ended questions, such as, "Did you have any difficulty using this device?" "If so, can you tell me about that?" The questions should explore performance of each critical task involved in the use of the device and any problems encountered. Since the labeling and instructions for use are considered part of the user interface for the device, the questions should cover those components as well. The analysis of performance and subjective data should be directed toward understanding user performance and, particularly, task failures. The analysis should determine the nature of failures, the causes of failures, and the clinical impact. Every participant who experiences a "failure" (does something that would have led to harm under actual conditions of use), should be interviewed about that failure to determine the cause of the failure from the perspective of the participant.

f. Protocol Review

CDRH offers to review human factors study protocols to ensure that the study(ies) align with published guidance.

<u>Product Quality</u>

Heavy metal content. The potential for heavy metal contamination of components in parenteral nutrition products during manufacturing exists. Although heavy metal content was monitored for individual drug substances per USP, there was no test acceptance criterion provided for the individual chambers or for the admixed final drug product. Since the volume of product administered is large ((b) (4) to 2556 mL per 24 hours), the potential exists for exposure to heavy metal levels that exceed daily allowable limits. In addition, patients receiving parenteral nutrition often have comorbidities (e.g., acid base imbalance, cardiac or pulmonary disease, renal or hepatic impairment) and may be less tolerant of higher-than-recommended heavy metal exposures if they exist.

On September 29, 2011, the applicant was requested to provide information for Kabiven and Perikabiven on the levels of chromium, manganese, arsenic, cadmium, lead, mercury, copper, selenium, and zinc in each chamber of the 3-chamber bag. Three batches each of drug product will need to be assessed.[2] In the complete response letter, the applicant will be further requested to control the daily intake of these metals by developing specifications and acceptance criteria for the levels of heavy metals contained in each chamber.

[2] On September 30, 2011, the Agency requested all manufacturers of total parenteral nutrition products to provide information on the levels of chromium, manganese, arsenic, cadmium, lead, mercury, copper, selenium, and zinc in three batches of each manufactured product. For multiple chamber products, the levels of these metals in each chamber would need to be reported. The manufacturers were also notified that the Agency had created a DARRTS Tracked Safety Issue to track the matter.

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Stability. In correspondence dated November 01, 2011, the applicant described their ongoing stability program in which four of the nine pivotal batches demonstrated results above the acceptance limit for particulate matter. The applicant identified the particles present in the lipid chamber of the IV bag as (b) (4). The particles are thought to be caused by migration of components from the stopper. A teleconference was held on November 4, 2011 with Office of New Drug Quality Assessment (ONDQA) reviewers to discuss these findings.

Based on the data submitted to the NDA, an expiration dating period for the product has not been established. The Agency agreed that a (b) (4)-month expiration period may be acceptable if data from additional studies, including refrigerated conditions, support the period. The Agency also recommended that the stoppers be tested for (b) (4) levels and limits for (b) (4) content be added to the stopper specification, once an acceptable level is established. This data will need to be included in the applicant's resubmission.

Container/closure system. Although the proposed primary packaging material for the 3-chamber bag, (b) (4) the applicant must confirm that the (b) (4)

Inspection issues. The Office of Compliance has issued an overall "Withhold" recommendation for the application due to deficiencies identified during the inspection of the (b) (4). manufacturing facilities in (b) (4) and the Fresenius Kabi manufacturing facility in Sweden. Satisfactory resolution of these deficiencies is required before the application may be approved.

(b) (4) **drug substance.** The holder of DMF# (b) (4) ((b) (4)) will need to address deficiencies conveyed on August 31, 2011, involving the lack of adequate controls for unknown impurities in the (b) (4) drug substance that have been detected as a result of a change in manufacturing involving the starting material.

Pediatric Considerations

The Pediatric and Maternal Health Staff was consulted to assess the acceptability of the applicant's request that (b) (4)

In a letter dated September 8, 2011, the Agency informed the applicant that (b) (4)

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(b) (4)

Established and Tradename Reviews

ONDQA reviewers noted that the applicant's proposed established name "(b) (4)" was not acceptable because it did not take into account all of the active substances present in the product. This finding was conveyed to the applicant via correspondence on June 17, 2011, and the established name "lipid injectable emulsion with amino acids and electrolytes and dextrose" was recommended.

The Division of Medication Error Prevention and Analysis (DMEPA) expressed concerns regarding the applicant's proposed proprietary names, "Kabiven" and "(b) (4)." First, (b) (4) should be avoided since one product should be administered by central vein only while the other product can be administered by peripheral or central vein. If the (b) (4) "(b) (4) is unintentionally omitted, there is a risk that the wrong product could be administered via the wrong route. In addition, the (b) (4) "(b) (4) is misleading since that product can be given centrally or peripherally, yet the name implies only "(b) (4) administration. For these reasons, DMEPA recommended the use of two unique proprietary names.

Following a conference call on September 2, 2011, the applicant withdrew the Kabiven and (b) (4) tradenames. On September 7, 2011, the applicant submitted an amendment with new primary proposed proprietary names: "Kabiven" (for the product administered by the central venous route only) and "Perikabiven" or "(b) (4) (for the product administered by the peripheral or central venous routes). DMEPA has found the "Kabiven" and "Perikabiven" tradenames to be acceptable.

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/s/

JULIE G BEITZ
11/20/2011

Cross-Discipline Team Leader Review

Date	November 18, 2011
From	Sue-Chih Lee, Clinical Pharmacology Team Leader CDER/OTS/OCP/DCP3
Subject	Cross-Discipline Team Leader Review
NDA#	NDA 200-656
Applicant	APP Pharmaceuticals
Date of Submission & Receipt	January 28, 2011
PDUFA Goal Date	November 28, 2011
Proprietary Names / Established (USAN) names	Kabiven and Perikabiven (2 drug products) / Lipid injectable emulsion with amino acids and electrolytes and dextrose
Dosage forms / Strength	Injection/ Kabiven*: 1026 mL, 1540 mL, 2053 mL, and 2566 mL Perikabiven*: 1440 mL, 1920 mL, and 2400 mL *For the components and composition of dextrose, amino acids, electrolytes and fatty acids in Kabiven and Perikabiven, see Appendix 1 of this review.
Proposed Indication and Dosage Regimens	For intravenous infusion into peripheral or central vein (Perikabiven), or central vein only (Kabiven) as a source of calories, protein and essential fatty acids for patients who require parenteral nutrition, for prevention of essential fatty acid deficiency, [redacted] (b) (4) or treatment of negative nitrogen balance [redacted] (b) (4) (b) (4) Proposed age range: Adults [redacted] (b) (4) Dosage is individualized and dependent on the patient's clinical condition, body weight and nutritional requirement.
Recommended Action	Complete response (CR) under 21 CFR 314

NOTE: Perikabiven is designated as [redacted] (b) (4) in many documents, including the Applicant's submissions and disciplinary reviews of this NDA.

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1. Introduction

In this NDA, the Applicant is pursuing the approval of two parenteral nutrition (PN) products, Kabiven and Perikabiven. This is a 505(b)(2) submission, referencing multiple approved parenteral nutrition products.

Each of the two proposed products comprises of (b) (4) drug substances representing seventeen amino acids, (b) (4) electrolytes, dextrose monohydrate, and purified soybean oil. The products are designed so that the dextrose solution, amino acid and electrolyte solution, and fat emulsion are contained in three separate chambers of a flexible clear (b) (4) bag (Figure 1). Peelable seals separate the chambers. Prior to administration, the seals between the chambers are broken and the three fluids are allowed to mix. The mixed fluid is delivered through a single IV port. An additive port provides flexibility for adding vitamins and other ingredients as needed. Kabiven has a higher osmolarity than Perikabiven. Thus, Kabiven is intended for central vein administration only while Perikabiven is for both central and peripheral vein administration.

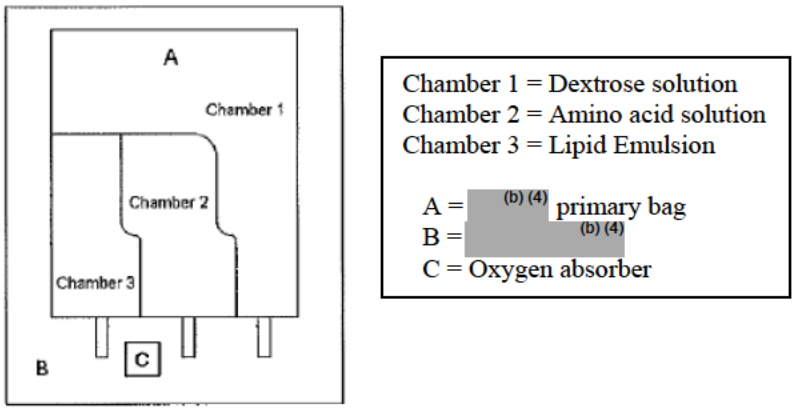

Figure 1: The three-Chamber bag

Reference ID: 3047445

Two ingredients (sodium glycerophosphate and egg phospholipid) serve as phosphate sources in the proposed products and, therefore, are considered active ingredients. As they are not active ingredients in any approved product, they are classified as NMEs in this NDA.

2. Background

Parenteral nutrition (PN) is the provision of nutrient requirements by the intravenous route to patients where the alimentary tract cannot or should not be used, gastrointestinal absorption of nutrients is impaired, metabolic requirements for protein and calories are substantially increased as with extensive burns, or morbidity or mortality may be reduced by replacing amino acids lost from tissue breakdown, thereby preserving tissue reserves. PN can either be administered via peripheral venous infusion (PPN) or through a central vein (CPN). To decrease the risk of thrombophlebitis in PPN, the osmolarity in PPN is lower than that in CPN and is generally less than 900 mOsm/L (usually with lower calcium and potassium concentrations with a final dextrose concentration between 5% to 12.5% according to the A.S.P.E.N. Parenteral Nutrition Handbook). PPN is generally not indicated for "extended periods of time." The A.S.P.E.N. guidelines for PPN recommend limiting it to short periods (up to 2 weeks). Note that the Clinical Team has communicated this point to the Applicant to revise their proposed indication so that Perikabiven [redacted] (b) (4)

2.1 Regulatory History

2.1.1 Parenteral Nutrition Drug Products

There are currently no 3-chamber bag formulations approved in the U.S. for an all-in-one, total parenteral nutrition (TPN). Individually approved 1-chamber or 2-chamber bag formulations are co-infused to provide all necessary nutrients for TPN.

In the early 1980's, it was found that some patients with end-stage renal disease on dialysis developed signs and symptoms thought to be associated with aluminum toxicity such as encephalopathy and bone pain. It was determined that aluminum present in dialysate was responsible, leading to the removal of aluminum from dialysis solutions. Aluminum accumulation in bone, serum and tissues of neonates receiving long term PN was also noted. In 2000, to address this metal toxicity issue, the FDA published a final rule that imposed certain requirements and limits for aluminum.

2.1.2 Regulatory History of Kabiven and Perikabiven Products

Kabiven was initially registered in Sweden and Denmark in 1999 and has now received registration approvals in more than [redacted] (b) (4) other countries worldwide for marketing. The Applicant indicated that more than [redacted] (b) (4) patients had been treated with the proposed products.

U.S. regulatory history: A pre-IND (105282) sponsor meeting for the proposed products was held on August 20, 2009, with a follow-up communication on January 25, 2010. These communications discussed the 505(b)(2) regulatory approach for the proposed NDA, the information needed to support the organic sodium glycerophosphate as a novel phosphate

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source and the rationale for the proposed ranges of electrolytes. Specifically, the sponsor was notified that a 505(b)(2) approach was acceptable and that both formulations could be submitted under one NDA.

2.2 Current Submission

For this 505(b)(2) application, the Applicant references four approved nutrition products (see Table 1). (Note: Although the Applicant includes Intralipid 20% as one of the reference products, this product is not considered a reference product for the 505(b)(2) purpose as it is owned by the Applicant's parent company and the Applicant has obtained the right of reference.) All four referenced products are utilized in parenteral nutrition regimens, similar to the proposed products when the enteral route is inadvisable, inadequate or not possible.

As sodium glycerophosphate is a new phosphate source to replace inorganic phosphates, the Applicant conducted nonclinical studies and two bioavailability studies to support this new source. The use of sodium glycerophosphate [redacted] (b) (4) (b) (4)

The Applicant also submitted data from 11 previously conducted small clinical trials as supporting evidence of safety and efficacy. No new clinical studies have been conducted

Table 1: Reference products as listed by the Applicant

Drug Product	NDA#	Approval Date
Intralipid 20% Intralipid 20% Pharmacy bulk package	NDA 018449 ANDA 020248	23-Jan-1981 07-Aug-1996
Novamine® 11.4% Injection	NDA 017957	03-Jan-1978
Clinimix® E Sulfite free with Electrolytes in Dextrose with Calcium (a 2-chamber bag product)	NDA 020678	26-Mar-1997
Aminosyn® II with Electrolytes in Dextrose 25% Injection with Calcium (a 2-chamber bag product)	NDA 019683	07-Nov-1988

Note: Intralipid 20% is not a reference product for the 505(b)(2) purpose.

<u>Formulations: proposed products vs. referenced approved products</u>
The formulations for the proposed products, Kabiven and Perikabiven, are given in Appendix I (Tables A1 and A2).

Specifically, the lipid component (Chamber 3) in Kabiven and Perikabiven is an emulsion for infusion identical to Intralipid® 20% (NDA 18-449), which is a soybean oil based lipid emulsion that provides essential and non-essential long chain fatty acids. As stated above, Intralipid® 20% is not considered a "reference product" for this 505(b)(2) application. Egg phospholipid in the lipid emulsion has dual functions in this application, i.e., as an [redacted] (b) (4)

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[redacted] (b) (4) and also as a source of phosphate, contributing to approximately [redacted] (b) (4) of the total phosphate in the products. Although it is considered an NME in this NDA, it is in the approved Intralipid® 20%, which precludes need of new studies to characterize this ingredient.

The amino acid content in Chamber 2 compares to that in Novamine 11.4 % (NDA 17-957) with minor modifications, including an [redacted] (b) (4) instead of a [redacted] (b) (4) (see Appendix I, Table A3). It is designated as [redacted] (b) (4) The Applicant also compares the amino acid composition to the admixture of the proposed products to that of 2 reference products (Aminosyn II 4.25% w/ Electrolytes in 25% Dextrose with Calcium; and Clinimix E Sulfite free with Electrolytes in Dextrose) (Appendix I, Table A4).

The dextrose solution in Chamber 1 was not compared to any product. Instead, the final composition of dextrose in the admixture of the proposed product (9.8% for Kabiven and 6.8% for Perikabiven) was used for comparison, which is within the range for the admixture of the approved Clinimix E sulfite free with electrolytes in dextrose with calcium (5%, 10%, 15%, 20%, 25% and 35%) (Appendix I, Table A5).

The electrolyte content in the admixture of the proposed products differs from that in the referenced Aminosyn II (NDA 19683) or Clinimix E (NDA 20-678) products (Appendix I, Table A5). However, this was discussed with the sponsor at the pre-submission meeting and a rationale in this regard was requested in the NDA for clinical review. This point is further discussed in Section 7. The electrolytes include sodium glycerophosphate (commercially available with a monograph in Ph.Eur.), [redacted] (b) (4), potassium chloride, [redacted] (b) (4) and [redacted] (b) (4). (As indicated above, egg phospholipids used as an [redacted] (b) (4) serves as another phosphate source.)

<u>Proposed dosing information:</u>
Both Kabiven and Perikabiven are packaged as 3-chamber bag products and are proposed to come in different bag sizes as shown below to better fit individual needs. Note that the Applicant proposed to use these products in patients [redacted] (b) (4)

Kabiven: 1026, 1540, 2053, and 2566 ml bags
Perikabiven: 1440, 1920, and 2400 ml bags

The four sizes of Kabiven bags are estimated to provide the option of administering a total energy content of [redacted] (b) (4) kcals/day, [redacted] (b) (4) kcals/day, [redacted] (b) (4) kcals/day or [redacted] (b) (4) kcals/day equivalent to a range from [redacted] (b) (4) kcals/kg/day for a [redacted] (b) (4) kg person if one bag is administered per day. The corresponding figures for the three bag sizes of Perikabiven are [redacted] (b) (4) kcals/day, [redacted] (b) (4) kcals/day and [redacted] (b) (4) kcals/day.

As for any parenteral nutrition products, the dose should be individualized and is dependent on the patient's clinical condition, body weight and nutritional requirements. The Applicant's proposed dosing information for Kabiven and Perikabiven is given in Tables 2-A and 2-B, respectively, which the Applicant indicated was based on the A.S.P.E.N. guidelines shown in Tables 3-A, 3-B and 3-C.

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Table 2-A: Proposed dosing information for Kabiven

Mode of Administration	Central Vein
Energy Requirement	Depends on clinical condition; often (b) (4) kcal/kg body weight/day
Dosing	(b) (4) Maximum daily dose is 40mL/kg/day. (b) (4) (b) (4) (b) (4)
Infusion Rate	Not more than 2.6mL/kg bw/hr (corresponding to 0.25g dextrose, 0.09g amino acid and 0.1g (b) (4) kg bw)
Recommended Infusion Period	12-24hr

Table 2-B: Proposed dosing information for Perikabiven

Mode of Administration	Peripheral or Central Vein
Energy Requirement	Depends on clinical condition; often 20-30kcal/kg bw/day
Dosing	(b) (4) (b) (4)
Infusion Rate	Not more than 3.7mL/kg bw/hr (corresponding to 0.25g dextrose, 0.09g amino acids, 0.13g (b) (4) kg bw)
Recommended Infusion Period	12-24hr

Table 3-A: Range of Minimum and Maximum Daily Provision of Nitrogen, Amino Acids, Dextrose, Fat, and Total Energy Based on ASPEN/ESPEN Recommended Dosing

	Daily Concentration Based on Recommended Dosing	
	Minimum	Maximum
Total nitrogen	(b) (4)	
Amino acids (protein)		
Dextrose		
Lipids (fat)		
Total energy		
Non-protein energy		

Calculations are based on a 70-kg patient and ASPEN/ESPEN guidelines using (b) (4) kcal/g dextrose, (b) (4) kcal/g lipids, and (b) (4) kcal/g protein, and (b) (4) nitrogen/g protein. Bolded numbers are from ASPEN Guidelines (Mirtallo 2004).

(b) (4)

Table 3-C: Electrolyte Provision from the Proposed Products in Comparison to Recommended Daily Requirements

ELECTROLYTE	Daily Requirements (mmol/kg)		Kabiven (mmol/daily dose[2])			(b) (4) (mmol/daily dose[2])		
	ASPEN 2004	ESPEN 2009	30mL/kg (min)	35mL/kg (maint)	40mL/kg (max)	30mL/kg (min)	35mL/kg (maint)	40mL/kg (max)
Sodium	1-2	1-1.5	(b) (4)					
Potassium	1-2	1-1.5						
Magnesium	0.06-0.14[1]	0.1-0.2						
Calcium	0.07-0.11[1]	0.1-0.15						
Phosphate/ Phosphorous	0.29-0.57[1]	0.3-0.5						
Chloride	As needed to maintain acid-base balance	1-1.5						

[1] Values are calculated to a 70 kg patient since the recommendations are in total daily dose for an individual
[2] Volume of daily dose is minimum, maximum and maintenance fluid requirements for an adult as per ASPEN and ESPEN parenteral nutrition guidelines respectively

Applicant's rationale for the three-in-one products:
The Applicant stated that the proposed products were designed to provide "all in one" total nutrient admixtures for PN for the following advantages:

- Reduced manipulation of bags and lines thereby minimizes risk of contamination.
- Reduced osmolarity of compounded mixture in Perikabiven permits its peripheral administration.
- A three-in-one product facilitates delivery and storage (particularly for patients on home parenteral nutrition) and is more cost effective with respect to preparation, handling and delivery. It is also less intimidating for patients and encourages patient mobility. Further, it facilitates pharmacy records. Additionally, labeling of bags ensures that medical and nursing attendants can easily confirm the precise composition of infused nutrients.
- Provision of energy as dextrose and fat enhances utilization compared to single energy regimens and minimizes risks of fluid overload, hypercapnia and hepatic accumulation of triglycerides.

Dr. Karyn Berry commented that the Applicant's drug development program did not evaluate risk of contamination, compliance, convenience or cost effectiveness of Kabiven/Perikabiven therapy over existing PN therapies.

2.3 Review Disciplines

The review disciplines that have provided written review documents are listed below:

- Clinical Pharmacology Review by Sandhya Apparaju/Sue-Chih Lee dated September 28, 2011
- ONDQA CMC Review by Tarun Mehta/Moo Jhong Rhee dated September 28 and November 8, 2011
- Product Quality Microbiology Review by Denise Miller/James McVey dated September 21, 2011
- CDRH Consult review by Nikhil Thakur/Jaqueline Ryan dated August 16, 2011 (in DARRTS on September 2, 2011)
- ONDQA Tertiary Review by Terrance Ocheltree dated November 8, 2011
- Pharm/Tox Review by B. Emmanuel Akinshola/Sushanta Chakder dated October 28, 2011
- Pharm/Tox Supervisory Memorandum by Sushanta Chakder dated November 8, 2011
- Clinical Review by Karyn Berry/Ruyi He dated November 15, 2011
- PMHS Review by Laurie Conklin/Hari Sachs/Lisa Mathis dated September 6, 2011
- OSI Report by Xikui Chen//Martin Yau/ Sam Haidar dated August 15, 2011
- DMEPA Proprietary Name review by Cathy A. Miller/Zachary Oleszczuk/Carol Haolquist dated November 10, 2011
- OPDP memorandum by Kathleen Klemm/Twyla Thompson/Lisa Hubbard/Shefali Doshi dated October 13, 2011

This memorandum summarizes selected information from the review documents, with primary emphasis on the issues emerged during the review. The individual reviews should be consulted for more specific details of the application.

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3. CMC

The CMC review was conducted by Dr. Tarun Mehta and Product Quality Microbiology review was conducted by Ms. Denise Miller. The tertiary review of ONDQA recommendation for "Complete Response" was conducted by Dr. Terrance Ocheltree, Director, Division of New Drug Quality Assessment II, ONDQA. In addition, the 3-chamber bag was primarily reviewed by Mr. Nikhil Thakur of CDRH. Please refer to their reviews for further details.

Overall Conclusion:
The initial ONDQA CMC review dated September 28, 2011, recommended a Complete Response action due to deficiencies associated with DMF (b) (4) for (b) (4), lack of purity assurance and adequate controls of heavy metals for the drug product, the "Withhold" recommendation from the Office of Compliance on the manufacturing and testing sites acceptability, and pending labeling issues. The Office of Compliance's "Withhold" Recommendation was updated on November 04, 2011, with the same overall recommendation. Additionally, due to a stability issue with particulate matter communicated to the FDA by the Applicant on November 1, 2011, an expiration dating period for the product cannot be established at this time. This was documented by Dr. Tarun Mehta in a review dated November 8, 2011.

The Product Quality Microbiology Review, by Denise Miller, dated September 21, 2011 recommends "to approve from a quality microbiology standpoint."

The CDRH review of the 3-chamber bag identified many issues, which are listed in Section 13.6. Only a brief summary is given in this section.

A. DRUG SUBSTANCES

The Drug Master Files (DMF) (b) (4) were reviewed for the drug substances utilized for this NDA and were found to be "Adequate" to support this NDA. Of note, egg phospholipid, which is commonly used as an excipient, is treated as a drug substance due to its contribution of phosphate to the drug product. This DMF (DMF (b) (4)) was found "Adequate" to support NDA 200-656. However, the DMF for the drug substance (b) (4) (DMF (b) (4)) by (b) (4) has been found to be "Inadequate" by Dr. Mehta to support this NDA. Specifically, the heavy metals and impurities in (b) (4) are not adequately assessed. The DMF holder has been notified of the deficiencies.

B. DRUG PRODUCTS

Dr. Mehta assessed the CMC for the drug product and found it acceptable except for the heavy metal limits. Chemical and physical in-use stability of the mixed three chamber bag was demonstrated for twenty-four hours for infusion at room temperature (25°C/77°F). The drug product was also found stable after 36 hours of refrigerated and room temperature cycle testing. Product should be used immediately after mixing and when additions have been made. If not used immediately, the in-use storage time and conditions prior to use should normally not be

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stored longer than twenty-four hours at 2°C to 8°C /36°F to 46°F. However, a stability issue related to particulate matter was revealed in November 2011, prompting a discussion between the Agency and sponsor.

Dr. Mehta reviewed the chemical aspect of the 3-chamber bag and indentified a deficiency in that the (b) (4) does not have (b) (4) Characterization of other properties (such as mechanical and biocompatibility testing) of the bag was reviewed by CDRH.

Heavy metal content in drug product:
An information Request letter was sent to the sponsor on September 29, 2011. The following request was made:
Data showing the levels of each of the heavy metals (arsenic, cadmium, lead, mercury, chromium, copper, manganese, selenium and zinc) in each of the compartments for three batches of your TPN products, with the information reported as ppm. Batches selected for testing should not be successively manufactured batches; batches from ongoing stability studies would be appropriate for this purpose. For multiple package sizes manufactured from a common batch, data for only one package size will need to be reported.
As a response has not been received, this will be included in the deficiency letter.

Stability issue regarding particulate matter:
Initially it was determined that the applicant had provided adequate stability data including additional 24 hours at ambient condition to support the label claim that the product may be stored under refrigerated conditions for 24 hours after being mixed. Although previously submitted data support the proposed 24-month expiration dating period for the product stored at room temperature, the Applicant has recently found a stability issue with particulate matter.

A teleconference between the chemistry team and the Applicant occurred on November 4, 2011, to discuss the November 1, 2011 amendment (via an email) describing their ongoing stability program in which four of the nine pivotal batches showed results above the specification limit of particulate matter. The Applicant has determined that the particles present in the lipid chamber of the IV bag are (b) (4) and are caused by migration of components from the stopper. The Applicant proposes the following corrective actions:

- The Applicant will implement a modified stopper to reduce the amount of (b) (4)
- New stability batches of Kabiven and Perikabiven using the newly identified stopper with reduced (b) (4) content will be manufactured and put on stability testing in accordance with the stability protocol used for the ongoing study with the addition that the particulate matter in the emulsion will be analyzed at each testing point.
- The target shelf life, aimed for the pivotal stability studies, was 24 months when stored at 25°C or lower. Considering the documented mechanism for formation of (b) (4) , the Applicant suggested to (b) (4)
- Not until corrective actions are implemented will shelf life be reverted to 24 months.

FDA agreed that a (b) (4)-month expiration dating period may be acceptable, but only if the Applicant conducts a refrigeration study. The study should be conducted with stability batches that contain relatively high levels of particulate matter but are still within specification limits. Also, the study should be conducted in the same manner as the refrigeration study that was conducted to support the recommendation for refrigerated storage in the proposed labeling. The Applicant agreed to conduct the study and the results will be submitted in an amendment for FDA review. It is expected that this data will be reviewed in the next review cycle.

In the telecon, FDA also agreed that shelf life may be extended to 24 months if the stability studies demonstrate conformance to all specification requirements over 24 months at the proposed storage conditions. FDA also recommended that the stoppers be tested for (b) (4) levels and limits for (b) (4) content be added to the stopper specification, once acceptable levels are established. The Applicant agreed to provide a certificate of analysis (CoA) from the stopper supplier in the NDA along with an explanation of how the process for manufacturing stopper is optimized.

Sterility:
A Product Quality Microbiology review was conducted by Denise Miller. Ms. Miller found no microbiology deficiencies.

The proposed product is sterilized by (b) (4). The Microbiology reviewer reviewed studies conducted to support the integrity of the container closure system. Microbial challenge revealed no bacterial growth in any of the challenged bags. All positive controls were positive for growth, negative controls were negative for growth and growth promotion was valid. Endotoxin specification did not exceed the endotoxin exposure limit for the maximum recommended dosage of this product for adults. Regarding stability data, all exhibit lots for each of the drug products completed stability testing through (b) (4) months with no failures reported. The Applicant also submitted additional supportive lots that had each completed 24 months of stability to support a 24 month expiry. No failures were reported for these lots.

C. THREE-CHAMBER BAG

ONDQA and DGIEP requested a review of the proposed products by CDRH. The CDRH reviewer, Nikhil Thakur, reviewed the packaging system with respect to (1) Device performance, (2) Biocompatibility testing and (3) Human Factors.

Device Performance:
The CDRH reviewer stated that it is unclear whether the Applicant adequately addressed concerns regarding the safety and effectiveness of the (b) (4) packaging. CDRH has the following concerns:

a) The Applicant's tests to demonstrate (b) (4) packaging's resistance to temperature, pressure and leakage appear inadequate. Per the CDRH reviewer it is unclear whether altitude was accounted for as part of the testing regimen. The Applicant will need to perform tests to evaluate

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the burst pressure. The Applicant should utilize a statistically significant sample size when performing this test. Basic statistical analyses should be used when interpreting the test results.

(b) (4)

c) The Applicant performed a test to demonstrate that the injection point does not leak when it is punctured by a 23 gauge needle. CDRH recommended that the Applicant conduct additional tests (multiple punctures using needles of different gauges) to assess for injection point leakage.

Biocompatibility Testing:
Per the CDRH reviewer there were no concerns regarding the biocompatibility aspects of the (b) (4) bag.

Human Factors:
The CDRH review team found the packaging very cumbersome to manipulate. The Applicant should perform a risk assessment to identify the use-related risks associated with their device, and demonstrate that these risks are no different than the usual risks that clinicians face when delivering drug product through other IV bags, to ensure that there are no unique risks associated with using the (b) (4) bag. Based on this use-related risk assessment, the Applicant can then determine which human factor testing should be conducted. The Applicant should review FDA's Guidance Medical Device Use-Safety: Incorporating Human Factors Engineering into Risk Management (July 18, 2000), when developing the appropriate Human Factors studies.

3.1 Final Recommendation

ONDQA recommends a Complete Response action due to deficiencies associated with DMF (b) (4) for (b) (4) lack of purity assurance and adequate controls of heavy metals for the drug product, the "Withhold" recommendation from the Office of Compliance on the manufacturing and testing sites acceptability, and pending labeling issues

CDRH consult review also identified issues related to the packaging system, which preclude approval at this time.

4. Nonclinical Pharmacology/Toxicology

Nonclinical pharmacology/toxicology data were reviewed by Dr. B. Emmanuel Akinshola and a supervisory memorandum by Dr. Sushanta Chakder was filed in DARRTS on November 8, 2011. Please refer to these documents for more information.

<u>Overall Conclusion:</u>
The safety of sodium glycerophosphate, and the lipid and amino acid components of Kabiven and Perikabiven has been adequately assessed in the nonclinical studies submitted. However, a

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safety assessment for the heavy metals was not possible due to a lack of adequate information. No information request by Pharm/Tox is planned as the issue with heavy metals will be resolved through a CMC approach.

Sodium glycerophosphate:

The applicant has submitted adequate nonclinical information comprising of pharmacology (including safety pharmacology), pharmacokinetic, single and repeat dose toxicity and genotoxicity data to support the safety of sodium glycerophosphate.

The potential cardiovascular adverse effects of sodium glycerophosphate was evaluated in cats using a dipeptide/amino acid solution ([redacted] (b) (4) %) containing 20 mmol/L sodium glycerophosphate. Anesthetized cats were administered [redacted] (b) (4) % solution corresponding to 29.4 mg/kg sodium glycerophosphate for 4 hours without any adverse cardiovascular effects.

Sodium glycerophosphate is hydrolyzed in vivo by nonspecific phosphatases to release phosphate. In vivo PK studies in rats and studies with human plasma showed that sodium glycerophosphate is rapidly hydrolyzed to inorganic phosphate and glycerol. Increased blood levels of inorganic phosphate, glycerol and total phosphate, along with increased urinary excretion of these substances following intravenous infusion of DL-glycerol-3-phosphate α-glycerophosphate) in rats suggest an intravascular hydrolysis of this compound.

The single and repeat dose toxicity studies are summarized in Table 4. Sodium glycerophosphate was well-tolerated following IV administration at doses higher than that to be administered at the maximum recommended dose of Kabiven or Perikabiven. Longer-term oral toxicity studies with high doses provide further support for the safety of sodium glycerophosphate.

Table 4: Single and repeat dose nonclinical toxicity studies

Species Studied	Route of Admin.	Treatment Duration	Findings
Rats	IV	Single dose	LD50: 3800 mg/kg (α-glycerophosphate); 3400 mg/kg (β –glycerophosphate)
Rats	IV	Dipeptide amino acid solution containing sodium glycerophosphate at 20 mg/kg/hour over 20 hours	No any adverse clinical signs or any morphological evidence of any organ toxicity
Rats	IV	Sodium glycerophosphate at the maximum recommended daily clinical dose for 13 weeks	No any adverse clinical signs or evidence of organ toxicity
Dogs	IV	648 mg/kg/day x 5 days (The dose is 13-fold the maximum recommended daily clinical dose)	Sodium glycerophosphate at the administered dose was well-tolerated without any significant adverse effects
Dogs	IV	Sodium α -glycerophosphate (1000 mg/kg twice daily for 14 days) or Sodium β-glycerophosphate (500 mg/kg/day for 14 days)	Well-tolerated without any signs of toxicity
Dogs	IV	Dipeptide amino acid solution containing sodium	No any adverse clinical signs or any morphological evidence of any

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		glycerophosphate at 11 mg/kg/hour over 6 hours in dogs for 4 weeks	organ toxicity
Dogs	IV	Sodium glycerophosphate at 34-fold the maximum recommended daily clinical dose	No any adverse clinical signs or evidence of organ toxicity
Dogs	Oral	Dietary administration of sodium β-glycerophosphate at 1900 mg/kg/day for 33 months	No any remarkable toxicity; the only treatment related finding was an increase in kidney weights*, without any histopathological changes
Squirrel monkeys	Oral	sodium β-glycerophosphate in drinking water for 15 months	No any remarkable toxicity; the only treatment related finding was an increase in kidney weights*, without any histopathological changes

* The increase in kidney weights could be related to the high sodium content in the formulation.

In a standard battery of genotoxicity studies, sodium glycerophosphate did not show any mutagenic potential. In addition, SMOFlipid 20% (a lipid emulsion containing 60 g/L of soybean oil) and Neoven (a dipeptide/amino acid solution) were not found to be genotoxic in standard genotoxicity studies.

Embryofetal developmental studies in rabbits with the amino acid solution ([redacted] (b) (4)) and the fat emulsion by the IV route did not reveal any embryotoxicity or teratogenicity. Reproductive toxicity studies have not been conducted with sodium glycerophosphate. However, the lack of reproductive toxicity is to be reflected in the labeling with a Pregnancy Category C. The labeling language is as follows:

Animal reproduction studies have not been conducted with [redacted] (b) (4) It is [redacted] (b) (4) not known whether Kabiven can cause fetal harm when administered to a pregnant woman [redacted] (b) (4) Kabiven/Perikabiven should be given to a pregnant woman only if clearly needed". Thus, the lack reproductive toxicity data for sodium glycerophosphate is not considered a deficiency.

Other components:
The nonclinical studies submitted included those for individual lipid and amino acid constituents of the proposed products. In the evaluation of these individual components, they appear to be safe at the maximum doses administered to the study animals, both rodents and non-rodents, with slight and reversible untoward effects.

Heavy metals:
The Applicant did not provide adequate information on the amount of heavy metals in each compartment of the 3-chamber bag formulations, or in the admixure. Thus, a safety assessment for the heavy metals was not possible due to a lack of adequate information.

Packaging system:
The applicant conducted an appropriate assessment for each component/constituent of the 3-chamber bag (3-CB) [redacted] (b) (4) packaging system. Safety evaluation was performed for potential migrants, leachables, extractables and [redacted] (b) (4) ([redacted] (b) (4)) from the primary 3-chamber bag, over-pouch, oxygen chamber, fill port, stopper, cap, printing ink ([redacted] (b) (4)

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(b) (4) and Intralipid 20%. The safety assessment for the potential migrants, leachables, extractables and the (b) (4) ((b) (4)) appears to be adequate.

4.1 Final Recommendation

The final recommendation by the Nonclinical Pharmacology/Toxicology discipline is Approval.

5. Clinical Pharmacology/Biopharmaceutics

Clinical pharmacology data were reviewed by Dr. Sandhya Apparaju. Please refer to her review for detailed information.

Overall Conclusion:
The application is acceptable from a clinical pharmacology perspective.

Bioavailability studies:
To support the proposed switch from inorganic phosphate to organic phosphate source, the Applicant provided results from two relative bioavailability studies. Note that sodium glycerophosphate is utilized in these formulations as one source of phosphate (approximately (b) (4) % of total phosphate). The egg phospholipids used as (b) (4) formulation provides another ~ (b) (4) % of phosphate.

A formal pharmacokinetic bridging for other active components was not necessary. For active ingredients in solution (e.g. amino acids, dextrose and electrolytes), bioavailability studies are generally not required. The lipid component for intravenous infusion in Kabiven and (b) (4) is exactly the same as in intralipid 20% that has been approved in the U.S since 1981. In the clinical setting, individual parenteral products are often co-administered to meet total nutritional requirements. Intralipid® 20% for example, can be infused into the same central or peripheral vein as carbohydrate/amino acids solutions by means of a y-connector near the infusion site. This allows for mixing of the emulsion immediately before entering the vein. Thus, the proposed 3-chamber presentation of Kabiven and Perikabiven formulations appears to provide all-in-one parenteral nutrition without other significant changes to the treatment paradigm itself. The differences in electrolytes will be a clinical judgment. The potential effect of the new organic phosphate source on the globule size in the lipid emulsion are addressed by the ONDQA CMC discipline.

Study Glyc-001-CP1: This was a single-centre, double-blind, randomized, two-treatment, two sequence, active-controlled phase 1 study to evaluate phosphate from glycerophosphate (Glycophos®; 20 mmol/h for 4 h; Fresenius Kabi, Norway) versus sodium phosphates (IPhosphates; 20 mmol/h for 4 h; Hospira, Inc, USA) in 24 healthy subjects, 18-45 years of age. Drugs were administered into a peripheral vein in the forearm. On Days 1 and 2 of each treatment period, baseline PK blood profiles were obtained. Drugs were infused on day 3. The two treatment periods were separated by washout duration of 7 days.

In this study the phosphate content of meals and water was standardized. No food was provided prior to and during infusion. The estimated total daily oral intake of phosphorus from food

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sources during this study per sponsor was ~ 1.1 g (35 mmol from lunch, snack and dinner provided at the end of infusion, 4h and 8h post-infusion, respectively). This corresponds to ~ 44% of the total intravenously infused dosage of phosphate (80 mmol). All subjects received the same standardized meals on days 1, 2 and 3 of the study, where days 1 and 2 were used for 24-hour baseline phosphate measurements, while test or reference drug infusions were administered on day 3. Baseline phosphate data was comparable for the test (Glycophos) and reference (inorganic I-Phosphate) groups in this study. Since on these baseline days subjects received the same phosphate-standardized diet, correcting the phosphate data from the study for baseline is more likely to correspond to contributions from drug sources alone. Regardless, study results should not be used from an absolute sense, as the use of supra-therapeutic doses of phosphate sources (80 mmol) as well as potential for additional phosphate intake from food sources makes it a less reliable measure for assessing absolute exposures. However, information regarding the relative performance of the two formulations with respect to phosphate provision can still be useful.

Table 5-A shows the serum phosphate PK parameters for the two treatments. For baseline-corrected data (AUC0-24h,bc in Table 5-A, and AUCbc in Table 5-B), the organic phosphate source (Glycophos) resulted in lower AUC than the inorganic phosphate source (I-Phospate). The relative bioavailablity was approximately 80% with a 90% confidence interval of 71% - 92%. Similar results were obtained based on urine data with a mean ratio of 84% (90% CI: 78-91%) (Table 6).

Relative bioavailability data in serum and urine samples suggest a phosphate provision of approximately 80% (Tables 5-B and 6), and in general support the inclusion of the organic source for phosphate provision. Analytical issues pertaining to suboptimal use of calibrators and QC samples in the assay identified by DBGC were taken into consideration and study data were viewed only in relative terms and not in absolute terms to provide a rough estimate of relative BA. This is considered acceptable because in clinical practice patients will be checked regularly for serum electrolytes and remedial actions will be taken to adjust the level as needed. Furthermore, compared to this study which employed supratherapeutic doses of the drugs, the differences in absolute serum phosphate levels would be smaller when clinically relevant doses are administered.

Table 5-A: Pharmacokinetic parameters of serum phosphate from Glycophos vs. I-Phosphate

Parameter	Glycophos® (T)	I-Phosphate (R)
$AUC_{+0\text{-}24h,\ bc}$ [h*mmol/L]	9.365 (8.557; 10.25)	11.32 (10.46; 12.25)
$AUC_{0\text{-}24h}$ [h*mmol/L]	37.05 (36.35; 37.76)	39.00 (37.88; 40.16)
C_{max} [mmol/L]	2.869 (2.763; 2.980)	3.362 (3.185; 3.549)
T_{max} [h]	4.00	3.97 (3.87; 4.08)
C_{ss} [mmol/L]	2.869 (2.763; 2.980)	3.349 (3.173; 3.534)
λ_z [1/h]	0.3341 (0.2778; 0.4017)	0.3074 (0.2624; 0.3601)
$t_{½}$ [hh:mm]	2:04 (1:43; 2:29)	2:15 (1:55; 2:38)

T Test, R reference, bc = baseline corrected, LL/UL - Lower/Upper Limit of the 95% confidence interval (CI) of the geometric mean

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Table 5-B: Statistical analysis for serum phosphate data

Serum Parameter	Test (Glycophos)	Reference (I-Phosphate)	Ratio T/R %	90%CI LL	90 % CI UL
AUC24 [mmol*h/L]	37.05	38.98	95.03	92.35	97.79
AUC*bc* [mmol*h/L]	9.01	11.13	80.89	71.06	92.08
Cmax [mmol/L]	2.86	3.36	85.36	80.86	90.12

Table 6: Statistical analysis for urine phosphate data

Urine Parameter	Test (Glycophos)	Reference (I-Phosphate)	Ratio T/R %	90 %CI LL	90 % CI UL
Ae [mmol/coll]	77.38	88.73	87.21	81.94	92.81
Ae, bc [mmol/coll]	53.04	62.97	84.23	78.02	90.94

Study KABI-003-CP1: A second study KABI-003-CP1 explored relative bioavailability of phosphate provision from the organic sodium glycerophosphate administered alone, versus when it is administered as part of the complete PN formulation containing (b) (4) total active components. Results from this study will not be considered as supportive information for this NDA, as the resultant phosphate data was heavily confounded by the contribution of phosphate from food sources that even exceeded study drug dose in mmol units.

NOTE: The bioanalysis of the bioavailability study data was not conducted by (b) (4), (b) (4).

5.1 Final Recommendation

The final recommendation by the Clinical Pharmacology discipline is approval.

6. Clinical Microbiology

N/A

7. Clinical - Efficacy

The clinical efficacy information was reviewed by Dr. Karyn Berry and no deficiencies were identified. Please refer to her review for further details.

The applicant proposes to demonstrate the efficacy of Kabiven and Perikabiven by referencing prior findings by the FDA for Intralipid 20% (NDA 018449 and NDA 020248), and Novamine 11.4% (NDA 017957), to support this application. In addition, the Applicant also refers to another two products with respect to levels of dextrose and electrolytes: the approved 2-CB products Aminosyn II with electrolytes in dextrose with calcium (NDA 019683) and CliniMix E sulfite free with electrolytes in dextrose with calcium (NDA 20678).

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Electrolyte profile of the proposed products:
The electrolyte content (in solution) in the proposed products doesn't exactly correspond to that in the referenced Aminosyn II (NDA 19683) or Clinimix (Table A5 in Appendix 1). The Applicant provided their rationale for the selection of electrolyte profile in the Kabiven products as follows:

(b) (4)

[redacted]

Clinical trial data:
The eleven supportive Kabiven and Perikabiven clinical trials (Appendix II, Tables A6 and A7) were generally seven day infusions of the products in patients requiring intravenous nutrition, with the exception of one Kabiven trial which was 4 weeks duration. All of the clinical trials were randomized, open-label except for one trial (00-3CB5-001) which was randomized, double-blinded. All of the subjects required PN and for four (4) of the Kabiven trials subjects were required to be status post GI surgery. None of the active comparator PN products used in these trials are approved for use in the US. None of the Perikabiven trials were conducted administering the product via a central vein.

None of the clinical trials had clinical efficacy endpoints, but three of the Kabiven trials had laboratory efficacy assessments. These included limited data for essential and non-essential amino acids, fatty acid components, urea, creatine, pre-albumin, beta-hydroxybutyrate, IGF-1/IGF-BP-1, insulin, leptin, HLA-DR and IL-6, and urinary excretion of amino acids, nitrogen, urea and creatinine. No formal hypothesis was established and no formal statistical analyses were performed. The results demonstrated that Kabiven was comparable to the active comparators with regard to efficacy based on these parameters in patients requiring PN.

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7.1 Final Recommendation

The clinical efficacy information has been reviewed by Dr. Karyn Berry and no approval issues have been identified although the use of Perikabiven for central administration is questioned.

8. Clinical - Safety

The clinical safety information was reviewed by Dr. Karyn Berry. Please refer to her review for further details.

Overall Conclusion:
The identified clinical deficiencies include: 1) inadequate data on the amount of heavy metals in each compartment of the 3-chamber bag and the total amount of heavy metals for the proposed products and 2) insufficient data to (b) (4)

Clinical trial safety results submitted in the NDA:
Dr. Berry examined safety results from 7 Kabiven clinical trials (Appendix II, Table A6), and 4 Perikabiven clinical trials (Appendix II, Table A7) and the 2 bioavailaiblity studies.

Bioavailaiblity studies:
In study Glyc-001-CP1, A total of 15 (60%) subjects reported at least one TEAE with a total of 28 TEAEs reported during and following administration of the drug products. Nine (36%) subjects reported 12 TEAEs for the treatment with Glycophos® (an organic phosphate) and 11 (44%) subjects reported 16 TEAEs for the treatment with I-phosphate (an inorganic phosphate). Note that this study use phosphate doses much higher than the intended clinical use dose. The Investigator considered 6 TEAEs reported by 4 subjects as related to Glycophos®, and 10 TEAEs, reported by 5 (20%) subjects as related to I-Phosphate. All episodes of hypocalcaemia were considered by the Investigator to be of mild intensity and the only TEAE considered to be related to the drug product. No severe TEAE occurred. None of the subjects died, no serious and no significant AE occurred, and none of the subjects were withdrawn due to a TEAE.
In study KABI-003-CP1: There are no TEAEs reported for the Perikabiven treatment.

Clinical trials:
These were small trials with the number of subjects ranging from 23 to 53 in each study. A total of 145 subjects received Kabiven, 93 subjects received Perikabiven and ten (10) healthy subjects received Perikabiven. The demographic make-up was adequate for both the Kabiven and Perikabiven clinical trials. There were no major demographic differences between treatment groups in those trials. Safety analyses were based on treatment emergent AEs (TEAEs), laboratory assessments and vital signs.

No deaths related to Kabiven or Perikabiven were reported by the Applicant. The incidence of AEs was similar between treatment groups in both the Kabiven and Perikabiven trials (Tables 7-A and 8-A). Adverse events observed in the clinical trials were similar to AEs listed in the Package Inserts of the RLDs, such as nausea, vomiting and pyrexia (Tables 7-B and 8-B).

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Abnormal electrolyte shifts were seen in both Kabiven and Perikabiven. The electrolyte shifts in the Kabiven subjects was similar to that observed in the comparator group. The electrolyte shifts for potassium, magnesium and phosphate were greater in the [redacted] (b) (4) group than in the comparators. Dr. Berry considers that close laboratory monitoring of electrolytes and supplementation will be necessary for both Kabiven and Perikabiven.

Table 7-A: Overview of TEAEs in Kabiven trials

	Kabiven Pooled N=145 n (%)	**Comparator Pooled N=144 n (%)**
Subjects with at least 1 TEAE	102 (70.3)	107 (74.3%)
Subjects with at least 1 severe TEAE	16 (11%)	16 (11.1%)
Subjects with at least 1 related TEAE	31 (21.4%)	39 (27.1%)
Subjects with at least 1 TEAE resulting in death	3 (2.1%)	4 (2.8%)
Subjects with at least 1 serious TEAE	10 (6.9%)	15 (10.4%)
Subjects with at least 1 serious related TEAE	0	0
Subjects with at least 1 resulting in discontinuation of study drug	12 (8.3%)	12 (8.3%)

Applicant's table ISS, p. 71

Table 7-B: TEAEs by system organ class and preferred terms for Kabiven trials

	Kabiven Pooled N=145		**Comparator Pooled N=144**	
Number (%) of subjects with at least one AE	102 (70.3)		107 (74.3)	
Number (%) of subjects	n	%	n	%
System organ class Preferred term				
Blood and lymphatic system disorders				
Anemia	5	3.4	7	4.9
Gastrointestinal disorders				
Nausea	22	15.2	20	13.9
Vomiting	8	5.5	10	6.9
Flatulence	4	2.8	9	6.3
Dyspepsia	4	2.8	6	4.2
General disorders and administration site conditions				
Pyrexia	13	9.0	13	9.0
Investigations				
Hemoglobin decreased	8	5.5	10	6.9
Total protein decreased	6	4.1	11	7.6
Blood potassium decreased	6	4.1	7	4.9
GGT increased	6	4.1	3	2.1
Metabolism and nutrition disorders				
Hyperglycemia	3	2.1	5	3.5
Hypokalemia	6	4.1	5	3.5
Vascular disorders				
Hypertension	12	8.3	14	9.7

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Table 8-A: Overview of TEAEs in Perikabiven Trials

	(b) (4) Pooled N=93 n (%)	Comparator Pooled N=91 n (%)
Subjects with at least 1 TEAE	40 (43.0)	38 (41.8)
Subjects with at least 1 severe TEAE	6 (6.5)	7 (7.7)
Subjects with at least 1 related TEAE	14 (15.1)	12 (13.2)
Subjects with at least 1 TEAE resulting in death	2 (2.2)	2 (2.2)
Subjects with at least 1 serious TEAE	3 (3.2)	5 (5.5)
Subjects with at least 1 serious related TEAE	0	1 (1.1)
Subjects with at least 1 resulting in discontinuation of study drug	4 (4.3)	4 (4.4)

Applicant's table, ISS p.134

Table 8-B: TEAEs (≥ 3%) by System Organ Class and Preferred Term for Perikabiven Trials

	Perikabiven Pooled N=93		Comparator Pooled N=91	
Number (%) of subjects with at least one AE	40 (43)		38 (41.8)	
Number (%) of subjects	n	%	n	%
System organ class Preferred term				
Blood and lymphatic system disorders				
Anemia	2	2.2	0	0
Gastrointestinal disorders				
Nausea	2	2.2	3	3.3
General disorders and administration site conditions				
Pyrexia	4	4.3	0	0
Investigations				
GGT increased	2	2.2	3	3.3
Blood alkaline phosphatase increased	2	2.2	0	0
Alanine aminotransferase Increased	2	2.2	1	1.1
Blood glucose increased	2	2.2	0	0
Blood triglycerides Increased	3	3.2	0	0
C-reactive protein increased	2	2.2	1	1.1
Blood urea increased	2	2.2	0	0
Metabolism and nutrition disorders				
Hyperglycemia	5	5.4	4	4.4
Hypokalemia	4	4.3	1	1.1
Hypoalbuminemia	2	2.2	0	0
Psychiatric disorders				
Insomnia	2	2.2	0	0
Vascular disorders				
Hypotension	2	2.2	0	0
Phlebitis	2	2.2	0	0

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Thrombophlebitis is a specific safety concern for Perikabiven. Thrombophlebitis may occur if peripheral veins are used for infusion of solutions that are hypertonic to body fluids. Several factors may contribute to thrombophlebitits including the type of cannula used and its diameter and length, the duration of the infusion, pH and osmolality of the infusion, infection and the number of manipulations. The Applicant stated that injection site reaction was assessed as Maddox grade 0 in nearly all patients at all assessment times throughout the study. Table 8-C summarizes the number of subjects with maximum modified Maddox scores of 4, 5, or 6. Thrombophlebitis/phlebitis are potential complications of PPN. The majority of injection site reactions were reported by the Applicant as mild. The incidence of observed injection site reactions was similar for Perikabiven as compared to the comparator treatment in the studies.

Table 8-C: Injection site reaction as assessed using modified Maddox score in Perikabiven trials

Modified Maddox Score	Perikabiven Pooled N=93 n(%)	Comparator Pooled N=91 n(%)
4	4 (4.3)	4 (4.4)
5	2 (2.2)	1 (1.1)
6	1 (1.1)	0

Applicant's table, 2.7.4 Summary of Clinical Safety

The Applicant has proposed the use of Perikabiven for peripheral or central intravenous administration. The Applicant did not submit clinical trial data for Perikabiven administered via central vein administration. Dr. Berry commented that it is unclear to her the benefit of giving Perikabiven through a central vein when it has a lower electrolyte content. Kabiven would be a more appropriate PN product since its content is intended for central use.

Postmarketing experience:

Reported postmarketing adverse drug reactions (ADRs) for Kabiven from March 1999 through October 2010 include 17 subjects who experienced 27 ADR as reported spontaneously, from regulatory authorities, in the literature and other sources. Twelve of these subjects experienced 19 SAEs. The relationship of the majority of AEs were reported as possible or probable related to the drug product. These AEs included pyrexia, injection site reaction, dyspnea, erythema multiforme, hypersensitivity, pruritus, hyperlipidemia, thrombocytopenia, leukopenia, liver disorder, abdominal pain, and vomiting.

Reported post marketing adverse drug reaction (ADR) for Perikabiven from December 1999 through November 2010 include 18 subjects who have experienced 29 ADRs as reported spontaneously, from regulatory authorities, in the literature and other sources. Sixteen of these subjects experienced 25 SAEs. The relationship of the majority of AEs were reported as possible or probable related to the drug product. These AEs included anaphylactoid reaction, Candidiasis, pyrexia, injection site reaction, bronchospasm/dyspnea, hypersensitivity, pruritus, hyperlipidemia, leukopenia, hepatitis, renal failure, vomiting, septicemia, hypertriglyceridemia, cholestasis and hypotension.

Dr. Berry noted that patients who receive PN often have multiple co-morbidities and some of these ADRs could be related to underlying medical conditions. Many of the ADRs for both Kabiven and Perikabiven, such as hypertriglyceridemia, phlebitis, infection and fever are similar to AEs listed in the PI of the RLDs.

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Literature and labeling information:
Based on literature articles and approved labeling for parenteral nutrition products, Dr. Berry considers that the population that receives PN often has multiple co-morbidities, such as acid-base imbalance, cardiac, pulmonary disorders that must be considered and followed when administering PN. Besides that, Dr. Berry focuses on heavy metals as it is unclear what the cumulative amounts of heavy metals is in overall PN products and specifically in the combination Kabiven and Perikabiven products. She noted that except for aluminum, this information has not previously been assessed. Therefore, additional data is needed from the Applicant. The label for Kabiven and Perikabiven should also incorporate some of the safety language found in the individual labels of the approved products referenced by the Applicant.

Deficiencies:

Issue with heavy metals: The Applicant did not test for heavy metals for either Kabiven or Perikabiven. The Applicant will need to assess levels of heavy metals in the individual compartments of the 3-chamber bag and in the combined mixed product for both Kabiven and Perikabiven. The assessment should include the following metals: arsenic, cadmium, lead, mercury, chromium, copper, manganese, selenium and zinc. The data will need to show the levels of each of the above metals in 3 batches of each product, with the information reported as parts per million (ppm).

Issue with (b) (4): The Applicant has proposed the use of Kabiven and Perikabiven (b) (4)

8.1 Final Recommendation

A complete response is recommended for this NDA application from a Clinical perspective.

9. Advisory Committee Meeting

This application was not presented to an Advisory Committee.

10. Pediatrics

A consult was requested from the Pediatrics and Maternal Health Staff to address the following questions:

1) The Applicant is requesting (b) (4)

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(b) (4)

2) The Applicant is requesting a waiver for use in children < 2 yrs of age, (b) (4) s this acceptable?

Dr. Laurie Conklin of PMHS performed the consult review. She noted that precipitation of calcium and phosphate is the most important physical incompatibility in PN, (b) (4). The most relevant factor in the solubility of calcium phosphate was the nature of the salt, with organic phosphate salt providing the greatest benefit over organic calcium salt in avoiding calcium phosphate precipitation. The Applicant indicated that sodium glycerophosphate containing products manufactured by Fresenius Kabi have been administered to approximately (b) (4) people over the last 10 years, with no reported serious adverse events associated with their use. A review of the literature reveals no reported concerns regarding the IV administration of organic phosphate and there may be potential benefit.

(b) (4) (b) (4) (b) (4) There are three commercially available FDA-approved amino acid solutions designed for infants (<12 months of age): Aminosyn 10%, TrophAmine 10% and Premasol 10%. (b) (4)

(b) (4)

A letter was sent to the Applicant on September 8, 2011, denying their request (b) (4)

The Applicant submitted a Pediatric Plan on October 21, 2011. The Pediatric Plan will be reviewed during the next review cycle.

11. Other Relevant Regulatory Issues

Although the Applicant specified Intralipid 20% as one of the reference products for this 505(b)(2) NDA, the Applicant has obtained right of reference to this product. Therefore, Intralipid 20% should be removed from the reference product list for this NDA.

11.1 Office of Scientific Investigations (OSI) audits

An OSI inspection report was filed in DARRTS by Xikui Chen on August 15, 2011.

The efficacy of the proposed product relies on demonstration of bioequivalence to the reference product. As such, the Clinical Pharmacology discipline initiated the request of OSI audits of both the clinical and analytical sites of the pivotal bioavailability study (Study#109148).

Following a request from the review division and DCP3, the Division of Bioequivalence and GLP compliance (DBGC) inspected the clinical site (Parexel International GmbH, Germany) and bioanalytical sites ([redacted] (b) (4)) for the relative bioavailability study Glyc-001-C P1 on [redacted] (b) (4), and [redacted] (b) (4). No Form 483 was issued for the clinical site. A form 483 was issued for the analytical portion of the inspection, with a final classification of VAI, i.e. Voluntary Action Indicated. The observation made on form 483 was as follows "Failure to include sufficient calibrator and quality control samples in each analytical run. Specifically, only one calibrator at 1.67 mmol/L phosphate and deionized water were used for a calibration curve. Only two QC samples at ~ 1.3 and 2.1 mmol/L phosphate were used for serum samples, and two QCs at 8.3 and 16.1 mmol/L phosphorus were used for urine samples". As the analytical procedures were found not to conform to regulatory standards, DBGC recommended that the agency not accept phosphate data from this study. Following an internal assessment of the DBGC recommendations and discussion with Drs. Dennis Bashaw and Hae-Young Ahn, Division Director and Deputy Division Director of DCP3, the Clinical Pharmacology review team determined that the phosphate results from the study will be accepted for review, albeit in relative terms rather than absolute values.

12. Labeling

12.1 Proprietary name

The proprietary name was reviewed by Ms. Cathy A. Miller of DMEPA. Please refer to her review dated November 10, 2011, for details.

DMEPA concludes the proposed proprietary names, Kabiven and Perikabiven,are acceptable from a promotional perspective and a safety perspective. 'Kabiven' for the central administration only product, and 'Perikabiven' for the central and peripheral administration product

On June 17, 2011, the Applicant submitted a request for review of the proposed names "Kabiven" and "[redacted] (b) (4)." Both the Division of Gastroenterology and Inborn Error

Products (DGIEP) and the Division of Medication Error Prevention and Analysis (DMEPA) had concerns about the Applicant's proposed nomenclature plan for these two products. While DMEPA found the proposed name 'Kabiven' acceptable from a safety and promotional aspect, both DMEPA and DGIEP had concerns about the proposed name '[redacted] (b) (4)' because of the misleading nature of the [redacted] (b) (4) for a product that can be administered peripherally or centrally, along with potential confusion that could lead to wrong route medication errors. The Applicant's alternate proposal included the use of the [redacted] (b) (4) for the product that could be administered centrally only. However, DMEPA and DGIEP had similar concerns about this proposal due to the potential for confusion that could occur if the [redacted] (b) (4) was inadvertently omitted and the name confusion lead to wrong route of administration medication errors.

On September 1, 2011, the Applicant was notified of the above concerns through a teleconference and agreed to withdraw the proprietary name request for the name pairs 'Kabiven' and '[redacted] (b) (4)' and consider another name pair that included 'Kabiven', and an alternate name that does not include [redacted] (b) (4)

On September 7, 2011, the Applicant submitted an amendment to NDA 200656, requesting the review of the proposed name pair 'Kabiven' for the central administration only product, and 'Perikabiven' for the central and peripheral administration product.

The Office of Prescription Drug Promotion (OPDP) determined the proposed names are acceptable from a promotional perspective. DMEPA and DGIEP concurred with the findings of OPDP's promotional assessment of the proposed name. DMEPA believes that the proposed nomenclature plan for the two proposed products provides orthographic and phonetic differentiation between the two products and no USAN stems are present within these proprietary names. However, given the similarities in the products (TPN products) and proposed packaging (similarly sized volume bags with the same trade dress features on the outer package and bag), DMEPA believes that distinction between these two products will also need to be provided through strong labels and labeling features, including packaging differentiation between Kabiven and Perikabiven, to provide distinction during all phases of the medication use cycle. DMEPA will review proposed labels and labeling for this NDA in a separate OSE Review and provide recommendations that address the concerns about the needed product differentiation between Kabiven and Perikabiven.

12.2 Physician Labeling / Medication Guide / Carton and Container Labeling

Labeling will be discussed and communicated to the Applicant at the next review cycle.

OPDP did not conduct a labeling review during this review cycle and requested that DGIEP submit a new consult request during the next review cycle.

13. Risk Benefit Assessment/Recommendations

Dr. Karyn Berry performed a risk/benefit assessment as laid out in her review.

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As new formulations of currently approved PN products, Kabiven and Perikabiven do not fill an unmet medical need. Although the Applicant proposes advantages of these products such as convenience of use, there is no clinical data to suggest that these products offer a therapeutic advantage over existing PN products that are approved for use in adults.

On the other hand, there are concerns regarding the lack of controls over heavy metal contents in the proposed products as described below.

The presence of heavy metals in PN can have significant adverse effects on organs and tissues, such as nephropathy (associated with excess chromium) and neurotoxicity and hepatotoxicity (associated with manganese) (Buchman A, et al, 2001). Over the years, there have been numerous reports in the literature regarding the presence of heavy metals in PN products (Leung F, et al 1995; Greene HL et al, 1988). The concern of clinicians is that some of these heavy metals are considered essential trace elements, such as zinc, copper, chromium and manganese and are commonly added to PN (Bemer Y, 1989). Studies have demonstrated that trace elements are often present in significant concentrations in components of PN. The concentrations may vary markedly among solutions from different manufacturers and from different lots. Inadequate data concerning baseline levels of these heavy metals in PN products creates the potential for toxicity. Populations especially at risk for heavy metal toxicity include patients on long term PN use, pediatrics patients, renal and hepatic impairment patients.

Heavy metals in the proposed product was monitored only for individual drug substances. The Applicant did not assess the individual chambers or the whole mixed product for heavy metals. Since the drug product daily dose is very large ((b) (4) mL to 2556 mL) the cumulative amounts of heavy metals in the products may surpass daily allowable limits. Therefore, the Applicant should test the amount of heavy metals in each compartment of the 3-CB and the total amount of heavy metals when the compartments are mixed together. Based on these results, appropriate limits of the various heavy metals present need to be determined and added to the product specifications.

<u>Conclusion</u>: Given the availability of alternative products for PN and the concerns about the need to assess heavy metals in the proposed products, at this time, the safety risks of treatment with these products outweigh the benefits.

References:

Buchman, A, Neely M, Grossie B, Truong L. Organ heavy metal accumulation during parenteral nutrition is associated with pathologic abnormalities in rats. Nutrition 17: 600-606, 2001.

Leung F. Trace elements in parenteral micronutrition. Clinical Biochemistry 1995; 28(6):561-566.

Greene HL, Hambridge KM, Schanler R, Tsang RC. Guidelines for the use of vitamins, trace elements, calcium, magnesium, and phosphorous in infants and children receiving total parenteral nutrition: report of the Subcommittee on Pediatric Parenteral Nutrient Requirements from the Committee on Clinical Practice Issues of the American Society for Clinical Nutrition. American Journal of Clinical Nutrition 1988; 48:1324-42.

Berner Y, Shuler TR, Nielsen FH. Selected ultatrace elements in total parenteral nutrition solutions. America Journal of Clinical Nutrition 1989;50:1079-83.

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13.1 Recommended Regulatory Action

There are deficiencies identified by several review disciplines, including clinical, CMC, and CDRH. As CDTL, I concur with the Complete Response recommendation.

13.2 Recommendation for Postmarketing Risk Evaluation and Mitigation Strategy Requirements (REMS)

To be evaluated during the next review cycle.

13.3 Recommendation for Postmarketing Required Pediatric Studies

To be evaluated during the next review cycle.

13.4 Recommendation for other Postmarketing Study Requirements (PMRs)

To be evaluated during the next review cycle.

13.5 Recommendation for Postmarketing Study Commitments (PMCs)

To be evaluated during the next review cycle.

13.6 Recommended Comments to Applicant

The following deficiencies should be communicated to the Applicant.

The following deficiencies pertains to Chemistry, manufacturing and controls:

1. The applicant has not provided adequate controls for the heavy metals in the drug product. Due to the large volumes of the drug product to be infused into patients, it is deemed critical to control the amount of daily intake of the heavy metals. They should be adequately controlled by the specification with proper method and adequate acceptance criteria. Additional data is needed from the Applicant which specifies the amount of heavy metals in each compartment of the three chamber bag. The Applicant will need to assess both Kabiven and Perikabiven for levels of the following metals: arsenic, cadmium, lead, mercury, chromium, copper, manganese, selenium and zinc. The data will need to show the levels of each of the above metals in 3 batches of the each product, with the information reported as parts per million (ppm). Batches selected for testing should not be successively manufactured batches; batches from ongoing stability studies would be appropriate for this purpose. For multiple package sizes manufactured from a common batch, data for only one package size will need to be reported.

2. DMF (b) (4) is not acceptable.

3. In view of the recently revealed stability issue with particulate matter for the proposed product, additional refrigeration studies should be conducted for the expiry dating of the products.

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4. The [redacted] (b) (4) does not have clearance certificate for [redacted] (b) (4)

5. The proposed established names of "[redacted] (b) (4)" and [redacted] (b) (4) are not acceptable. We recommend an established name of "Lipid Injectable Emulsion with Amino Acids and Electrolytes and Dextrose."

6. The Office of Compliance has issued an overall "Withhold" recommendation for the application.

The following deficiencies pertains to the [redacted] (b) (4) 3-chamber bag as identified by CDRH:

Device Performance

1. You performed a test to demonstrate the [redacted] (b) (4) packaging's resistance to temperature, pressure and leakage, per the recommendations within ISO 15747 and D IN 58363-15. Based on the description of the test within these standards, it is unclear whether altitude was accounted for as part of testing regimen. For instance, your test states that the [redacted] (b) (4) bag is conditioned for 24 hours at a temperature of 50 +/- 5 degree C. The bag is then exposed to a pressure of 500 mbar (50 kPa) for 15 seconds. The bag is considered to pass the test if it does not leak any fluids. Our concern is that atmospheric pressure changes significantly with altitude (for example, the typical atmospheric pressure in Denver, Colorado, which is approximately 1 mile above sea level, is approximately 85 kPa). Given the difference in pressure based on varying altitude, temperature and humidity, we believe that it is more relevant to demonstrate the pressure at which the [redacted] (b) (4) bag bursts. If the burst pressure significantly exceeds (factor of 2x) the typical change in atmospheric pressure as it relates to altitude, then our concerns of the bag bursting due to this environmental change will have been mitigated. You should utilize a statistically significant sample size when performing this test. You should use basic statistical analyses when interpreting the test results.

[redacted] (b) (4)

3. You performed a test to demonstrate that the injection point does not leak when it is punctured by a 23 gauge needle. The test entails puncturing the injection point of the [redacted] (b) (4) bag with a 23 gauge needle, and then removing the needle. Next, a pressure of 200 mbar (20 kPa) is exerted on the bag for 15 seconds. The bag should demonstrate that it does not leak. From the summary provided in the submission, it appears that the septum at the injection point was punctured only once before subjecting the bag to the 20 kPa pressure. However, from the device description (Section 3.2.P.7.1), it appears that one of the points are utilized to spike the bag with medication

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after the contents are mixed. It is conceivable that this septum would be penetrated multiple times prior to beginning the infusion. Also, it is unclear whether the 23 gauge needle will adequately test the non-coring nature of the septum at the injection point. You should:
a. Clarify whether the injection point could be penetrated multiple times, and if so, modify the test to account for multiple punctures, prior to testing the bag for leakage.
b. Test the injection point leakage after the septum is punctured with a 19 or 21 gauge needle, as we believe this is more representative of an extreme needle size for penetrating the injection point septum.

Human Factors
4. Regarding Human Factors testing, you should perform a risk assessment to identify the use-related risks associated with their device, and demonstrate that these risks are no different than the usual risks that clinicians face when delivering drug product through other IV bags, to ensure that there are no unique risks associated with using the (b) (4) bag. Based on this use-related risk assessment, you will have a better idea of the extent to which simulated use testing is required. You should review FDA's Guidance Medical Device Use-Safety: Incorporating Human Factors Engineering into Risk Management (July 18, 2000), when developing the appropriate Human Factors studies.

If you identify use-related risk associated with the use of the (b) (4) bag, you should conduct Human Factors testing as outlined in CDRH's Guidance (referenced above). When performing this testing, you should consider the following:

a. Devices and Labeling Used and Training
For design validation, the devices used in your testing should represent the final design, which includes instructions for use, or any other labeling materials.

The training you provide to your test participants should approximate the training that your actual end users will receive. Please describe the training you plan to provide in your validation study and how it corresponds to realistic training levels.

Your participants should assess the clarity of the instructions for use and you should assess the extent to which the instructions support safe and effective use of your device. If any of the other labeling (e.g., packaging, inserts) is critical to use, include them in your validation testing as well. You may include these assessments in your validation testing or conduct them in a separate study.

If you decide to include the assessment of clarity of instructions for use and training as part of the validation study, FDA expects that the results demonstrating effectiveness of your training and instructions for use are analyzed separately from the results of use performance.

b. User Tasks and Use-Related Risks Analysis
FDA expects to see a clear description of how you determined which user tasks would be included in the testing and how many trials each participant would complete. In order to adequately assess user performance and safety, the tasks selected for testing should be

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derived from the results of a comprehensive assessment of use-related hazards and risks that consider all functions of the device. The tasks should be prioritized to reflect the relative magnitude and severity of the potential impact of inadequate task performance on the safety of the device and the user.

Provide a use-related risk analysis, describe and provide a rationale for the tasks you include in your testing and their relative priority. Also, describe all activities in which your test participants will engage during the test.

c. Use Environment and Conditions

You should conduct your validation testing in an environment that includes or simulates all key aspects of the real-world environments in which you anticipate your device would be used.

Identification of potentially challenging use conditions should be derived through analyses of use hazards prior to conducting validation testing and aspects of use that can be reasonably anticipated, such as use with gloves or wet fingers, dim lighting, noisy situations, etc., should be included in your testing. Evaluate use of your device under whatever conditions you identify as potentially occurring and hazardous.
Describe the testing environment and realism of the simulated use in sufficient detail for us and justify how they were appropriate for validation testing.

d. Study Participants

FDA expects you to test a minimum of 15 participants from each major user group for validation of device use. Your test participants should be representative of your intended end-user populations, as described in your indications for use statement. If users with distinctly different characteristics (e.g., age ranges, skill sets, or experience levels, level of disabilities/impairments) will use your device, you should include 15 from each distinct group.

For devices that are intended to be marketed within the United States (US), FDA expects that the human factors testing would be conducted in the US with (American) English speaking participants.

Regardless of the number of groups you test, please provide a rationale that these groups are representative of the overall population of users for your device. Note that study participants should not be your own employees, or those that have been exposed to the products prior to the testing.

e. Data Collection

Any data collected and analyzed in a validation study should be described in terms of how it supports the safety case claim that your device can be used safely and effectively by the indicated users. FDA expects you to collect both empirical and qualitative data in a design validation study.

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Empirical Data - Your test participants should be given an opportunity to use the device independently and in as realistic a manner as possible, without guidance, coaching, praise or critique from the test faciltator/moderator. Some data, such as successful or failed performance of key tasks or time taken to perform tasks - if time is a safety-critical criterion - should be measured directly rather than soliciting participant opinions. Observing participant behavior during the test is also important, in order to assess participants' adherence to protocol and proper technique and especially to assess and understand the nature of any errors or problems that occur.

Qualitative Data - The Agency expects you to ask open-ended questions of participants at the end of a usability validation, such as, "Did you have any difficulty using this device? (If sol can you tell me about that?" The questions should explore performance of each critical task involved in the use of the device and any problems encountered. Note that since the labeling and instructions for use are considered part of the user interface for your device, the questions should cover those components as well.

Your analysis of performance and subjective data should be directed toward understanding user performance and particularly task failures. The analysis should determine the nature of failures, the causes of failures, and the clinical impact. Every test participant who experiences a "failure" (does something that would have led to harm under actual conditions of use), should be interviewed about that failure to determine the cause of the failure from the perspective of the participant.

Describe and provide a rationale for including each type of data you collect.

f. Protocol

To ensure that the protocol is aligned with the rationale expressed in the Human Factors Guidance document, we recommend that you provide a proposed protocol for FDA to review prior to conducting the Human Factors study.

The following deficiencies pertains to the Pediatric plan:

As communicated to you in our September 8, 2011 letter, you must submit [redacted] (b) (4)

In addition, you must submit [redacted] (b) (4)

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14. Appendix I: Formulations

Table A1: Composition and Nutrient Contents in the Admixture of Kabiven Product (4 different bag sizes)

(b) (4)

[redacted]

Table A2: Composition and Nutrient Contents in the Admixture of Perikabiven Product (3 different bag sizes)

(b) (4)

[redacted]

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Table A3: Components and Composition - Individual Chambers of the Proposed Products vs. that of the Referenced Products

Product	Intralipid 20 %	Novamine 11.4 %	Aminosyn II with Electrolytes in Dextrose with Calcium	Kabiven	(b) (4)
NDA No (approval)	18-449 (1981-01-23) 20-248 (1996-08-07)	17-957 (1978-01-03)	19-683 (1988-11-07)	--	--
Packaging: No of Chambers in Bag	1	1	2	3	3
Individual chamber Composition (%)					
Soybean Oil	20	--	--		
Glucose	--	--	50		
(b) (4) Amino Acid	--	11.4	8.5		
Individual Amino Acids[1] (mg/ml)					
Alanine	--	16.50	8.44		
Arginine	--	11.20	8.65		
Aspartic Acid	--	3.30	5.95		
Glutamic Acid	--	5.70	6.27		
Glycine	--	7.90	4.25		
Histidine	--	6.80	2.55		
Isoleucine	--	5.70	5.61		
Leucine	--	7.90	8.50		
Lysine	--	9.00	8.93		
Methionine	--	5.70	1.46		
Phenylalanine	--	7.90	2.53		
Proline	--	6.80	6.14		
Serine	--	4.50	4.50		
Threonine	--	5.70	3.40		
Tryptophan	--	1.90	1.70		
Tyrosine	--	0.30	1.87		
Valine	--	7.30	4.25		
Electrolytes[1] (mmol/l)					
Sodium	--	--	84		
Potassium	--	--	66		
Magnesium	--	--	5[2]		
Calcium	--	--	--[2]		
(b) (4) phosphorous	--	--	30		
Chloride	--	--	96		
Acetate	--	--	61		

[1] In the amino acid and electrolyte solution
[2] In the dextrose solution

Table A4: Amino acids in the admixture of Kabiven products vs. two referenced products (Aminosyn II 4.25% w/ Electrolytes in 25% Dextrose with Calcium, and Clinimix E Sulfite free with Electrolytes in Dextrose)

Product	Kabiven	(b) (4)	Aminosyn II 4.25 % w/ Electrolytes in 25 % Dextrose w/Ca	Clinimix E Sulfite free w/Electrolytes in Dextrose w/Ca
NDA No (approval)	--	--	19-683 (1988-11-07)	20-678 (1997-03-26)
Packaging: No of Chambers in Bag	3	3	2	2
Glucose (mg/ml)	98	68	250	350
Individual Amino Acids[1] (mg/ml)				
Alanine	4.67	3.33	4.22	10.35
Arginine	3.30	2.35	4.32	5.75
Aspartic Acid	0.99	0.71	2.98	--
Cysteine	--	--	--	--
Glutamic Acid	1.64	1.16	3.14	--
Glycine	2.31	1.64	2.12	5.15
Histidine	1.99	1.41	1.28	2.4
Isoleucine	1.64	1.16	2.80	3.0
Leucine	2.31	1.64	4.25	3.65
Lysine	2.63	1.87	4.46	2.9
Methionine	1.64	1.16	0.73	2.0
Phenylalanine	2.31	1.64	1.26	2.8
Proline	1.99	1.41	3.07	3.4
Serine	1.31	0.94	2.25	2.5
Threonine	1.64	1.16	1.70	2.1
Tryptophan	0.55	0.40	0.85	0.9
Tyrosine	0.067	0.048	0.93	0.2
Valine	2.13	1.52	2.12	2.9
Electrolytes[1] (mmol/l)				
Sodium	31.2	22.1	42	35
Potassium	23.4	16.7	33	30
Magnesium	3.9	2.8	2.5	2.5
Calcium	1.9	1.4	2.5	2.2
(b) (4) phosphorous	9.7	7.5	15	15
Chloride	45.2	32.5	48	39
Acetate	37.8	27.1	30.6	80

[1] In the mixed bag

Table A5: Glucose content (admixture of Kabiven and Perikabiven vs. that of Clinimix E) and Electrolyte contents (admixture of Kabiven and Perikabiven vs. that of Clinimix E and Aminosyn II)

	Kabiven	(b) (4)	Aminosyn® II		Clinimix® E		
Packaging: No of Chambers	3	3	2		2		
Glucose (g%)	9.8	6.8	20	25	5	10	25
Electrolytes (mmol/L)							
Sodium	31	22	42	40	35	35	35
Potassium	23	17	33	33	30	30	30
Magnesium	3.9	2.8	2.5	2.5	2.5	2.5	2.5
Calcium	1.9	1.4	2.5	2.5	2.2	2.2	2.2
(b) (4) phosphorous	9.7	7.5	15	15	15	15	15
Chloride	45	(b) (4)	48	48	39	39	39
Acetate	38	27	30.6	25.2	51	51	70
Sulfate[1]	3.9	2.8	--	--	--	--	--

15. Appendix II: List of Clinical Trials

Table A6: Kabiven Trials

Trial Name Dates Country	Trial Type	Trial Design	Treatment Products(s) Dosage Regimen/ Route of Administration	Number of patients treated	Trial Duration	Population
97-3CB1-001 06/98-12/98 UK	Safety Tolerance	Multi-center Randomized Open label Active Comparator	Pharmamix (Kabiven) Kabimix 14 30 mL/kg/d over 16-24hrs	Total – 50 Pharma -24 Kabimix - 26	7 days	Adult patients requiring TPN for ≥ 7 days
98-3CB1-002 09/98-11/99 UK	Safety Tolerance	Multi-center Randomized Open label Active Comparator	Pharmamix (Kabiven) Kabimix 14 25-30 mL/kg/d over 10-24hrs	Total – 23 Pharma – 12 Kabimix- 11	4 weeks	Inpatient adults with stable nutritional requirements for ≥ 4 weeks
98-3CB1-003 12/98-03/99 Germany	Safety Tolerance	Single Center Randomized Open label Parallel Group Active Comparator	Pharmamix (Kabiven) Mix of Vamin 18 EF, Glc, Intralipid 20%, ELKO-mix 30 mL/kg/d over 16-24hrs	Total – 41 Pharma – 20 Ref prod - 21	7 days	Adult patients status post GI surgery
00-3CB4-001 07/01-05/02 UK	Safety Tolerance Efficacy	Single center Randomized Open label Active comparator	Kabiven-30mL/kg/d 3CB Structo EL 23mL/kg/d Over 14-24 hrs	Total- 38 Kabiven-19 3CB Structo EL-19	7 days	Adult patients requiring TPN for ≥ 7 days
00-3CB5-001 04/01-11/01 Germany	Safety, Tolerance Efficacy	Single center Randomized Double blind Active comparator	Kabiven electrolyte modified AIO StructoQEl 30mL/kg/d	Total-42 21 in each grp	7 days	Post-operative adult patients
01-3CB5-002 10/02-03/03 Germany	Safety Tolerance Efficacy	Single Center Randomized Open label Active Comparator	Kabiven 3 CB StructoQ EL	Total-42 Kabiven-22 3CB- 20	7 days	Post-operative (major GI) adult patients
03-3CB7-001 07/04-02/05 Germany	Safety Tolerance	Single Center Randomized Open label Active Comparator	Kabiven 3CB SMOF EL 15mL/kg/d-P-1; 22 5-30ml/kg/d P- 2,3,4 & 15-30ml/kg/d P 5,6,7	Total 53 Kabiven – 27 3CB- 26	7 days	Post-operative (major GI) adult patients

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Table A7: Perikabiven Trials

Trial Name Dates Country	Trial Type	Trial Design	Treatment Products(s) Dosage Regimen/ Route of Administration	Number of patients treated	Duration of treatment	Population
98-3CB2-001 06/99-08/00 UK	Safety Tolerance (systemic and local)	Single center Randomized Open label Parallel Groups Active Comparator	PharmaMix Trio Peripheral (Kabiven P) Kabimix 9 1 bag/d over 12-24 hr	Total-46 Pharma – 24 Kabimix - 22	7 days	Adult subjects requiring TPN for ≥ 7 days; subjects could not have high needs of TPN
98-3CB2-002 11/99-11/00 France	Safety Tolerance (systemic and local)	Single center Randomized Open label Parallel Groups Active Comparator	Kabiven P Clinomel N4-550 Over 12-24 hrs	Total-45 Kabiven P-23 Clinomel -22	7 days	Adult subjects requiring TPN for ≥7 days
01-3CB6-001 05/02-12/03 UK		Single Center Randomized Open label Active Comparator	Kabiven P 3CB StructoPeri EL 1bag over 14-24 hr	Total- 41 Kabiven P-21 3CB-20	7 days	Adult subjects requiring TPN for ≥7 days
03-3CB8-001 07/04-10/05 Germany	Safety Tolerance	Multi-center Randomized Open label Active comparator	Kabiven P 3CB SMOF Peri EL 1 bag/d over 14-24hr	Total – 52 Kabiven P- 25 3 CB - 27	7 days	Adult subjects requiring TPN for 5-7 days

Modified applicant's table

Reference ID: 3047445

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/s/

SUE CHIH H LEE
11/18/2011

CLINICAL REVIEW

Application Type	NDA
Application Number(s)	200656
Priority or Standard	Standard
Submit Date(s)	28 January 2011
Received Date(s)	28 January 2011
PDUFA Goal Date	28 November 2011
Division / Office	ODE III, DGIEP (HFD-180)
Reviewer Name(s)	Karyn L. Berry, MD, MPH
Review Completion Date	03 November 2011
Established Name	Lipid injectable emulsion with amino acids and electrolytes and dextrose (pending)
(Proposed) Trade Name	Kabiven [redacted] (b) (4) (pending) and [redacted] (pending)
Therapeutic Class	Solutions for Parenteral Nutrition
Applicant	APP Pharmaceuticals, LLC
Formulation(s)	Intravenous
Dosing Regimen	Kabiven [redacted] (b) (4) The dose should be individualized and is dependent on the patient's clinical condition, body weight and nutritional requirements.

- Adult dosage: 19 to 38 mL/kg/day (0.63 to 1.26 g/kg/day of amino acids, 0.74 to 1.48 g/kg/day of fat, 1.85 to 3.71 g/kg/day of dextrose)

(b) (4)

(corresponding to 0.25 g/kg/hour of dextrose, the limiting factor, 0.09 g/kg/h of amino acids, and 0.1 g/kg/hour of fat). Recommended infusion period is 12 to 24 hours

(b) (4)

The dose should be individualized and is dependent on the patient's clinical condition, body weight and nutritional requirements.

- Adult dosage: 27 to 40 mL/kg/day (0.64 to 0.94g/kg/day of amino acids, 0.95 to 1.4 g/kg/day of fat, 1.83 to 2.71 g/kg/day of dextrose) (2)
- (b) (4)
- The maximum infusion rate is 3.7 mL/kg/h (corresponding to 0.25 g/kg/h of dextrose, the limiting factor, 0.09 g/kg/h of amino acids, 0.13 g/kg/h fat). The recommended infusion period is 12 to 24 hours (2)

Indication(s)

Kabiven (b) (4)

For intravenous infusion into a central vein as a source of calories, protein and essential fatty acids for patients requiring parenteral nutrition (b) (4) (b) (4) prevention of essential fatty acid deficiency (b) (4) or treatment of negative nitrogen balance (b) (4)

(b) (4)

(b) (4)

(b) (4)

Intended Population(s)

(b) (4)

Template Version: March 6, 2009

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Figure 1: 3 Chamber Bag 15

1 Recommendations/Risk Benefit Assessment

The Applicant, APP Pharmaceuticals, LLC, presents this 505(b)(2) application to support the drug products, Kabiven (b) (4) (also referred to as Kabiven) and (b) (4) (also referred to as (b) (4)) for the following indications:

<u>Kabiven</u>
For intravenous infusion into a central vein as a source of calories, protein and essential fatty acids for patients requiring parenteral nutrition (b) (4) prevention of essential fatty acid deficiency (b) (4) or treatment of negative nitrogen balance (b) (4)

(b) (4)

(b) (4)

For intravenous infusion into a peripheral or central vein as a source of calories, protein and essential fatty acids for patients requiring parenteral nutrition (b) (4) prevention of essential fatty acid deficiency (b) (4) or treatment of negative nitrogen balance (b) (4)

(b) (4)

The Applicant references prior findings by the FDA of safety and efficacy for Intralipid 20% (NDA 018449 and NDA 020248), Novamine 11.4% (NDA 017957) and two (2)-chamber bag (CB) products Aminosyn II with electrolytes in dextrose with calcium (NDA 019683) and CliniMix E sulfite free with electrolytes in dextrose with calcium (NDA 20678).

Kabiven and (b) (4) contain sodium glycerophosphate, an organic form of phosphate, which is not approved in the US. Since this will be the first use of this material in the US as an active ingredient in a pharmaceutical preparation, it is considered a new molecular entity (NME).

Kabiven [redacted] (b) (4) and [redacted] (b) (4) are new combination products that propose to provide parenteral nutrition (PN) in a three (3) chamber plastic bag. These solutions are stored in separate compartments of the multi-chamber bag, which is manufactured using a [redacted] (b) (4) The compartments are separated by breakable seals, which on opening result in a standardized "all in one" admixture. The individual chambers in Kabiven and [redacted] (b) (4) contain: Glucose [redacted] (b) (4)% [Kabiven] and Glucose [redacted] (b) (4)% [[redacted] (b) (4)] (Chamber 1); Amino acids ([redacted] (b) (4)) including electrolytes (Chamber 2), and Intralipid 20% (Chamber 3).

1.1 Recommendation on Regulatory Action

From a clinical standpoint, the submitted data are not adequate to support the recommendation of US marketing approval for Kabiven [redacted] (b) (4) or [redacted] (b) (4) for the proposed indications. It is the recommendation of this reviewer that a complete response (CR) action be taken for this application.

This recommendation is based on safety issues and deficiencies identified for both Kabiven and [redacted] (b) (4) by this reviewer and reviewers in other disciplines, such as Chemistry, Manufacturing and Control (CMC) and Centers for Devices and Radiological Health (CDRH).

The identified clinical deficiencies include: 1) inadequate data on the amount of heavy metals in each compartment of the 3-CB and the total amount of heavy metals in the combined products and 2) insufficient data to [redacted] (b) (4)

The Applicant's assessment of heavy metals, such as chromium, manganese, arsenic, cadmium, lead, mercury, copper and selenium in both Kabiven and [redacted] (b) (4) is inadequate. The Applicant did not test for heavy metals in the individual compartments of the 3-CBs nor in the combined mixed products.

Additional data is needed from the Applicant which specifies the amount of heavy metals in each compartment of the 3-CB and the total amount of metals when the compartments are mixed together. The Applicant will need to assess both Kabiven and [redacted] (b) (4) for levels of the following metals: arsenic, cadmium, lead, mercury, chromium, copper, manganese, selenium and zinc. The data will need to show the levels of each of the above metals in 3 batches of the each product, with the information reported as parts per million (ppm).

The Applicant also has not provided sufficient data to [redacted] (b) (4) The Applicant has proposed [redacted] (b) (4)

Reference ID: 3044686

(b) (4)
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The Applicant submitted a pediatric plan in Amendment #14 (October 21, 2011). Review of the plan will be deferred until the next review cycle.

Additional safety issues identified by other discipline reviewers are: 1) inadequate information to assure the purity of the drug product, i.e. heavy metals and impurities in (b) (4), 2) *Withhold* recommendation from the Office of Compliance and 3) inadequate tests to demonstrate the products packaging resistance to temperature, pressure, leakage, dropping and performance of human factor testing to ensure that use-related risks have been identified and mitigated. The various review disciplines have outlined the actions and studies needed to resolve these deficiencies.

1.2 Risk Benefit Assessment

As new formulations of currently approved PN products, Kabiven (b) (4) and (b) (4), do not fill an unmet medical need. While, the Applicant proposes advantages of these products, such as convenience of use, there is no clinical data to suggest that these products offer a therapeutic advantage over existing PN products that are approved for use in adults.

Heavy metal content in Kabiven and (b) (4) was monitored only for individual drug substances, the Applicant did not assess the individual chambers or the whole mixed product. Since the drug product daily dose is very large ((b) (4) mL to 2556 mL) the cumulative amounts of heavy metals in the products could surpass daily allowable limits. Data is needed from the Applicant which specifies the amount of heavy metals in each compartment of the 3-CB and the total amount of heavy metals when the compartments are mixed together. Based on these results, appropriate limits of the various heavy metals present need to be determined and then added to package inserts.

The presence of heavy metals in PN can have significant adverse effects on organs and tissues, such as nephropathy (associated with excess chromium) and neurotoxicity and hepatotoxicity (associated with manganese).[1] Over the years, there have been numerous reports in the literature regarding the presence of heavy metals in PN products.[2,3] The concern of clinicians is that some of these heavy metals are considered essential trace elements, such as zinc, copper, chromium and manganese and are commonly added to PN.[4]

Studies have demonstrated that trace elements are often present in significant concentrations in components of PN.[1,4] The concentrations may vary markedly among solutions from different manufacturers and from different lots.[1,4] Inadequate data concerning baseline levels of these heavy metals in PN products creates the potential for toxicity. Populations especially at risk for heavy metal toxicity include patients on long term PN use, pediatrics patients, renal and hepatic patients.

Given the availability of alternative products for PN and the concerns about the need to assess Kabiven [redacted] (b) (4) and [redacted] (b) (4) for heavy metals, at this time, the safety risks of treatment with these products outweighs the benefits.

1.3 Recommendations for Postmarket Risk Evaluation and Mitigation Strategies

Postmarket risk evaluation and marketing will be evaluated during the next review cycle.

1.4 Recommendations for Postmarket Requirements and Commitments

Postmarket requirements and commitments will be evaluated during the next review cycle.

2 Introduction and Regulatory Background

Parenteral nutrition (PN) is the provision of intravenous nutrients to patients whose gastroinstestinal (GI) tract is not functioning or cannot be accessed. PN may also be administered to patients whose nutritional needs cannot be met with oral diets or enteral tube feedings alone. The nutritional components of PN include crystalline amino acids, dextrose, fat emulsion, sterile water for injection, electrolytes, vitamins and minerals, administered intravenously. There are two types of PN admixtures. These are 1) 2-in-1 formulations which are mixtures of dextrose, amino acids, sterile water for injection, electrolytes, vitamins and minerals. Intravenous fat emulsion (IVFE) is administered separately and 2) 3-in-1 or all-in-one formulations which contain IVFE in the same container with dextrose, amino acids, sterile water for injection, electrolytes, vitamins and minerals.[5]

PN can either be administered via peripheral venous infusion (PPN) or through a central vein (CPN). The components of PN determine its osmolarity and infusion route. PPN has a similar composition as CPN, but lower concentrations of nutrient components to allow for peripheral administration. PPN has a lower final dextrose concentration, between 5% to 12.5%, than CPN. To decrease the risk of thrombophlebitits in PPN, the

osmolarity is generally less than 900 mOsm/L and calcium and potassium concentrations are lower.[5]

The applicant proposes to demonstrate the safety and efficacy of Kabiven and [redacted] (b) (4) two 3 chamber bag (CB) drug products for PN, by referencing prior findings by the FDA of safety and efficacy for Intralipid 20% (NDA 018449 and NDA 020248) and Novamine 11.4% (NDA 017957), to support a US Food, Drug, and Cosmetic Act (FD&C) 505(b)(2) marketing application. According to the Applicant, the proposed Kabiven products also deliver dextrose and electrolytes similar to those in the approved 2-CB products Aminosyn II with electrolytes in dextrose with calcium (NDA 019683) and CliniMix E sulfite free with electrolytes in dextrose with calcium (NDA 20678).

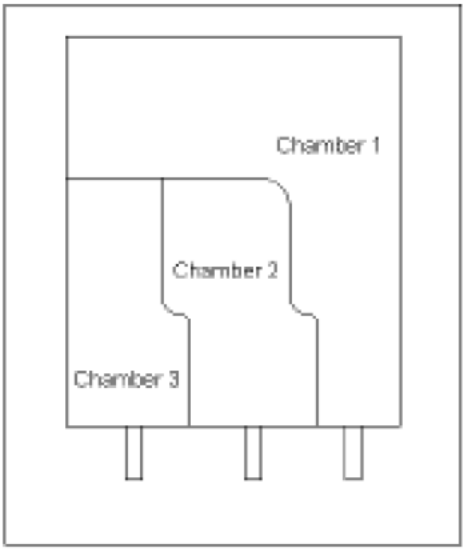
Kabiven and [redacted] (b) (4) are new combination products that provide parenteral nutrition in a three chamber plastic bag. These solutions are stored in separate compartments of the multichamber bag, which is manufactured using a [redacted] (b) (4) The compartments are separated by breakable seals, which on opening result in a standardized "all in one" admixture. The individual chambers in Kabiven and [redacted] (b) (4) contain: Glucose [redacted] (b) (4)% [Kabiven] and [redacted] (b) (4)% [redacted] (b) (4) (Chamber 1); Amino acids ([redacted] (b) (4)) including electrolytes (Chamber 2), and Intralipid 20% (Chamber 3).

The Applicant stated that Kabiven and [redacted] (b) (4) are products that are designed to provide "all in one" total nutrient admixtures for PN. The advantages of this product as per the Applicant are:

- Reduced manipulation of bags and lines thereby minimizing risk of contamination
- Reduced osmolarity of compounded mixture may permit peripheral administration
- Facilitates delivery and storage particularly for patients on home parenteral nutrition
- Support cost effective with respect to preparation, handling and delivery
- Provision of energy as glucose and fat enhances utilization compared to single energy regimens and minimizes risks of fluid overload, hypercapnia and hepatic accumulation of triglycerides
- Less intimidating for the patient and encourages patient mobility
- Labeling of bags ensures that medical and nursing attendants can easily confirm the precise composition of infused nutrients
- Facilitates pharmacy records

Medical Reviewer's comments: The Applicant did not submit data that evaluated the risk of contamination, compliance, convenience or cost effectiveness of Kabiven/ [redacted] (b) (4) *therapy over existing PN therapy.*

Figure 1: 3 Chamber Bag



The smallest chamber (chamber 3) always contains lipid [redacted] (b) (4) the middle chamber (chamber 2) contain the amino acid solution and the chamber next to the handle (chamber 1) contains the glucose solution.

Table 1: Reference Listed Drugs (RLDs)

Name of Drug Product	NDA #	Approval Date
Intralipid 20% Intralipid 20% Pharmacy bulk package	NDA 018449 ANDA 020248	23-Jan-1981 07-Aug-1996
Novamine® 11.4% Injection	NDA 017957	03-Jan-1978
Clinimix® E Sulfite free with Electrolytes in Dextrose with Calcium	NDA 020678	26-Mar-1997
Aminosyn® II with Electrolytes in Dextrose 25% Injection with Calcium	NDA 019683	07-Nov-1988

2.1 Product Information

The individual referenced products of Kabiven and [redacted] (b) (4) have been approved in the United States as components of PN. The IVFE, Intralipid 20%, a Fresenius Kabi product, is a soybean oil based lipid emulsion that provides essential and non-essential long chain fatty acids. In PN it is also an energy source.

The amino acid component is [redacted] (b) (4). According to the applicant it [redacted] (b) (4) to Hospira's Novamine 11.4% (NDA 017957). [redacted] (b) (4) The difference between [redacted] (b) (4) and Novamine 11.4% [redacted] (b) (4) versus [redacted] (b) (4) in Novamine 11.4%.

Kabiven and [redacted] (b) (4) electrolyte solution contain sodium glycerophosphate, an organic form of phosphate, which is not approved in the US, and the following electrolytes: sodium acetate trihydrate, potassium chloride, magnesium [redacted] (b) (4) heptahydrate and calcium chloride dihydrate. Sodium glycerophosphate is manufactured by [redacted] (b) (4) Sodium glycerophosphate is commercially available with a monograph in Ph.Eur. Since this will be the first use of this material in the US as an active ingredient in a pharmaceutical preparation, it is considered a new molecular entity (NME). The Applicant states that the use of sodium glycerophosphate a [redacted] (b) (4)

The Applicant stated that the electrolyte profile in the Kabiven products was selected to [redacted] (b) (4)

Table 2: Electrolyte content of proposed products in comparison to recommended daily requirements

ELECTROLYTE	Daily Requirements (mmol/kg)		Kabiven (mmol/daily dose[2])			[redacted] (b) (4) (mmol/daily dose[2])		
	ASPEN 2004	ESPEN 2009	30mL/kg (min)	35mL/kg (maint)	40mL/kg (max)	30mL/kg (min)	35mL/kg (maint)	40mL/kg (max)
Sodium	1-2	1-1.5	[redacted] (b) (4)					
Potassium	1-2	1-1.5						
Magnesium	0.06-0.14[1]	0.1-0.2						
Calcium	0.07-0.11[1]	0.1-0.15						
Phosphate/ Phosphorous	0.29-0.57[1]	0.3-0.5						
Chloride	As needed to maintain acid-base balance	1-1.5						

[1] Values are calculated to a 70 kg patient since the recommendations are in total daily dose for an individual
[2] Volume of daily dose is minimum, maximum and maintenance fluid requirements for an adult as per ASPEN and ESPEN parenteral nutrition guidelines respectively

Medical Reviewer's comments: The CMC reviewer notes that egg phospholipids have been extensively used as an excipient ([redacted] (b) (4)) in parenteral lipid products, but in the current product it also function as an active ingredient since it contributes to the labeled phosphorous content of the product, along with the glycerophosphate. Since this is the first use of egg phospholipid as an active ingredient, the CMC reviewer has classified egg phospholipids as an NME. The Applicant notes that close monitoring of electrolytes and electrolyte supplementation may be needed, especially with [redacted] (b) (4)

Proposed trade names: Kabiven [redacted] (b) (4) (Kabiven) and [redacted] (b) (4) [redacted]

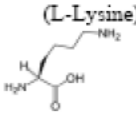
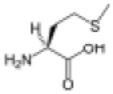
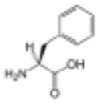
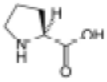
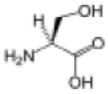
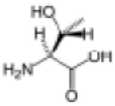
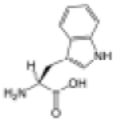
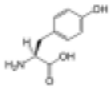
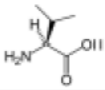
Pharmacological class: Solutions for parenteral nutrition, ATC code B05BA10

Manufacturer: Fresenius Kabi AB, Sweden

Distributor: APP Pharmaceuticals

Chemical Name and Structure of Components:

Name	Molecular Formula	Structure
Lipids		
Soybean oil	Triacylglycerol with fatty acid chains mainly C16:0, C18:1, C18:2	R=Fatty Acid Chains
Carbohydrate		
Glucose monohydrate (Dextrose)	$C_6H_{12}O_2.H_2O$	
Amino Acids		
L-Alanine	$C_3H_7NO_2$	
L-Arginine	$C_6H_{14}N_4O_2$	
L-Aspartic acid	$C_4H_6NO_4$	
L-Glutamic acid	$C_5H_8NO_4$	
Glycine	$C_2H_5NO_2$	
L-Histidine	$C_6H_9N3O_2$	
L-Isoleucine	$C_6H_{13}NO_2$	

Name	Molecular Formula	Structure
L-Leucine	$C_6H_{13}NO_2$	
L-Lysine hydrochloride	$C_6H_{14}N_2O_2.HCl$	(L-Lysine) 
L-Methionine	$C_5H_{11}NO_2S$	
L-Phenylalanine	$C_9H_{11}NO_2$	
L-Proline	$C_5H_9NO_2$	
L-Serine	$C_3H_7NO_3$	
L-Threonine	$C_4H_9NO_3$	
L-Tryptophan	$C_{11}H_{12}N_2O_2$	
L-Tyrosine	$C_9H_{11}NO_3$	
L-Valine	$C_5H_{11}NO_2$	
Electrolytes		
Calcium chloride dihydrate	$CaCl_2.2H_2O$	-
Sodium glycerophosphate	$C_3H_5(OH)_2PO_4Na_2.xH_2O$	-
Magnesium [redacted] (b) (4) heptahydrate	$MgSO_4.7H_2O$	-
Potassium chloride	KCl	-
Sodium acetate trihydrate	$CH_3COONa.3H_2O$	-

Applicant's table

Proposed indication for Kabiven

For intravenous infusion into a central vein as a source of calories, protein and essential fatty acids for patients requiring parenteral nutrition [redacted] (b) (4) [redacted] prevention of essential fatty acid deficiency [redacted] (b) (4) or treatment of negative nitrogen balance [redacted] (b) (4) [redacted] (b) (4)

(b) (4)

Proposed indication for (b) (4)

For intravenous infusion into a peripheral or central vein as a source of calories, protein and essential fatty acids for patients requiring parenteral nutrition (b) (4) prevention of essential fatty acid deficiency (b) (4) or treatment of negative nitrogen balance (b) (4)

(b) (4)

Medical Reviewer's comments: Peripheral PN is generally not indicated for (b) (4)." The A.S.P.E.N. guidelines for PPN recommend limiting it to short periods (up to 2 weeks). This was conveyed to the Applicant and clarification was provided by the Applicant on August 18, 2011. In that letter the Applicant stated that this was a transcription error and the Package insert for (b) (4) was revised by deleting '(b) (4)."

Proposed aged groups for Kabiven and (b) (4): (b) (4)

Medical Reviewer's comments: The use of Kabiven and (b) (4)

Dosing and Administration Kabiven and (b) (4):

The ability to eliminate fat and to metabolize dextrose should govern the dosage and infusion rate of Kabiven and (b) (4). The dosage should be made with regard to the patient's clinical condition, body weight and nutritional requirement.

Kabiven is produced in 4 sizes for patients with high, moderately increased, basal or low nutritional requirements. The four sizes of Kabiven bags proposed are: 1026 ml, 1540 ml, 2053 ml and 2566 ml. The components of Kabiven are Intralipid 20%, (b) (4) with electrolytes and Glucose (b) (4)%.

Table 3: Dosing Information for Kabiven

Mode of Administration	Central vein
Energy requirement	Dependent on clinical condition; usually (b) (4) kcal/kg of body weight/day
Dosing	(b) (4)
	Maximum daily dose: 40 mL/kg/day. (b) (4)
(b) (4)	(b) (4)
Infusion Rate	Not more than 2.6mL/kg bw/hr (corresponding to 0.25g dextrose, 0.09g amino acid and 0.1g (b) (4)/kg bw)
Recommended Infusion Period	12 to 24 hours

Applicant's table, ISS p.107

Table 4: List of components in all packaging of Kabiven

(b) (4)

(b) (4) is produced in 3 sized for patients with moderately increased, basal or low nutritional requirements. The three sizes of (b) (4) bags proposed are 1440 ml, 1920 ml and 2400 ml. The components of (b) (4) are Intralipid 20%, (b) (4) with electrolytes and Glucose (b) (4)%.

Table 5: Dosing Information for (b) (4)

Mode of Administration	Peripheral or Central vein
Energy requirement	Dependent on clinical condition; often 20 to 30 kcal/kg of body weight/day
Dosing	(b) (4)
(b) (4)	(b) (4)

(b) (4)

Infusion Rate	Not more than 3.7 mL/kg/hr (corresponding to 0.25 g/kg dextrose, 0.09g/kg amino acid and 0.13 g/kg (b) (4)
Recommended Infusion Period	12 to 24 hours

Applicant's table, ISS

Table 6: List of components in all packaging sizes of (b) (4)

(b) (4)

Table 7: Kabiven and [redacted] (b) (4) Product Composition

	Kabiven	[redacted] (b) (4)
Pack sizes (ml)	2566 2053 1540 1026	2400 1920 1440
Composition		
Individual Chamber (per 1000 ml)		
[redacted] (b) (4)		
Combined mixture (mg/ml)		
Purified Soybean Oil	39	35
Glucose	98	68
Amino acids		
Alanine	4.67	3.33
Arginine	3.30	2.35
Aspartic Acid	0.99	0.71
Glutamic Acid	1.64	1.16
Glycine	2.31	1.64
Histidine	1.99	1.41
Isoleucine	1.64	1.16
Leucine	2.31	1.64
Lysine	2.63	1.87
Methionine	1.64	1.16
Phenylalanine	2.31	1.64
Proline	1.99	1.41
Serine	1.31	0.94
Threonine	1.64	1.16
Tryptophan	0.55	0.40
Tyosine	0.067	0.048
Valine	2.13	1.52
Electrolytes		
[redacted] (b) (4)		

N.A. Not applicable
Applicant's table: Document #43 169/02; p.4

Medical Reviewer's comments: [redacted] (b) (4)

Table 8: Comparison of Composition of FDA Approved Products with Proposed Products

Product	Intralipid 20 %	Novamine 11.4 %	Aminosyn II with Electrolytes in Dextrose with Calcium	Kabiven	(b) (4)
NDA No (approval)	18-449 (1981-01-23) 20-248 (1996-08-07)	17-957 (1978-01-03)	19-683 (1988-11-07)	--	--
Packaging: No of Chambers in Bag	1	1	2	3	3
Individual chamber Composition (%)					
Soybean Oil	20	--	--	(b) (4)	
Glucose	--	--	50		
(b) (4) Amino Acid	--	11.4	8.5		
Individual Amino Acids[1] (mg/ml)					
Alanine	--	16.50	8.44	(b) (4)	
Arginine	--	11.20	8.65		
Aspartic Acid	--	3.30	5.95		
Glutamic Acid	--	5.70	6.27		
Glycine	--	7.90	4.25		
Histidine	--	6.80	2.55		
Isoleucine	--	5.70	5.61		
Leucine	--	7.90	8.50		
Lysine	--	9.00	8.93		
Methionine	--	5.70	1.46		
Phenylalanine	--	7.90	2.53		
Proline	--	6.80	6.14		
Serine	--	4.50	4.50		
Threonine	--	5.70	3.40		
Tryptophan	--	1.90	1.70		
Tyrosine	--	0.30	1.87		
Valine	--	7.30	4.25		
Electrolytes[1] (mmol/l)					
Sodium	--	--	84	(b) (4)	
Potassium	--	--	66		
Magnesium	--	--	5[2]		
Calcium	--	--	--[2]		
(b) (4) phosphorous	--	--	30		
Chloride	--	--	96		
Acetate	--	--	61		

[1] In the amino acid and electrolyte solution
[2] In the dextrose solution
Applicant's table: Document # 43 169/02 p. 5

Table 9: Component Concentrations after mixing of Multi-Chamber Bag Products

Product	Kabiven	(b) (4)	Aminosyn II 4.25 % w/ Electrolytes in 25 % Dextrose w/Ca	Clinimix E Sulfite free w/Electrolytes in Dextrose w/Ca
NDA No (approval)	--	--	19-683 (1988-11-07)	20-678 (1997-03-26)
Packaging: No of Chambers in Bag	3	3	2	2
Glucose (mg/ml)	98	68	250	350
Individual Amino Acids[1] (mg/ml)				
Alanine	4.67	3.33	4.22	10.35
Arginine	3.30	2.35	4.32	5.75
Aspartic Acid	0.99	0.71	2.98	--
Cysteine	--	--	--	--
Glutamic Acid	1.64	1.16	3.14	--
Glycine	2.31	1.64	2.12	5.15
Histidine	1.99	1.41	1.28	2.4
Isoleucine	1.64	1.16	2.80	3.0
Leucine	2.31	1.64	4.25	3.65
Lysine	2.63	1.87	4.46	2.9
Methionine	1.64	1.16	0.73	2.0
Phenylalanine	2.31	1.64	1.26	2.8
Proline	1.99	1.41	3.07	3.4
Serine	1.31	0.94	2.25	2.5
Threonine	1.64	1.16	1.70	2.1
Tryptophan	0.55	0.40	0.85	0.9
Tyrosine	0.067	0.048	0.93	0.2
Valine	2.13	1.52	2.12	2.9
Electrolytes[1] (mmol/l)				
Sodium	(b) (4)	(b) (4)	42	35
Potassium			33	30
Magnesium	3.9	2.8	2.5	2.5
Calcium	1.9	1.4	2.5	2.2
(b) (4) phosphorous	9.7	7.5	15	15
Chloride	(b) (4)	(b) (4)	48	39
Acetate			30.6	80

[1] In the mixed bag

Applicant's table: Document No. 43 169/02 p. 6

2.2 Tables of Currently Available Treatments for Proposed Indications

There are a number of products currently available that are components of parenteral nutrition. These include: intravenous lipid emulsions (IVLE), amino acids, electrolytes, dextrose, trace elements and vitamins.

Table 10: Commercially Available IV Lipid Emulsions in US

Brand Name	Type	Concentration
Liposyn III	Long chain triglycerides/soybean oil	10%, 20%, 30% (Pharmacy bulk package)
Intralipid	Long chain triglycerides/soybean oil	10%, 20%, 20% (Pharmacy bulk package), 30% (Pharmacy bulk package)

Reviewer's table

Table 11: Commercially Available Crystalline Amino Acid Solutions

Brand Name	Type/Indication	Stock Concentration
Aminosyn II	Standard	3.5%, 4.25%, 5%, 7%, 8.5%, 10%, 15%
Clinosol	Standard/fluid restriction	15%
FreAmine III	Standard	8.5%, 10%
Prosol	Standard/ fluid restriction	20%
Travasol	Standard	3.5%, 4.25%, 5.5%, 8.5%, 10%,
HepatAmine	Hepatic failure	8%
Hepatasol	Hepatic failure	8%
Aminosyn- HBC	Metabolic stress	7%
BranchAmin	Metabolic stress	4%
FreAmine HBC	Metabolic stress	6.9%
Aminosyn -RF	Renal failure	5.2%
NephrAmine	Renal failure	5.4%
Ren Amin	Renal failure	6.5%
Aminosyn -PF	Neonates	7%
PremaSol	Neonates	6%, 10%
Trophamine	Neonates	6%, 10%

*contains essential amino acids+arginin
**Contains essential amino acids only
***contains essential amino acids and some non-essential amino acids
[5]A.S.P.E.N. Parenteral Nutrition Handbook, 2009. p. 133

Table 12: Commercially Available Parenteral Electrolyte Salts

Electrolyte	Salt form
Sodium	Chloride, Acetate, Phosphate
Potassium	Chloride, Acetate, Phosphate
Chloride	Sodium, Potassium
Acetate	Sodium, Potassium
Calcium	*Gluconate, Gluceptate, Chloride
Magnesium	*Sulfate, Chloride

*Preferred salt form for use in PN formulations
[5]A.S.P.E.N. Parenteral Nutrition Handbook 2009, p. 136

Glucose: Dextrose from 2.5% to 70% in various solutions

2.3 Availability of Proposed Active Ingredient in the United States

Sodium glycerophosphate, an NME, is not currently marketed in the US. Please refer to Section 8 for safety information from other countries. Various formulations of IV lipid emulsions, amino acids, electrolytes and dextrose are marketed in the US. Please refer to Sections 2.2 and 2.4 for additional information related to the RLDs.

2.4 Important Safety Issues With Consideration to Related Drugs

The individual components of the 3 chamber bag: IVFE, dextrose, and amino acids with electrolytes have widespread distribution and a generally good safety profile. However, there are potential safety issues/complications associated with PN products. These include 1) the risk of heavy metal contamination of these products during the manufacturing process, 2) the risk of metabolic complications such as hyper/hypoglycemia, refeeding syndrome, electrolyte imbalances, lipid abnormalities, acid-base disturbance, hepatobiliary disorders and bone disease and 3) the risk of mechanical and septic complications such as central vascular access complications, mechanical complications, catheter related infections and catheter occlusion and thrombosis.[10]

Potential heavy metal toxicities as a result of PN products have been associated with various disorders. In the literature there have been reports of heavy metal contamination of TPN solutions. For example, chromium toxicity related to PN has been associated with nephropathy, manganese toxicity has been associated with neurotoxicity and possible hepatotoxicity in children. Pharmacology/Toxicology studies by Buchman, et.al., demonstrated that this contamination can lead to organ deposition of heavy metals and subsequent histologic abnormalities.[1]

In the early 1980's it was found that some patients with end-stage renal disease on dialysis developed signs and symptoms thought to be associated with aluminum toxicity such as encephalopathy and bone pain. It was determined that aluminum present in diasylate was responsible, leading to the removal of aluminum from dialysis solutions. Aluminum accumulation in bone, serum and tissues of neonates receiving long term PN was also noted.[11] In 2000, to address this metal toxicity issue, the FDA published a final rule that imposed certain requirements and limits for aluminum containing large volume parenteral, small volume parenteral and pharmacy bulk packages and set limits on the aluminum content in PN products.[12]

Current control of metal impurities is primarily based on pharmacopoeial requirements for Heavy Metals, which have been widely used for routine screening of pharmaceutical ingredients for many years. The October 2006 International Conference on Harmonization (ICH) Q3A *Impurities in New Drug Substances* guidance classifies impurities as organic, inorganic, and residual solvents. It provides guidance on the reporting and control of impurities, analytical procedures, reporting impurity content of batches, listing of impurities in specifications and qualification of impurities.[13]

Table 13: Predominate sources for heavy metal contamination in total parenteral nutrition[1]

Metal	Source
Aluminum	Calcium gluconate, potassium phosphate, amino acids
Arsenic	Lipid emulsion, amino acids, vitamins, dextrose
Barium	Dextrose
Chromium	Dextrose, amino acids, trace element solution
Germanium	Amino acids
Lead	Amino acids
Manganese	Trace elements
Tin	Lipid emulsion, amino acids, dextrose

Table from Buchman et. al.

The Package Inserts (PIs)of the RLDs and other PN products were reviewed to assess safety labeling such as contraindications, warnings, precautions and listed adverse reactions.[14]

More frequent AEs listed for Intralipid include: contamination of the I.V. catheter and results in sepsis, or vein irritation by hypertonic solutions, thrombophlebitis. Less frequent reactions reported in clinical trials at incidence of < 1% are dyspnea, cyanosis, allergic reactions, hyperlipemia, hypercoagulability, nausea, vomiting, headache, flushing, increase in temperature, sweating, sleepiness, pain in chest and back, hepatomegaly, jaundice due to cholestasis, splenomegaly, thrombocytopenia, leukopenia, transient increase in liver function tests.

AEs listed for Aminosyn II are hyperosmolar syndrome, febrile response, infection at the site of the injection, venous thrombosis or phlebitis extending from the site of injection, extravasation, hypervolemia, generalized flushing, fever and nausea.

Table 14: Safety Labeling in components of Parenteral Nutrition

Safety Labeling in components of Parenteral Nutrition
Intralipid: Contraindications: Patients demonstrating disturbances in normal fat metabolism, such as pathologic hyperlipemia, lipoid nephrosis or acute pancreatitis if accompanied by hyperlipemia Boxed Warnings: Deaths in preterm infants after infusion of IV fat emulsion have been reported in the medical literature. Autopsy findings included intravascular fat accumulation in the lungs.Treatment of premature and low birth weight infants with IV fat emulsion must be based upon careful benefit-risk assessment. Warning: Product contains aluminum that may be toxic. Aluminum may reach toxic levels with prolonged parenteral administration if kidney function is impaired. Research indicates that patients with impaired kidney function, including premature neonates, who receive parenteral levels of aluminum at > 4-5 mcg/kg /day accumulate aluminum at levels associated with CNS and bone toxicity.

Precautions: When administered, patients capacity to eliminate infused fat from the circulation must be monitored by use of an appropriate laboratory determination of serum triglycerides. Overdosage must be avoided. During long term admin, liver function tests should be performed. If these tests indicate that liver function is impaired, therapy should be withdrawn. Frequent (some advise daily) platelet counts should be done in neonatal patients receiving Intralipid.

Liposyn

Contraindications: Patients demonstrating disturbances in normal fat metabolism, such as pathologic hyperlipemia, lipoid nephrosis or acute pancreatitis if accompanied by hyperlipemia

Boxed Warnings: Deaths in preterm infants after infusion of IV fat emulsion have been reported in the medical literature. Autopsy findings included intravascular fat accumulation in the lungs.Treatment of premature and low birth weight infants with IV fat emulsion must be based upon careful benefit-risk assessment.

Warnings: Caution should be exercised in administering Liposyn to patients with severe liver damage, pulmonary disease, anemia or blood coagulation disorders or when there is danger of fat embolism. Too rapid admin can cause fluid and/or fat overloading resulting in dilution of serum electrolytes, overhydration, congested states, pulmonary edema, impaired pulmonary diffusion capacity or metabolic acidosis.

Product contains aluminum that may be toxic. Aluminum may reach toxic levels with prolonged parenteral administration if kidney function is impaired. Research indicates that patients with impaired kidney function, including premature neonates, who receive parenteral levels of aluminum at > 4-5 mcg/kg /day accumulate aluminum at levels associated with CNS and bone toxicity.

Precautions: Free fatty acids displace bilirubin bound to albumin, use of lipid infusions in jaundiced or premature infants should be done with caution. During admin, patient's hemogram, blood coagulation, liver function, platelet count and plasma lipid profile must be closely monitored.

Aminosyn II with electrolytes in Dextrose

Contraindication: Should not be used in patients with hepatic coma or metabolic disorders involving impaired nitrogen utilization. Solutions are too concentrated for use in infants

Warnings: Solutions in dextrose with a final concentration of 20% or 25% are hypertonic and don't admin by peripheral vein. Concentrated dextrose solution, if admin too fast may result in significant hyperglycemia and possible hyperosmolar syndrome. IV infusion may induce a rise in BUN, appropriate lab test should be performed periodically and infusion D/C if BUN levels exceed normal postprandial limits. Administration of amino acid solutions to a patient with hepatic insufficiency may result in serum amino acid imbalances, metabolic alkalosis, prerenal azotemia, hyperammonemia, stupor and coma. Administration of amino acid solutions in the presence of impaired renal function may augment an increasing BUN, as does any protein dietary component. Solutions containing sodium ion should be used with great care, if at all, in patients with congestive heart failure, severe renal insufficiency and in clinical states in which there exists edema with sodium retention. Solutions containing potassium ions should be used with great care, if at all, in patients with hyperkalemia, severe renal failure and in conditions in which potassium retention is present. Solutions containing acetate ion should be used with great care in patients with metabolic or respiratory alkalosis. Acetate should be administered with great care in those conditions in which there is an increased level or an impaired utilization of this ion, such as severe hepatic insufficiency. This product contains aluminum that may be toxic. Aluminum may reach toxic levels with prolonged parenteral administration if kidney function is impaired. Premature neonates are particularly at risk because their kidneys are immature, and they require large amounts of calcium and phosphate solutions, which contain aluminum.

Precautions: Special care must be taken when administering glucose to diabetic or prediabetic patients. To control and minimize hyperglycemia and consequent glycosuria, it is desirable to monitor blood and urine glucose and, if necessary, add insulin. Because of its antianabolic activity, concurrent administration of tetracycline may reduce the nitrogen sparing effects of infused amino acids. Intravenously administered amino acids should be used with caution in patients with history of renal disease, pulmonary disease, or with cardiac insufficiency so as to avoid excessive fluid accumulation.

Special Precautions for Central Infusions
Clinimix Contraindication: Patients having intracranial or intraspinal hemorrhage, in patients who are severely dehydrated, in patients hypersensitive to one or more amino acids, and in patients with severe liver disease or hepatic coma.
Warnings: Frequent clinical evaluation and laboratory determinations are necessary for proper monitoring during administration. This product contains aluminum that may be toxic. Aluminum may reach toxic levels with prolonged parenteral administration if kidney function is impaired. Premature neonates are particularly at risk because their kidneys are immature, and they require large amounts of calcium and phosphate solutions, which contain aluminum.
Precautions: hyperglycemia, glycosuria, and hyperosmolar syndrome may result. Blood and urine glucose should be monitored on a routine basis in patients receiving. Use with caution when administering to patients with anuria or renal failure.

Medical Reviewer's comments: The population that receives PN often has multiple co-morbidities, such as acid-base imbalance, cardiac, pulmonary disorders that must be considered and followed when administering PN. Regarding heavy metals, it is unclear what the cumulative amounts of heavy metals is in overall PN products and specifically in the combination Kabiven and [redacted] (b) (4) products. Except for aluminum, this information has not previously been assessed. Additional data is needed from the Applicant which specifies the amount of metals in each compartment of the 3-CB and the total amount of metals when the compartments are mixed together. The Applicant will need to assess both Kabiven and [redacted] (b) (4) for levels of the following metals: arsenic, cadmium, lead, mercury, chromium, copper, manganese, selenium and zinc. The data will need to show the levels of each of the above metals in 3 batches of the each product, with the information reported as ppm. Based on the results, limits may need to implemented and listed in the PI, similar to what was done with Aluminum. The PI for Kabiven and [redacted] (b) (4) should also incorporate the safety language that is found in the individual labels of the RLDs.

2.5 Summary of Presubmission Regulatory Activity Related to Submission

The following is a summary of pre-submission regulatory activities related to this current submission. Submissions were done under IND 105,282.

September 2010 [redacted] (b) (4)
The sponsor's request for [redacted] (b) (4)

July 30, 2010 (Sponsor's response to FDA advice/information letter dated 01/01/2010)
The sponsor agreed to submit Kabiven and [redacted] (b) (4) as a single 505(b)(2) NDA application. The sponsor also agreed to provide scientific rationale and data for the electrolytes concentrations in Kabiven and [redacted] (b) (4) in the NDA submission.

The sponsor acknowledged and the need to further characterize sodium glycerophosphate in humans and agreed to conduct a relative bioavailability study in healthy volunteers to demonstrate the equivalence of sodium glycerophoshpate (organic phosphate) that is present in Kabiven and [redacted] (b) (4) to inorganic phosphate.

The sponsor stated that demonstrating bioequivalence of the phosphate moiety using the complete product containing all [redacted] (b) (4) components of Kabiven and [redacted] (b) (4) is not possible due to physiological effects of the nutrients on phosphate metabolism. The sponsor stated that the requested characterization is feasible using products that contain the phosphate component only and that additional determination and characterization of any interactions or matrix effects of other components of the TPN on the availability of phosphate will be determined by a bridging study comparing the glycerophosphate in Kabiven and [redacted] (b) (4) versus glycerophosphate alone.

<u>July 9, 2010</u> [redacted] (b) (4))
Sponsor submitted request for [redacted] (b) (4) [redacted] (b) (4) [redacted].

<u>January 25, 2010</u> (Advice/Information letter)
Sponsor's three questions were addressed by the FDA:

The FDA agreed with the sponsor's request for a single NDA submission for Kabiven and [redacted] (b) (4) using §505(b)(2) of the US Food, Drug, and Cosmetic Act. The Sponsor intends to demonstrate comparability of Kabiven and [redacted] (b) (4) based on FDA's previous findings of safety and efficacy on dextrose solution (NDA 017521), Fresenius Kabi's Intralipid 20% (NDA 018449 and NDA 020248), and Hospira's Novamine 11.4% (NDA 017957).

FDA reiterated the requirement that the sponsor provide additional characterization of sodium glycerophosphate for use in humans, since the proposed product is different from the referenced product in terms of phosphate. The sponsor was told that they must demonstrate the relative bioavailabity between the proposed products and the reference product by conducting a relative bioavailability study in healthy subjects.

The FDA informed the sponsor that their proposed CTD was not adequate. The sponsor was informed that the submission must include available efficacy and safety summaries of clinical trial and nonclinical study data from the literature as they related to the three component products of Kabiven and [redacted] (b) (4), as well as the combined products. The sponsor was also informed that they would need to include an integrated summary of safety that details safety data from the bioavailability study.

July 20, 2009 (Type B Meeting)
The Applicant submitted proposed background package for a meeting to discuss the NDA submission. Sponsor's questions were related to 1) referencing currently marketed products for 505(b)(2) application, 2) seeking the Agency's agreement that the clinical and nonclinical data submitted demonstrated safety and efficacy of sodium glycerophosphate, and 3) the sponsor's proposed CTD structure of available safety and efficacy information.

The discussion about 505(b)(2) centered around the Agency's assessment that the electrolyte content of the proposed products differed significantly from the currently marketed products. The Agency agreed to reconsider when additional information was provided by the sponsor. Regarding sodium glycerophosphate, the Agency agreed that no additional characterization of the non-clinical safety of sodium glycerophosphate was required. The Agency did request that the sponsor conduct studies to demonstrate relative bioavailability of their proposed products in healthy volunteers and indicated patient population. The sponsor was informed that the proposed CTD structure was inadequate. In addition to overall summaries of clinical and non-clinical studies, the sponsor must also include integrated summaries of efficacy and safety related to the use of the 3-CB.

September 30, 2003 (Pre-NDA meeting)
Division of Anesthetics, Critical Care and Addiction Drug Products

The sponsor requested a meeting to discuss bringing their products Kabiven and [redacted] (b) (4) to the US market. The discussion focused on comments from the various disciplines (Clinical, CMC and Pharmacology/toxicology).

2.6 Other Relevant Background Information

The sponsor of Novamine Amino Acids Injection NDA 17957submitted a request on [redacted] (b) (4) to withdraw the application for this product. The sponsor stated that the product is not currently marketed and the withdrawal is not associated with any safety or efficacy issues. The sponsor of Aminosyn II with Electrolytes in Dextrose Injection with Calcium NDA 19683 submitted a request on [redacted] (b) (4) to withdraw the application for this product. The sponsor stated that the product is not currently marketed and the withdrawal is not associated with any safety or efficacy issues.

Medical Reviewer's comments:
This application refers to the above listed drugs. A preliminary review of annual reports and the literature has not identified any safety or effectiveness issues related to the drugs. Since this application will not be approved during this review, a determination of whether these drug products are being withdrawn for reasons of safety or effctiveness will be made during the next review cycle.

3 Ethics and Good Clinical Practices

3.1 Submission Quality and Integrity

After submission of information requests, the overall quality of the clinical information contained in this submission was adequate for review.

3.2 Compliance with Good Clinical Practices

According to the Applicant, all clinical trials were conducted in accordance with the US Code of Federal Regulations (CFR) governing the protection of human subjects (21 CFR 50), IRBs (21 CFR 56) and the obligations of clinical investigators (21 CFR 312). These trials were also conducted in accordance with US Title 21 CFR on Good Clinical Practices (GCPs) which is consistent with the ethical principles set forth in the Declaration of Helsinki, the International Conference on Harmonization and the Food and Drug Administration.

Please see the review of Dr. Sandhya Apparaju for comments on compliance with Good Clinical Practices. In addition, the Division of Scientific Investigations conducted an inspection of pharmacology study Glyc-001-C-P1. An audit of the analytical portion of the study was conducted and Form FDA-483 was issued for “failure to include sufficient calibrator and quality control samples in each analytical run.” The Division of Bioequivalence and GLP Compliance (DGBC) recommended that the phosphate data from this study not be accepted for Agency review. Refer to the review of Dr. Xikui Chen dated August 14, 2011 for full details.

3.3 Financial Disclosures

The sponsor stated that Financial Disclosure was obtained from the Principal Investigator and Co-investigator for Glyc-001-CP1 and KABI-003-CP1 Bioequivalence studies. The sponsor stated that they have not entered into any financial arrangement with these investigators whereby the value of compensation to the investigator could be affected by the outcome of the study. Neither clinical investigator had a proprietary interest in the product or a significant equity in the sponsor.

The applicant stated that the investigators for the supportive studies are no longer in contact with the Applicant and their contact information was not obtainable. The sponsor though confirms that none of the listed investigators had any material financial connection with the company and that none of the investigators were employed by the sponsor nor were they the recipients of significant payments .

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The Applicant provided a signed copy of FDA Form 3454 certifying that they have not entered into any financial arrangement with their clinical investigators, whereby the value of compensation to the investigator could be affected by the outcome of the study as defined in 21 CFR 54.2(a). The Applicant also certified that each clinical investigator had no proprietary interest in this product or significant equity in the Applicant as defined by 21 CFE 54.2(b). As defined by 21 CFR 54.2(f), the Applicant certified that no clinical investigator was the recipient of any significant payments of any other sorts.

4 Significant Efficacy/Safety Issues Related to Other Review Disciplines

4.1 Chemistry Manufacturing and Controls

The CMC reviewer, Dr. Tarun Mehta , identified a number of deficiencies in the Application and has recommended not approving the Application until these deficiencies are resolved. The deficiencies cited in Dr. Mehta's review's include the following:

- The applicant has not provided adequate controls for the heavy metals in the drug product. Due to the large volumes of the drug product to be infused into patients, it is deemed critical to control the amount of daily intake of the heavy metals. They should be adequately controlled by the specification with proper method and adequate acceptance criteria.
- The applicant has not provided adequate controls for the impurities in [redacted] (b) (4) which is one of the drug substances in the drug product.
- The applicant has not provided sufficient information on the container/closure system in terms of adequacy for food additive requirements.
- The Office of Compliance has issued an overall "Withhold" recommendation for the application
- Labels/labeling do not have an adequate information including the established name.

The CMC reviewer stated that the heavy metal content in the drug product was monitored only for individual drug substances per USP, but no test acceptance criterion was given for individual chambers or for the whole mixed chamber product. The CMC reviewer has determined that there is potential for the cumulative amount of heavy metals to easily surpass the daily allowable limits, especially since the drug product daily dose is very large ([redacted] (b) (4) mL to 2556 mL). Per the CMC reviewer, the drug product specification is inadequate due to the absence of controlling the heavy metals. The CMC reviewer recommends that the heavy metals should be controlled for the levels of each of the specified metals in each compartment for three batches of the TPN product, with the information reported as ppm.

All amino acids conform to USP requirements with the exception of glutamic acid, which conforms to the European Pharmacopoeia (Ph.Eur.P). Manufacturing information regarding the amino acids were found by CMC to be acceptable, except for DMF [redacted] (b) (4) for [redacted] (b) (4) of which a purity issue has not been resolved. The CMC reviewer stated that due to a manufacturing change involving the starting material, the total unknown impurities in [redacted] (b) (4) are [redacted] (b) (4) and added new unknown impurities. These should be adequately controlled. All inorganic electrolytes, glucose and purified soybean oil meet USP requirements.

The CMC reviewer noted that the Applicant's proposed established name "[redacted] (b) (4) [redacted] (b) (4)" was not acceptable because it did not take into account all of the active substances present in the product. This and the following recommended established name of Lipid Injectable Emulsion with Amino Acids and Electrolytes and Dextrose was conveyed to the Applicant via correspondence on June 17, 2011. On August 18, 2011, the Applicant submitted the following revised established name, "Kabiven [redacted] (b) (4) [redacted]" CMC has found that the Applicant's proposed revised established name is not acceptable. This will be deferred until the next review cycle.

The CMC reviewer stated that the proposed primary packaging material for the 3-CB, [redacted] (b) (4), [redacted] (b) (4) [redacted] The CMC reviewer has therefore found that the proposed 3-CB is unacceptable for the drug product.

Per the CMC reviewer, the data submitted by the Applicant supports the proposed 24 month expiration dating period for the product stored at room temperature. The applicant has also provided adequate data support the label claim that the product may be stored under refrigerated conditions for 24 hours after being mixed. The mixed product specification was found to be adequate. It met USP requirements, with testing for traces of aluminum, sterility, endotoxins and mean globule size and globule size distribution as recommended in USP <729>.

Please refer to the full CMC review by Dr. Tarun Mehta dated September 27, 2011.

4.2 Clinical Microbiology

A Product Quality Microbiology review was conducted by Denise Miller. Ms. Miller found no microbiology deficiencies and recommended to approve from a quality microbiology standpoint.

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The Microbiology reviewer reviewed studies supporting the integrity of the container closure that were conducted. Microbial challenge revealed no bacterial growth in any of the challenged bags. All positive controls were positive for growth, negative controls were negative for growth and growth promotion was valid. Endotoxin specification did not exceed the endotoxin exposure limit for the maximum recommended dosage of this product for adults. Regarding stability data, all exhibit lots for each of the drug products completed stability testing through (b) (4) months with no failures reported. The Applicant also submitted additional supportive lots that had each completed 24 months of stability in support of the requested 24 month expiry dating for this application. No failures were reported for these lots.

Please refer to the full Microbiology review by Ms. Miller dated September 21, 2011.

4.3 Preclinical Pharmacology/Toxicology

A Pharmacology/Toxicology review was conducted by Dr. B. Emmanuel Akinshola. Dr. Akinshola found that the Applicant provided adequate nonclinical information in support of the safety of sodium glycerophosphate. He recommended approval of this application from a nonclinical perspective.

Please refer to the full Pharmacology/Toxicology review by Dr. Akinshola dated October 28, 2011.

4.4 Clinical Pharmacology

Dr. Sandhya Apparaju, the Clinical Pharmacology reviewer, found this application to be acceptable from a clinical pharmacology perspective. Please refer to the full review by Dr. Apparaju dated September 28, 2011.

To support the change from inorganic phosphate to sodium glycerophosphate, an organic phosphate source, the Applicant submitted the results of two relative bioavailability studies. Study Glyc-001-CP1 compared phosphate provision from equimolar doses (80 mmol over 4 hours) of the two phosphate sources alone (inorganic phosphates vs. organic sodium glycerophosphate) in healthy volunteers and study KABI-003-CP1 which explored relative bioavailability of phosphate provision from the organic sodium glycerophosphate administered alone, versus when it is administered as (b) (4). Results from study KABI-003-CP1 were not considered as supportive information for this NDA, since the resultant phosphate data was heavily confounded by the contribution of phosphate from food sources that even exceeded study drug dose in mmol units.

4.4.1 Mechanism of Action

Kabiven and [redacted] (b) (4) administered intravenously provide biologically utilizable source material for protein synthesis and serves as a source of calories, electrolytes, [redacted] (b) (4) The lipid component of Kabiven™ [redacted] (b) (4) (Intralipid® 20%) is metabolized and utilized as a source of energy causing, a decrease in respiratory quotient and increase in oxygen consumption. The infused fat particles are cleared from the blood stream in a manner thought to be comparable to the clearing of chylomicrons.

4.4.2 Pharmacodynamics

Per the Clinical Pharmacology reviewer the pharmacodynamics of interest, calcium, sodium, potassium, parathormone demonstrated an expected trend of change with exogenenous phosphate administration. The extent of change in PD was comparable for the two sources.

4.4.3 Pharmacokinetics

Serum pharmacokinetics of phosphate from the Clinical Pharmacology review (Study Glyc-001-CP1)

Parameter	Glycophos® (T)	I-Phosphate (R)
$AUC_{+0\text{-}24h,\ bc}$ [h*mmol/L]	9.365 (8.557; 10.25)	11.32 (10.46; 12.25)
$AUC_{0\text{-}24h}$ [h*mmol/L]	37.05 (36.35; 37.76)	39.00 (37.88; 40.16)
C_{max} [mmol/L]	2.869 (2.763; 2.980)	3.362 (3.185; 3.549)
T_{max} [h]	4.00	3.97 (3.87; 4.08)
C_{ss} [mmol/L]	2.869 (2.763; 2.980)	3.349 (3.173; 3.534)
λ_z [1/h]	0.3341 (0.2778; 0.4017)	0.3074 (0.2624; 0.3601)
$t_{½}$ [hh:mm]	2:04 (1:43; 2:29)	2:15 (1:55; 2:38)

T Test, R reference, bc = baseline corrected, LL/UL - Lower/Upper Limit of the 95% confidence interval (CI) of the geometric mean

4.4.4 Other consults

Centers for Devices and Radiological Health (CDRH)
CMC and the Division requested a review of these combination products by CDRH. The CDRH reviewer, Nikhil Thakur, reviewed the following issues related to this combination product: 1) Device performance, 2) Biocompatibility testing and 3) Human Factors

Device Performance
The CDRH reviewer stated that it is unclear whether the Applicant adequately addressed concerns regarding the safety and effectiveness of the [redacted] (b) (4) packaging. CDRH has the following concerns:

1) The Applicant's tests to demonstrate [redacted] (b) (4) packaging's resistance to temperature, pressure and leakage were not adequate. Per the CDRH reviewer it is unclear whether altitude was accounted for as part of the testing regimen. The Applicant will need to perform tests to evaluate the burst pressure. The Applicant should utilize a statistically significant sample size when performing this test. Basic statistical analyses should be used when interpreting the test results.

[redacted] (b) (4)

3) The Applicant performed a test to demonstrate that the injection point does not leak when it is punctured by a 23 gauge needle. CDRH recommended that the Applicant conduct additional tests to assess for injection point leakage.

Biocompatibility Testing
Per the CDRH reviewer there were no concerns regarding the biocompatibility aspects of the [redacted] (b) (4) bag.

Human Factors
The CDRH review team found the packaging very cumbersome to manipulate. The Applicant should perform a risk assessment to identify the use-related risks associated with their device, and demonstrate that these risks are no different that the usual risks that clinicians face when delivering drug product through other IV bags, to ensure that there are no unique risks associated with using the [redacted] (b) (4) bag. Based on this use-related risk assessment, the Applicant can then determine which human factor testing should be conducted. The Applicant should review FDA's Guidance Medical Device Use-Safety: Incorporating Human Factors Engineering into Risk Management (July 18, 2000), when developing the appropriate Human Factors studies.

Please refer to the full review by Nikhil Thakur, LCDR USPH, Senior Engineering Reviewer.

Division of Medication Error Prevention and Analysis (DMEPA)
The DMEPA had the following concerns with the Applicant's proposed proprietary names:
1) the [redacted] (b) (4), since one product can be administered via a central vein only (Kabiven) and the other product can be

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administered peripheral vein or central vein. If the [redacted] (b) (4) is omitted at any stage of drug usage, there is a potential that the wrong product could be administered via the wrong route (i.e. peripheral versus central or vice versa).
2) the [redacted] (b) (4) is misleading since this formulation can be given centrally or peripheral, yet the name implies [redacted] (b) (4) administration.

Based on these concerns, DMEPA recommended that the best nomenclature plan included the use of two unique proprietary names.

A conference call was conducted with the Applicant on September 2, 2011 to communicate the concerns regarding the current proposed names and recommend that the Applicant use two unique proprietary names for these two products, one of which can be Kabiven, and another unique name [redacted] (b) (4) [redacted].

On September 2, 2011, the Applicant submitted correspondence to DMEPA that they were withdrawing their request for a review of the proposed proprietary names Kabiven and [redacted] (b) (4). DMEPA sent correspondence to the Applicant on September 15, 2011 acknowledging withdrawal of the proposed proprietary names. On September 7, 2011 the Applicant submitted an amendment with new primary proposed proprietary names: Kabiven (for the product administered by the central venous route only) and PeriKabiven or [redacted] (b) (4) (for the product administered by the peripheral or central venous route). This amendment is currently under review by DMEPA.

Pediatrics and Maternal Health Staff
See section 7.6.3

5 Sources of Clinical Data

5.1 Tables of Studies/Clinical Trials

Tables 15, 16 and 17 summarize the clinical pharmacology studies and supportive trials submitted by the Applicant for review of this NDA to evaluate bioavailability and safety of Kabiven and [redacted] (b) (4).

Table 15: Relative Bioavailability Studies

Trial Name Dates Country	Trial Type	Trial Design	Treatment Products(s) Dosage Regimen/ Route of Administration	Number of patients treated	Duration of treatment	Population
Glyc-001-c P1	BA/BE of phosphate from glycerophosphate vs sodium phosphate	Double-blind, randomized, 2-way crossover, active control	Glycerophosphate (Glycophos) Inorganic phosphate (sodium phosphate injections) Both: 20 mmol/hr, 4-hr IV infusion into a peripheral forearm vein	25 (male/female)	2 single infusions of 4-hrs; 7-day washout period	Healthy subjects
KABI-003-CP1	Relative BA of phosphate from [redacted] (b) (4) vs Glycerophosphate	Single Center, Double-blind, randomized, Phase 1, exploratory study	[redacted] (b) (4) Glycerophosphate (Glycophos) diluted in 0.9% sodium chloride Both: 13.3 mL/kg bw/8-hr, 0.10 mmol phosphate/kg bw/8-hr IV infusion into forearm peripheral vein.	10 (male/female)	2 single infusions of 8 hrs; 88-hr washout period	Healthy subjects

BA-Bioavailibility
BE-Bioequivalence

Table 16: Kabiven Trials

Trial Name Dates Country	Trial Type	Trial Design	Treatment Products(s) Dosage Regimen/ Route of Administration	Number of patients treated	Trial Duration	Population
97-3CB1-001 06/98-12/98 UK	Safety Tolerance	Multi-center Randomized Open label Active Comparator	Pharmamix (Kabiven) Kabimix 14 30 mL/kg/d over 16-24hrs	Total – 50 Pharma -24 Kabimix - 26	7 days	Adult patients requiring TPN for ≥ 7 days
98-3CB1-002 09/98-11/99 UK	Safety Tolerance	Multi-center Randomized Open label Active Comparator	Pharmamix (Kabiven) Kabimix 14 25-30 mL/kg/d over 10-24hrs	Total – 23 Pharma – 12 Kabimix- 11	4 weeks	Inpatient adults with stable nutritional requirements for ≥ 4 weeks
98-3CB1-003 12/98-03/99 Germany	Safety Tolerance	Single Center Randomized Open label Parallel Group Active Comparator	Pharmamix (Kabiven) Mix of Vamin 18 EF, Glc, Intralipid 20%, ELKO-mix 30 mL/kg/d over 16-24hrs	Total – 41 Pharma – 20 Ref prod - 21	7 days	Adult patients status post GI surgery

00-3CB4-001 07/01-05/02 UK	Safety Tolerance Efficacy	Single center Randomized Open label Active comparator	Kabiven-30mL/kg/d 3CB Structo EL 23mL/kg/d Over 14-24 hrs	Total- 38 Kabiven-19 3CB Structo EL-19	7 days	Adult patients requiring TPN for ≥ 7 days
00-3CB5-001 04/01-11/01 Germany	Safety, Tolerance Efficacy	Single center Randomized Double blind Active comparator	Kabiven electrolyte modified AIO StructoQEI 30mL/kg/d	Total-42 21 in each grp	7 days	Post-operative adult patients
01-3CB5-002 10/02-03/03 Germany	Safety Tolerance Efficacy	Single Center Randomized Open label Active Comparator	Kabiven 3 CB StructoQ EL	Total-42 Kabiven-22 3CB- 20	7 days	Post-operative (major GI) adult patients
03-3CB7-001 07/04-02/05 Germany	Safety Tolerance	Single Center Randomized Open label Active Comparator	Kabiven 3CB SMOF EL 15mL/kg/d-P-1; 22.5-30ml/kg/d P- 2,3,4 & 15-30ml/kg/d P 5,6,7	Total 53 Kabiven – 27 3CB- 26	7 days	Post-operative (major GI) adult patients

Table 17: (b) (4) Trials

Trial Name Dates Country	Trial Type	Trial Design	Treatment Products(s) Dosage Regimen/ Route of Administration	Number of patients treated	Duration of treatment	Population
98-3CB2-001 06/99-08/00 UK	Safety Tolerance (systemic and local)	Single center Randomized Open label Parallel Groups Active Comparator	PharmaMix Trio Peripheral (b) (4) Kabimix 9 1 bag/d over 12-24 hr	Total-46 Pharma – 24 Kabimix - 22	7 days	Adult subjects requiring TPN for ≥ 7 days; subjects could not have high needs of TPN
98-3CB2-002 11/99-11/00 France	Safety Tolerance (systemic and local)	Single center Randomized Open label Parallel Groups Active Comparator	(b) (4) Clinomel N4-550 Over 12-24 hrs	Total-45 (b) (4) 23 Clinomel -22	7 days	Adult subjects requiring TPN for ≥7 days
01-3CB6-001 05/02-12/03 UK		Single Center Randomized Open label Active Comparator	(b) (4) 3CB StructoPeri EL 1bag over 14-24 hr	Total- 41 (b) (4) 21 3CB-20	7 days	Adult subjects requiring TPN for ≥7 days
03-3CB8-001 07/04-10/05 Germany	Safety Tolerance	Multi-center Randomized Open label Active comparator	(b) (4) 3CB SMOF Peri EL 1 bag/d over 14-24hr	Total – 52 (b) (4) - 25 3 CB - 27	7 days	Adult subjects requiring TPN for 5-7 days

Modified applicant's table

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5.2 Review Strategy

The Applicant's submission consisted of two components: 1) PK bridging studies (compare glycerophosphate with inorganic phosphate) and 2) supporting documentation from previously conducted clinical trials and the literature.

A review of the supportive clinical trials was conducted using the sponsor's submitted data (i.e. clinical sections of the NDA, including study reports, narrative, etc).

Other sources of clinical data used in this review include:

- http://dailymed.nlm.nih.gov/dailymed/about.cfm
- Electronic orange book
- Literature review

As a 505(b)(2) application, the clinical review of efficacy relies on evidence previously submitted and reviewed by the Agency. The clinical review of safety will examine safety results from the 7 Kabiven clinical trials, the 4 [redacted] (b) (4) clinical trials and the 2 pharmacokinetic studies.

5.3 Discussion of Individual Studies/Clinical Trials

All Kabiven and [redacted] (b) (4) clinical trials were submitted by the applicant as supportive documentation. Of the seven clinical trials using Kabiven, three included a prior defined efficacy analysis: Study 00-3CB4-001, Study 00-3CB5-001, and Study 01-3CB5-002. In these studies no formal hypothesis testing was planned or performed. The sample sizes were determined based on practical considerations. No prior defined efficacy analysis was conducted in the [redacted] (b) (4) trials. None of the [redacted] (b) (4) trials were conducted infusing the product via central veins. None of the active comparator drug products used in these trials are approved for use in the US. See Table 18 for a list of comparator drug treatments used in these trials.

Kabiven Trials that had predefined laboratory efficacy analysis:

Trial 3CB4-001
A randomized, open study evaluating the safety, tolerance and efficacy of 3CB Structo EL compared to Kabiven in subjects requiring parenteral nutrition for seven days.

Study Period
July 05, 2001 to May 11, 2002

Study Objectives
The primary objective was to compare the safety and tolerance of 3CB Structo EL with Kabiven for seven days in subjects requiring PN.

The secondary objective was to compare the efficacy and utilization of 3CB Structo EL with Kabiven during the trial in subjects requiring PN. Standard variables for measuring efficacy and utilization of nutrition were to be investigated as well as newly discussed variables to monitor nutritional interactions and to compare the influence on these variables of 3CB Structo EL with Kabiven.

The efficacy of the study treatments was to be assessed by laboratory efficacy variables in the plasma and serum.

The safety and tolerance of the study treatments were to be assessed by the adverse event (AE) profile, laboratory safety values determined from plasma/serum/blood, and vital signs.

Study Design

This Phase 3 single center, randomized, open, parallel-group, active controlled clinical study was conducted in subjects with a requirement for parenteral nutrition who were unable to sustain an adequate oral or enteral food intake for 7 days.

40 patients (20 patients in each treatment group were planned). 41 patients were enrolled; 3 patients did not receive study medication due to meeting an exclusion criteria, difficulty obtaining a central line and hemodynamic instability. 38 patients qualified for ITT analysis (19 patients in each treatment group) and 34 patients who received at least 5 day treatment were analyzed per-protocol (16 patients in the 3 CB Structo EL group and 18 patients in the Kabiven group).

The patients were randomized to receive one of the two treatments. The subjects of group A received 3CB Structo EL (investigational product). The subjects of group B received Kabiven (reference products). The two subject groups were to receive similar amounts of nutrients but in different volumes and composition. A trial day (in this study referred to as a period) was defined as a 24 hour period starting immediately before initiation of treatment. All 7 periods lasted 24 hours each. The dose regimen for patients in the 3CB Structo EL group was to be 23 ml/kg/body weight/day (period) and for the patients in the Kabiven group the dose regimen was to be 30 ml/kg body weight/day (period), to be administered via central intravenous infusion.

Study Population

Patients were included if they met the following criteria:

- Male and female subjects between 18 and 85 years of age
- Unable to sustain an adequate oral or enteral food intake for 7 days
- Written informed consent from the subject

Patients were excluded for the following:

- Pregnant or lactating

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- Acute pulmonary edema, hyper-hydration and decompensated cardiac insufficiency
- Hypersensitivity to egg or soy protein or any of the ingredients
- Severe blood coagulation disorders
- Body weight exceeded 90 kg
- Shock necessitating acute rescuscitation at the discretion of the investigator
- Diabetes mellitus with known ketoacidosis within 7 days of onset of study treatment
- Renal insufficiency or receiving dialysis
- Severe liver dysfunction
- Type IV hyperlipidemia or hypertriglyceridemia
- Known inborn error of amino acid metabolism
- Unstable angina pectoris
- Chemotherapy or radiation therapy within 7 days of onset of study treatment
- Contraindication or difficulty obtaining central venous catheter access

Treatment
Investigational Product: 3CB Structo EL which contained amino acids with electrolytes, lipids and glucose in a volume of 1970 ml, separated in three chambers. The study dose of the IP was 23 ml/kg bw/period

Reference Product: Kabiven contains amino acids with electrolytes, lipids, and glucose in a volume of 2566 ml, separated in three chambers. The study dose of the RP was 30 ml/kg bw/period.

Study Procedures
A trial day was defined as a 24 hour period starting immediately before initiation of treatment. All 7 periods lasted 24 hours each. The dose regimen for patients in the 3CB Structo EL group was 23 ml/kg body weight/day (period) and the Kabiven group the dose regimen was 30 ml/kg body weight/day (period), both administered via central intravenous infusion. The infusion time was to follow this 24 hours schedule (i.e. 9 am to 9 am of the following day for all periods). The daily infusion time was to last approximately 14 to 24 hours. The safety and tolerance were evaluated by measurements of routine clinical and laboratory variables. The efficacy and utilization were primarily evaluated by pre-albumin, triglycerides, etc.

The serious adverse event reporting period was extended for 7 to 10 days post discontinuation of trial treatment.

Efficacy and Safety Endpoints
The clinical variables used to measure safety and tolerance were: systolic and diastolic blood pressure (mm Hg), heart rate (beats/minute) and oral/axillary body temperature. These assessments wre to be performed before beginning daily study treatments,

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periods 1 (baseline), 2, 3, 4, 5, 6, 7 and directly after completion of the last study treatment.

The laboratory variables selected to assess safety and tolerance were: CBC, total bilirubin, ALT, GGT, alkaline phosphatase, triglycerides, serum glucose, electrolytes, renal function, albumin and CRP. These assessments were performed before beginning daily study treatments, period 1 (baseline), 4, 6 and directly after completion of the last study treatment.

No clinical efficacy assessments were performed. Laboratory variables measured for efficacy were: CRP, triglycerides, amino acid pattern, urea, pre-albumin, total fatty acid pattern, b-hydroxybutyrate, IGF-1, IGFBP-1, insulin, leptin. All efficacy assessments were performed before beginning of the daily study treatment periods 1, 4, and 6, and directly after completion of the last study treatment.

Statistical Plans
No formal hypothesis testing was planned. The sample size was determined on the basis of practical considerations.

Data from all assessments were to be tabulated and plotted using descriptive statistical methods. The intention to treat sample (ITT) was to include all patients who received at least one dose of study medication. The per protocol (PP) sample was to include patients without major protocol deviation and who received treatment for at least 5 period. Patients who were treated for 5 periods but received less than 50% of the determined trial treatment dose over any of the 5 periods were not considered as per protocol evaluable patients although they were included in the ITT sample.

Trial 3CB5-001
A randomized, double-blind study evaluating the safety, tolerance and efficacy of AIO StructoQ EL compared to Kabiven in post-operative patients requiring parenteral nutrition.

Study Period
23 April 2001 to 01 November 2001

Study Objectives
The primary trial objective was to compare the safety and tolerance of AIO StructoQ EL (3CB StructoQ EL) with Kabiven during 7 days, in post-operative patients (major gastrointestinal surgery) requiring PN

The second objective was to compare the efficacy of AIO StructoQ EL (3CB StructoQ EL) with Kabiven during the trial.

The third objective was to study emerging factors to monitor nutritional and immunological interactions and to compare the influence of AIO StructoQ EL (3CB StructoQ EL) and Kabiven on these factors.

The safety and tolerance of the trial treatments was assessed by the adverse event profile, laboratory safety values measured in plasma/serum/blood and vital signs. The efficacy of the trial treatments were assessed by laboratory efficacy values measured in plasma/serum and urine.

Study Design

This was a Phase 3, single center, randomized, double-blind, active controlled, parallel group trial. The investigational product was AIO StructoQ EL (group A) and the reference product was Kabiven (group B). 42 patients (21 in each treatment group) were enrolled and qualified for ITT analysis. Trial treatment started post-operatively on period 1 (the day after surgery) provided that the patient was hemodynamically stable

Study Population

Patients were included if they met the following criteria:

- Male and female patients between the ages of 18 and 85 years
- Major gastrointestinal surgery and anticipated to require PN for ≥ 7 days

Patients were excluded for the following:

- Pregnant or lactating
- Severely malnourished or overweight defined by Body Mass Index
- Body weight exceeded 95 kg
- Septic shock defined as hypotension and 2 or more of the following
    - Sustained fever
    - Thrombocytopenia
    - Acute documented infection
- Diabetes mellitus with known ketoacidosis within 7 days of onset of study treatment
- Renal insufficiency or receiving dialysis
- Acute liver dysfunction
- Type IV hyperlipidemia or hypertriglyceridemia
- Known inborn error of amino acid metabolism
- Unstable angina pectoris
- Chemotherapy or radiation therapy within 7 days of onset of study treatment
- Contraindication or difficulty obtaining central venous catheter access

Treatment

The dosage of the treatment was based on the patients weight. A trial day (period) was defined as a 24 hour period starting before initiation of trial treatment period 1, which

was to be the first post-operative day. All 7 periods were to have 24 hours each and the daily infusion time was to be approximately 24 hours.

AIO StructoQ EL, 2626 mL, is a one chamber bag containing a mixture of Aminoven (10%), Dipeptiven, Glucose 40%, ELKO-Mix (contained sodium, potassium, calcium, magnesium, zinc, chloride, glycerophosphate, glycerol, dihydrogenphosphate, malate, xylitol and acetate), Structolipid (20%) and Water. The dose was 15 mL/kg bw in period 1 and 30 mL/kg bw in periods 2, 3, 4, 5, 6 and 7.

Kabiven electrolyte modified, 2626 mL, a one chamber bag, contained a mixture of Kabiven 2626 to which 60 mL of additional electrolytes have been added, sodium chloride and calcium. The dose was 15 mL/kg bw in period 1 and 30 mL/kg bw in periods 2, 3, 4, 5, 6 and 7.

Study Procedures

Screening of patients was to be performed before surgery. A basic physical examination, including weight and height, was to be performed and recorded. Presurgery laboratory data were also to be recorded. The Body Mass Index was to be determined. Blood samples (fasting) were to be collected for laboratory analyses. Randomization/inclusion was to take place before surgery if all inclusion criteria and none of the exclusion criteria were fulfilled.

A patient was to be included before the triglyceride result, taken at the time of inclusion, was available but treatment was not to be started before the evaluation of this assessment had been performed. If the triglyceride value was above 4 mmol/l (354 mg/dL), the patient had to be withdrawn before start of treatment. Demographic data, surgery diagnosis and results of clinical and laboratory data were to be recorded in the CRF as well as in the hospital records.

Trial treatment was to start post-operatively on period 1 (the day after surgery) according to the protocol, provided that the patient was hemodynamically stable. The dose of period 1 was to be 15 ml/kg bw (50% of the full dose) and was to continue with 30 ml (full dose)/kg bw/period on periods 2, 3, 4, 5, 6, and 7. On periods 5, 6 and 7 limited amounts of oral/enteral nutrition were to be accepted, if the patient was able and, according to medical aspects, was also allowed by the attending physician to start oral food intake again after the postoperative fasting period. Study treatment was to be reduced correspondingly. The duration of the infusion was to last approximately 24 hours. The actual time was to be recorded in the CRF.

Clinical assessments were to be performed before commencement of daily study treatment at period 1, 2, 3, 4, 5, 6, and 7, and directly after completion of the last study treatment. Laboratory assessments (blood/serum/plasma) were to be performed before commencement of daily study treatment at period 1, 4, and 6, and directly after

completion of the last study treatment. Twenty four (24) hours urine collections were to be performed during five consecutive days (periods, 5x24 h), starting before commencement of study treatment (period 1) and ending directly after completion of study treatment (period 5).

From the time of receiving the first dose of trial treatment, all adverse events were to be recorded in the CRF. This was to be done until after completion of the last trial treatment. Serious adverse event reporting period was to be extended for 7-10 days postdiscontinuation of trial treatment. The investigator was to make a follow-up contact with the subject 7-10 days after the end of the last infusion to ensure that no serious adverse event had occurred or not been reported.

Efficacy and Safety Variables
The safety and tolerance of the trial treatments were assessed by the adverse event profile, laboratory safety values assessed in plasma/serum/blood and vital signs. The efficacy of the study treatments were assessed by laboratory efficacy values assessed in plasma/serum and urine.

No clinical efficacy assessments were performed. Laboratory variables measured were:

Plasma/serum
- CRP, triglycerides, amino acid pattern, urea, creatinine, pre-albumin, total fatty acid pattern, B-hydroxybutyrate, HLA-DR, IL6, stimulated IL-6 and TNF, IGF-1, IGFBP-1, insulin and leptin

Urine
- Amino acid pattern, total nitrogen, urea and creatinine

Statistical Plans
Data from all assessments were to be tabulated and plotted using descriptive statistical methods. Standard summary statistics and two-tailed 95% confidence intervals were calculated as appropriate. Categorical data were to be presented in frequency tables. Missing data were not to be replaced.

The intention-to-treat (ITT) sample included all patients who had received at least one dose of study medication. The analysis of safety and tolerance was to be based on the ITT population (all patients treated with study medication).

Trial 3CB5-002
A randomized, open study evaluating the safety, tolerance and efficacy of 3CB Structo EL compared to Kabiven in post operative subjects requiring parenteral nutrition

Study Period

Reference ID: 3044686

October 17, 2002 to March 19, 2003

Study Objectives
The primary objective was to compare the safety and tolerance of 3CB Structo EL with Kabiven during 7 days treatment in post-operative patients requiring PN.

The secondary objective was to compare the efficacy of 3CB Structo EL with Kabiven during during 7 days treatment, in post-operative patients requiring PN.

The efficacy of the study treatments was to be assessed by laboratory efficacy variables in plasma/serum and urine.

The safety and tolerance of the study treatments were to be assessed by the adverse event (AE) profile, laboratory safety values assessed in plasma/serum/blood and vital signs.

Study Design
This Phase 3 single center, randomized, open, parallel-group, active controlled clinical study was conducted in post-operative (major gastrointestinal surgery) subjects with a requirement for parenteral nutrition who were unable to sustain an adequate oral or enteral food intake for 7 days. Patients were randomized to receive one of two treatments, 3CB StructoQ EL or Kabien in 3 chamber bags.

40 patients (20 patients in each treatment group were planned). 45 patients were enrolled; 3 patients were removed from the study after randomization; 42 patients qualified for ITT analysis.

Study Population
Patients were included if they met the following criteria:

- Male and female subjects between 18 and 85 years of age
- Major gastrointestinal surgery and anticipated to require PN for ≥ 7 days
- Written informed consent from the subject

Patients were excluded for the following:

- Pregnant or lactating
- Severely malnourished or overweight defined by Body Mass Index
- Body weight exceeded 95 kg
- Septic shock defined as hypotension and 2 or more of the following
    - Sustained fever
    - Thrombocytopenia
    - Acute documented infection
- Diabetes mellitus with known ketoacidosis within 7 days of onset of study treatment

- Renal insufficiency or receiving dialysis
- Acute liver dysfunction
- Type IV hyperlipidemia or hypertriglyceridemia
- Known inborn error of amino acid metabolism
- Unstable angina pectoris
- Chemotherapy or radiation therapy within 7 days of onset of study treatment
- Contraindication or difficulty obtaining central venous catheter access

Treatment

The patients were randomized to receive one of the two treatments, 3CB Structo EL (investigational product) or Kabiven (reference products). The dosage of the treatment was based on the patients weight. A trial day (period) was defined as a 24 hour period starting before initiation of trial treatment period 1, which was to be the first post-operative day. All 7 periods were to have 24 hours each and the daily infusion time was to be approximately 24 hours.

Investigational Product: 3CB Structo EL which contained amino acids with electrolytes, lipids and glucose in a volume of 1970 ml, separated in three chambers. The study drug was administered via central vein. The study dose of the IP was 15 ml/kg bw/day in period 1; 30 mL/kg bw/day in periods 2, 3 and 4; 22.5-30 mL/kg bw/day in period 5; 15-30 mL/kg bw/day in periods 6 and 7. The recommended duration of the daily infusion was approximately 24 hours.

Reference Product: Kabiven was a 3CB that contained amino acids with electrolytes, lipids, and glucose in a volume of 2566 ml. The study dose of the RP was 15 ml/kg bw/day in period 1; 30 mL/kg bw/day in periods 2, 3 and 4; 22.5-30 mL/kg bw/day in period 5; 15-30 mL/kg bw/day in periods 6 and 7. The recommended duration of the daily infusion was approximately 24 hours.

Study Procedures

Trial treatment was to start post-operatively on period 1 (the day after surgery) if the S-triglyceride assessment at the time of inclusion was less than 4 mmol/L, the patient was hemodynamically stable and had not experienced any AE between randomization/inclusion and beginning the study treatment (i.e. severe intra-operative bleeding or intra-operative cardiac arrest).

Clinical assessments were made before beginning the study treatment in periods 1, 2, 3, 4, 5, 6, 7 and directly after completion of the last study treatment. Laboratory assessments (blood/serum/plasma) were to be performed before beginning study treatment in periods 1, 4, 6 and directly after completing the last study treatment. Twenty-four hour urine collections were to be performed during 5 consecutive days/periods (five 24 hour periods) starting at study treatment in period 1 and ending directly after completing study treatment in period 5.

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From the time of receiving the first dose of study treatment, all AEs were to be recorded in the CRF. This was to be done until the last dose of the study treatment was completed. Serious AE reporting period was extended for 7 to 10 days after the completion of the last study treatment or until discharge from the hospital after an uneventful post-operative course and then after Day 12.

Efficacy and Safety Assessments
No clinical efficacy assessments were to be performed. Laboratory variables to be measured for efficacy were:

Plasma/serum:
CRP, triglycerides, urea, creatinine, pre-albumin
All of these assessments were to be performed before beginning the daily study treatments in periods 1 (baseline), 4 and 6 as well as directly after completion of the last study treatment.

Urine:
Total nitrogen, urea, creatinine,
24 hour urine collections were to be performed during 5 consecutive days/periods starting at the beginning of the study treatment in period 1 and ending directly after completion of the study treatment of period 5.

The clinical variable used to measure safety and tolerance were:
Systolic and diastolic blood pressure (mmHg)
Hear rate (beats/minute)
Oral/axillary body temperature

These assessments were to be done before starting the daily study treatment in periods 1 (baseline), 2, 3, 4, 5, 6, and 7 as well as directly after completion of the last study treatment.

The laboratory variables used to measure safety and tolerance were: CBC, electrolytes, glucose, bilirubin, GOT, AP, creatinine, trigylcerides, albumin and CRP. These assessments were to be done before beginning the daily study treatment in periods 1 (baseline), 4 and 6, as well as directly after completion of the last study treatment.

Statistical Plans
No formal hypothesis testing was planned. The sample size was determined on the basis of practical considerations. All data recorded on the CRFs were to be tabulated and/or plotted using descriptive statistical methods.

Data from all assessments were to be tabulated and plotted using descriptive statistical methods. The intention to treat sample (ITT) was to include all patients who received at

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least one dose of study medication. The per protocol (PP) sample was to exclude patients with major protocol deviations.

Summaries of other Kabiven and [redacted] (b) (4) Trials that were submitted:

Kabiven Trials

Trial 97-3CB1-001
Title: Safety and tolerance of the three chamber bag, Pharmamix Trio Central, compared to KabiMix 14 in subjects requiring total parenteral nutrition

This was a phase 3, open label, parallel-group trial performed at 3 centers in the UK. The infusion dose for both Kabiven and KabiMix was 30 mL/kg/day. Both products contained glycerophosphate. A 7-day treatment duration was planned with infusion duration from 16 to 24 hours/day. 40 subjects (20 in each treatment group) were planned and 50 were enrolled (24 subjects in the Kabiven group and 26 subjects in the KabiMix 14 group. The main inclusion criteria were that patients require TPN for ≥ 7days and be between the ages of 18 and 85 years old. The trial protocol was amended to change the trial population inclusion criteria from post-operative subjects to "subjects," i.e. any adult patient in need of TPN.

There was no clinical efficacy evaluation in this trial. Safety evaluation included the following: adverse event monitoring; clinical assessments: blood pressure (mmHg), hear rate (beats/minute) and temperature (C): and laboratory assessments: hemoglobin, leucocytes, platelets, erythrocytes INR, sodium, chloride, magnesium, potassium, glucose, calcium, phosphate, ALAT, GGT, ALP, total bilirubin, triglycerides, creatine, urea, total protein, albumin.

Variables were analyzed using descriptive statistical methods.

Trial 98-3CB1-002
Trial: Safety and tolerance of Pharmamix Trio Central compared to KabiMix 14 in subjects requiring long term total parenteral nutrition (TPN)

This was a phase 3, open label, randomized, parallel-group trial performed at 2 centers in the UK that handled the majority of home parenteral patients in middle and northern England. The recommended infusion dose was 25 mL/kg/period and provided 23 kcal/kg. Treatments were provided during 10 to 24 hour/periods in 5 to 7 periods/week for up to 4 weeks. 20 subjects (10 in each treatment group) were planned. 23 subjects were enrolled: 12 in the Kabiven treatment group and 11 in the comparator group. The main inclusion criteria were the following: inpatients anticipated to require long term TPN (≥ 4 weeks) with stable nutritional requirements and be between the ages of 18 and 80 years old

The Applicant stated that no efficacy variables were evaluated in this trial. Safety assessments performed in this trial included: Adverse event monitoring; Clinical safety assessments: systolic and diastolic blood pressure (mmHg), heart rate (beats/minute) and body temperature (C) and laboratory safety assessments. No laboratory efficacy assessments were performed in this trial. Laboratory safety assessments that were performed included hematological and biochemical.

Variables were analyzed using descriptive statistical methods.

Trial 98-3CB1-003
Safety and tolerance of the three chamber bag, Pharmamix Trio Central, compared to pharmacy compounding bags, containing Vamin 18 EF, Dextrose 20% and Intralipid 20% and electrolytes in postoperative subjects requiring total parenteral nutrition.

This was a Phase 3, open label, randomized, parallel-group, active controlled trial conducted at a single center in Germany. Kabiven was compared with a pharmacy compounded bag containing Vamin 18 EF, Dextrose 20% and Intralipid 20% and electrolytes in postoperative subjects. The infusion dose was 30 mL/kg/day, equal to 27 kcal. The duration of infusion was 24 hours, but could range from 16 to 24 hours. The treatment period was planned for 7 days.

40 subjects were planned (20 in each treatment group. 41 subjects were enrolled (20 in the Kabiven group and 21 in the control group. The main inclusion criteria were that subjects be status post gastrointestinal surgery anticipated to require TPN for ≥ 7days and be between the ages of 18 and 80 years old.

There was no clinical efficacy evaluation in this trial. Safety evaluation included the following: adverse event monitoring; clinical assessments: blood pressure (mmHg), hear rate (beats/minute) and temperature (C): and laboratory assessments: hemoglobin, leucocytes, platelets, erythrocytes INR, sodium, chloride, magnesium, potassium, glucose, calcium, phosphate, ALAT, GGT, ALP, total bilirubin, triglycerides, creatine, urea, total protein, albumin.

Variables were analyzed using descriptive statistical methods.

Trial 03-3CB7-001
Title: A randomize, open study evaluating the safety and tolerance of 3CB SMOF EL compared to Kabiven in post-operative subjects requiring parenteral nutrition.

This was a Phase 3, open label, randomized, parallel-group, active controlled trial conducted at a single center in Germany. The two products, Kabiven and SmofKabiven, were infused at a dose of 15 mL/kg/day the first day and thereafter at a maximum dose of 30 mL/kg/day. The treatment duration was 7 days with 7 to 10 days of SAE follow-up.

40 subjects (20 subjects in each treatment group) were planned. 60 subjects were enrolled due to premature termination of 17 subjects. 53 subjects qualified SMOF EL). The main inclusion criteria were post-operative major intestinal tract surgery patients who were anticipated to require PN for ≥ 5 days.

Safety and tolerance were assessed by the adverse event profile, vital signs and laboratory safety assessment in plasma/serum/ blood.

[redacted] (b) (4) **Trials**

In all of the [redacted] (b) (4) trials, the trial treatment and comparators were infused via peripheral intravenous access.

Trial 98-3CB2-001

Title: Safety and tolerance of the three chamber bag, Pharmamix Trio Peripheral, compared to KabiMix 9, in subjects requiring total parenteral nutrition.

This was a Phase 3, open label, randomized, active controlled, parallel-group trial conducted at a single center in the UK. The investigational products were [redacted] (b) (4) [redacted] (b) (4) and KabiMix 9. The infusion was done over 12 to 24 hours, usually overnight, and the treatment duration was 7 days.

40 subjects who were surgical and gastroenterological patients were planned. 47 patients were enrolled and 46 were evaluated (24 [redacted] (b) (4) and 22 KabiMix 9). The main inclusion criteria were 18 years of age and older and anticipated to require TPN for ≥ 7days.

There was no clinical efficacy evaluation in this trial. Safety evaluation included the following: adverse event monitoring; clinical assessments: blood pressure (mmHg), hear rate (beats/minute) and temperature (C): and laboratory assessments: hemoglobin, leucocytes, platelets, erythrocytes INR, sodium, chloride, magnesium, potassium, glucose, calcium, phosphate, ALAT, GGT, ALP, total bilirubin, triglycerides, creatine, urea, total protein, albumin. Local vein tolerance was assessed by using the Modified Maddox scoring system

Variables were analyzed using descriptive statistical methods.

Trial 98-3CB2-002

Title: Safety and local tolerance of the three chamber bag [redacted] (b) (4), compared to Clinomel N4-550, in subjects requiring total parenteral nutrition.

This was a Phase 3, open label, randomized, active controlled, parallel-group trial conducted at a single center in France. The investigational products were [redacted] (b) (4) [redacted] (b) (4) and Clinomel N4-550. The [redacted] (b) (4) group received organic phosphate as glycerophosphate and the control group received inorganic phosphate.

The infusion was done over 12 to 24 hours per day and the treatment duration was 7 days.

40 subjects (20 in each treatment group) were planned. 45 subjects were enrolled (23 in the [redacted] (b) (4) group and 22 in the control group). The main inclusion criteria were 18 years of age and older and anticipated to require TPN for ≥ 7days.

There was no clinical efficacy evaluation in this trial. Safety evaluation included the following: adverse event monitoring; clinical assessments: blood pressure (mmHg), hear rate (beats/minute) and temperature (C): and laboratory assessments: hemoglobin, leucocytes, platelets, erythrocytes INR, sodium, chloride, magnesium, potassium, glucose, calcium, phosphate, ALAT, GGT, ALP, total bilirubin, triglycerides, creatine, urea, total protein, albumin. Local vein tolerance was assessed by using the Modified Maddox scoring system

Variables were analyzed using descriptive statistical methods.

Trial 01-3CB6-001
Title: A randomized, open study evaluating the safety and tolerance of 3CB StructoPeriEL compared to [redacted] (b) (4) in subjects requiring parenteral nutrition.

This was a Phase 3, open label, randomized, active controlled, parallel-group trial conducted at a single center in the UK. The investigational products were [redacted] (b) (4) [redacted] (b) (4) and StructoKabiven Peripheral. Both trial products contained sodium glycerophosphate. The infusion was done over 14 to 24 hours per day, for 7 days.

40 subjects (20 in each treatment group) were planned. 44 subjects were enrolled and 41 were included in the ITT analysis (21 in the [redacted] (b) (4) group and 20 in the control group). The main inclusion criteria were 18 years of age and older and anticipated to require TPN for ≥ 7days.

There was no clinical efficacy evaluation in this trial. Safety evaluation included the following: adverse event monitoring; clinical assessments: blood pressure (mmHg), hear rate (beats/minute) and body temperature (C): and laboratory assessments: hemoglobin/hematocrit, leucocytes, granulocytes, lymphocytes, platelets, sodium, chloride, magnesium, potassium, glucose, calcium, phosphate, ALT, GGT, ALP, total bilirubin, triglycerides, creatine, urea, albumin, CRP. Local vein tolerance was assessed by using the Modified Maddox scoring system.

Data from all assessments were tabulated and/or plotted using descriptive statistical methods.

Trial 03-3CB8-001
Title: Safety and tolerance of 3CB SMOF Peri EL compared to [redacted] (b) (4)

This was a Phase 3, randomized, open-label, parallel-group study performed at three centers in Germany. The investigational products were [redacted] (b) (4) and SmofKabiven Peripheral. Treatments were infused over approximately 14 to 24 hr/day for 5 to 7 days.

50 subjects (25 in each treatment group) were planned. 52 subjects were enrolled (25 in the [redacted] (b) (4) group and 27 in the SmofKabiven Peripheral group). There was unbalanced recruitment among the 3 participating centers: 40, 9, and 3 subjects were enrolled at each of the 3 centers respectively. The main inclusion criteria were subjects between the ages of 18 and 85 years old and unable to sustain adequate oral or enteral food intake for 5 to 7 days.

The study hypothesis was that both 3CB products are comparable with regards to safety and tolerance. No formal hypothesis testing was planned. Data from all assessments were to be tabulated and/or plotted using descriptive statistical methods.

Clinical Pharmacology Trials

Please see the clinical pharmacology review by Dr. Sandhya Apparaju for a full review and discussion of the clinical pharmacology studies.

Glyc-001-C P1

Title: Single-Centre, Double-Blind, Randomized, Two-Treatment, Two-Sequence, Active-Controlled Phase-I-Study to Evaluate Bioequivalence of Phosphate from Glycerophosphate (Glycophos®) versus Sodium Phosphates (Hospira, Inc, USA) in Healthy Subjects

This was a Phase 1 study conducted in a prospective, active-controlled, double-blind, single center (Germany), randomized, two-way cross-over design with healthy male and female subjects. 24 subjects were planned, 27 subjects were enrolled, 25 subjects completed the study (2 subjects withdrew), 18 subjects were analyzed for sample size calculation, 25 subjects were included in the safety analysis; 21 subjects were analyzed for PK and PD analysis in urine and 25 subjects were analyzed for serum PK and PD.

The test product was Glycophos (sodium glycerophosphate) and the reference products was sodium phosphate (inorganic phosphate) referred to in the study report at I-Phosphate.

The objectives of the study were to:

- To demonstrate bioequivalence of phosphate from glycerophosphate (Glycophos®) and from inorganic phosphate (Sodium Phosphates Injections, Hospira, Inc) regarding pharmacokinetic characteristics

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- To compare safety and pharmacodynamic characteristics of glycerophosphate and Sodium Phosphate (Hospira).

KABI-003-C P1
Title: Single-Centre, Double-Blind, Randomised Phase I Study to Evaluate the Relative Bioavailability of Phosphate from [redacted] (b) (4) Versus Glycerophosphate (Glycophos®) in Healthy Subjects

This was a Phase 1 study conducted in a prospective, double-blind, single center (Germany), randomized, two sequence, two-way cross-over design with 10 healthy male and female subjects. 10 subjects were planned, 10 subjects were enrolled, 0 subjects withdrew; 10 subjects were analyzed for safety analysis; 10 subjects were analyzed for PK analysis.

The test product was [redacted] (b) (4) and the reference product was Glycophos (sodium glycerophosphate). The duration of treatment was two single infusions of 8 hours duration, one of the test drug and one of the reference drug with a wash-out period of 88 hours.

The study objective was to explore the bioavailability of phosphate from [redacted] (b) (4) [redacted] (b) (4) and pure glycerophosphate in 0.9% sodium chloride with regard to pharmacokinetic characteristics and safety.

Table 18: Description of IV Lipid Emulsion Products used in clinical trials

Marketed Name (generally used in this document)	Approved for Marketing in European Union	Working Name	Brief Details on Composition [a]
Kabiven™	Yes	Pharmamix Trio Central	(Central) A 3-chamber bag (3CB) with soybean oil emulsion (same as Intralipid® 20%), amino acids (similar to Novamine 11.4% and marketed in [redacted] (b) (4) with electrolytes, and [redacted] (b) (4) dextrose in solution. Kabiven has an osmolarity suitable for central venous infusion.
[redacted] (b) (4)	Yes	Pharmamix Trio Peripheral	[redacted] (b) (4)) Same as Kabiven except lower osmolarity ([redacted] (b) (4) dextrose), amino acids, and higher proportion of fat (relative to the amino acid and dextrose content) for administration via peripheral vein.
KabiMix® 9		—	[redacted] (b) (4)) Industrially produced [redacted] (b) (4) with Intralipid, [redacted] (b) (4) (amino acid solution), and dextrose.
KabiMix® 14		—	[redacted] (b) (4)) Industrially produced [redacted] (b) (4) with Intralipid, [redacted] (b) (4) (amino acid solution), and dextrose.
StructoKabiven®		3CB Structo EL	[redacted] (b) (4)
StructoKabiven® Peripheral		3CB Structo Peri EL	
—	No	AIO StructoQ EL	

Marketed Name (generally used in this document)	Approved for Marketing in European Union	Working Name	Brief Details on Composition [a]
—	No	(b) (4)	(b) (4)
SMOFlipid®		SMOFlipid 200mg/mL emulsion for infusion	A lipid emulsion containing 4 different types of fatty acids as triglycerides: S=Soybean oil, M=Medium Chain Triglycerides (from (b) (4) O=Olive oil, F=Fish oil
SmofKabiven®		3CB SMOF EL	(Central) SmofKabiven differs from StructoKabiven (b) (4) (b) (4) Alpha-tocopherol also added as (b) (4) (b) (4)
SmofKabiven® Peripheral		3CB SMOF Peri EL	(Peripheral) Same as SmofKabiven except with different fat component and proportions between the nutrients to allow administration via peripheral veins.
Vamin 18 series similar to Novamine 11.4%		—	The Vamin 18 series of amino acid solutions has been marketed for >35 years. The original version contains 18 amino acids including all essential amino acids and cysteine as a nonessential amino acids.

Ca^{++}=calcium, K^{+}=potassium, Mg^{++}=magnesium, Na^{+}=sodium, Zn^{++}=zinc

6 Review of Efficacy

Efficacy Summary

Efficacy of this application was assessed by clinical pharmacology studies. The Applicant submitted two (2) relative bioavailability studies (Study Glyc-001-CP1 and Study KABI-003-C P1) to provide pharmacokinetic bridging of the phosphate moiety in order to justify the change from inorganic phosphate to sodium glycerophosphate (novel organic phosphate source) that is proposed for use in both Kabiven and (b) (4) .

The results of Study Glyc-001-CP1 demonstrated comparability of phosphate provision from the new organic sodium glycerophosphate to that of equimolar doses of the approved inorganic phosphate. The relative bioavailability results support the

incorporation of sodium glycerophoshate as a source of phosphate provision into the proposed PN products. The results of Study KABI-003-C P1 demonstrated no significant differences in serum levels of phosphate when given as sodium glycerophosphate alone or as part of [redacted] (b) (4). The results from this Study though were not considered, by the Clinical Pharmacology reviewer as supportive information for this application because the results were potentially confounded by the contribution of phosphate from food sources.

See section 4.4 Clinical Pharmacology and the Clinical Pharmacology review by Dr. Sandhya Apparaju.

The eleven supportive Kabiven and [redacted] (b) (4) clinical trials were generally seven day infusions of the products requiring intravenous nutrition, with the exception of one Kabiven trial which was 4 weeks duration. All of the clinical trials were randomized, open-label except for trial 00-3CB5-001, which was randomized, double-blinded. All of the subjects required PN and for four (4) of the Kabiven trials subjects were required to be status post GI surgery. None of the active comparator PN products used in these trials are approved for use in the US. None of the [redacted] (b) (4) trials were conducted administering the product via a central vein.

None of the clinical trials had clinical efficacy endpoints, but three (3) of the Kabiven trials had laboratory efficacy assessments. These included limited data for essential and non-essential amino acids, fatty acid components, urea, creatine,pre-albumin, beta-hydroxybutyrate, IGG-1/IGF-BP-1, insulin, leptin, HLA-DR and IL-6, and urinary excretion of amino acids, nitrogen, urea and creatinine. No formal hypothesis was established and no formal statistical analyses were performed. The results demonstrated that Kabiven was comparable to the active comparators with regard to efficacy of these parameters in patients requiring PN.

6.1 Indication

The Applicant's proposed indication for Kabiven [redacted] (b) (4) (central vein infusion) and [redacted] (b) (4) (peripheral vein or central vein infusion) is Total Parenteral Nutrition: For intravenous infusion as a source of calories, protein, and essential fatty acids for patients requiring parenteral nutrition [redacted] (b) (4) [redacted] prevention of essential fatty acid deficiency [redacted] (b) (4) or treatment of negative nitrogen balance [redacted] (b) (4):

[redacted] (b) (4)

6.1.1 Methods

The clinical data from the Kabiven and [redacted] (b) (4) clinical trials was reviewed to determine whether a clinical benefit was demonstrated in patients requiring parenteral nutrition. None of the trials included formal hypothesis testing.

6.1.2 Demographics

See section 7.2.1

6.1.3 Subject Disposition

See Section Section 7.3.3

6.1.4 Analysis of Primary Endpoint(s)

Analysis of the following clinical trials clinical laboratory efficacy assessments was done using descriptive statistics. Limited data was available and no formal statistical analysis was performed.

<u>Study 00-3CB4-001</u>

Amino acid pattern
The Applicant reported that no differences in mean concentration at baseline or post-baseline time points (LOCF minus Period 1) were determined for the majority of amino acids. Alanine, histidine, methionine, phenylalanine, and threonine increased by Period 1 to Period 4 (LOCF), then remained at a stable level through the final examination.

Uea
The Applicant reported that urea levels in the Kabiven group were stable from Period 1 through the final examination, with arithmetic means of 31.58±26.67mg/dL at Period 1, 28.68±20.78mg/dL at Period 4 (LOCF), 31.00±19.24mg/dL at Period 6 (LOCF), and 29.17±17.79mg/dL at the final examination. Higher urea concentrations were observed with the StructoKabiven formulation compared to Kabiven.

Total fatty acids
A similar availability of total fatty acids was detected in the Kabiven group at Period 1 and subsequent time points for C10, C18, and C18:1. The availability of C16 and C16:1 declined approximately 20% between Period 1 and Period 4, then remained relatively stable through Period 6. Conversely, the availability of C18:2 increased approximately 30% between Period 1 and Period 4, then remained relatively stable through Period 6.

Pre-albumin
Pre-albumin levels in the Kabiven group increased slightly from Period 1 through the final examination, with arithmetic means of 126.89±49.36mg/L at Period 1, 143.66±69.37mg/L at Period 4 (LOCF), 170.17±79.72mg/L at Period 6 (LOCF), and 172.44±99.05mg/L at the final examination. The median levels of serum pre-albumin increased steadily in both treatment groups from Period 1 to final examination (LOCF).

B-Hydroxybutyrate
B-Hydroxybutyrate can appear in elevated levels in tissue, blood, or urine during periods of starvation, digestive disorders, frequent vomiting, and diabetes. Mean B-hydroxybutyrate levels in the Kabiven group dropped between Period 1 (9.72–11.62mg/dL) and Period 4 (LOCF; 4.85–8.61mg/dL), then were relatively stable through Period 6 (LOCF; 4.55–8.71mg/dL) and the final examination (LOCF;4.58–8.70mg/dL). These results indicate that no ketoacidosis occurred in this population.

IGF-1/IGF-BP-1
Mean serum IGF-1 increased between Period 1 (87.74–46.69mg/L) and Period 4 (LOCF; 136.37–50.57mg/L), then remained relatively stable through Period 6 (LOCF; 138.53–59.53mg/L) and the final examination (LOCF; 154.37–59.65mg/L). Increases in IGF-1 are characteristically associated with active growth and development.

IGF-BP-1 declined from Period 1 (75.84–77.42 mg/L) to Period 4 (LOCF; 26.68–26.57 mg/L), with a concentration of 44.53–48.96 mg/L at Period 6 (LOCF) and 26.74–27.78 mg/L at the final examination (LOCF) in the Kabiven group.

Insulin
Mean serum insulin levels increased considerably in the Kabiven group between Period 1 and Period 4, then remained relatively stable: the mean concentration of insulin at Period 1 was 7.63–5.60mU/L, at Period 4 (LOCF) was 26.58–36.37mU/L, at Period 6 (LOCF) was 20.53–17.14mU/L, and at the final examination (LOCF) was 26.26–24.19mU/L.

Leptin
The mean concentration of serum leptin increased during the treatment period until the end of the study: 3.49–2.11mg/L at Period 1, 8.82–6.71mg/L at Period 4 (LOCF), 8.98–6.91mg/L at Period 6 (LOCF), and 8.33–7.01mg/L at the final examination (LOCF) in the Kabiven group.

Trial 00-3CB5-001

Amino Acid Pattern - plasma
No differences in mean concentrations at baseline or post-baseline time points (LOCF minus Period 1) were observed for essential amino acids isoleucine, leucine, lysine, phenylalanine, tryptophan, and valine. Essential amino acids methionine and threonine

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increased from Period 1 to Period 4 (LOCF), then remained relatively stable through the final examination.

Urea – plasma
Mean serum urea levels in the Kabiven group were relatively stable from Period 1 through the final examination, with arithmetic means of 3.69±1.90mmol/dL at Period 1, 4.26±2.57mmol/dL at Period 4 (LOCF), 4.64±2.55mmol/dL at Period 6 (LOCF), and 4.92±2.65mmol/dL at the final examination.

Creatinine
The levels of serum creatinine stayed constant during the study indicating that kidney function (glomerular filtration) was not affected in this population. Arithmetic means in the Kabiven group were 78.26±21.10mmol/L at Period 1, 77.17±45.18mmol/dL at Period 4 (LOCF), 72.50±23.51mmol/L at Period 6 (LOCF), and 73.67±24.20mmol/L at the final examination.

Total fatty acids
Similar mean availabilities of total fatty acids were detected in the Kabiven group at Period 1 and subsequent time points for C16, C18, and C18:1. The availability of C16:1 and C22:1 declined by approximately one third (34% each) between Period 1 and Period 4, then remained relatively stable through Period 6. Conversely, the availability of C18:2 increased almost two thirds (64%) between Period 1 and Period 4 (LOCF), and rose an additional ~25% at Period 6 (LOCF). The availability of C10 increased approximately 17% between Period 1 and Period 4, then remained relatively stable through Period 6.

Pre-albumin
Mean pre-albumin levels in the Kabiven group decreased initially from Period 1 but than reached the same levels as in Period 1 in the final examination, with arithmetic means of 154.28±35.61mg/L at Period 1, 122.24±37.33mg/L at Period 4 (LOCF), 137.08±43.62mg/L at Period 6 (LOCF), and 161.77±62.30mg/L at the final examination.

B-hydroxybutyrate
The concentration of b-hydroxybutyrate was detectable at only Period 1 for 14 of the 21 subjects (67%) in the Kabiven group. The levels of b-hydroxybutyrate were too low to measure for the majority of subjects in the subsequent periods.

Insulin
The normal mean fasting level lies below 20mU/L. Serum insulin levels increased considerably in the Kabiven group between Period 1 (10.67–6.00mU/L), Period 4 (LOCF; 16.71–8.62mU/L), and Period 6 (LOCF; 22.24–15.94mU/L); the value at final examination (LOCF) was 16.00–9.74mU/L.

IGF-1/IGF-BP-1
Mean serum IGF-1 increased over the duration of the study: Period 1 (109.95–45.19mg/L), Period 4 (LOCF; 122.81–45.52mg/L), Period 6 (LOCF; 138.62–53.72mg/L), and the final examination (LOCF; 163.81–78.71mg/L). Concentration of the IGF-BP-1 is inversely related to the concentration of IGF-1. The concentration of IGF-BP-1 declined from Period 1 (54.71–37.11mg/L) to Period 4 (LOCF;12.19–8.65mg/L), then was relatively stable at Period 6 (LOCF; 14.00–19.98mg/L) and at the final examination (LOCF; 12.43–12.05mg/L) in the Kabiven group.

Leptin
Leptin is a protein hormone that has been considered to play important roles in regulating energy intake and energy expenditure, including appetite and metabolism. The mean concentration of serum leptin increased from Period 1 (8.98–9.65mg/L) to Period 4 (LOCF; 12.15–13.03mg/L), then remained relatively stable through Period 6 (LOCF; 12.33–11.01mg/L) and the final examination (LOCF; 11.80–11.49mg/L) in the Kabiven group.

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C-Reactive Protein
C-reactive protein is a general marker for inflammation and infection. The mean serum CRP concentration in the Kabiven group decreased from Period 1 (116.77–43.59mg/L) through Period 6 (LOCF; 72.05–62.90mg/L); at the final examination (LOCF), the CRP concentration was (87.50–87.65mg/L). Despite the decrease, CRP levels still exceeded the normal range in all subjects at the final examination.

Triglycerides
Mean triglyceride concentration increased from Period 1 (74.18–30.33mg/dL) through Period 6 (LOCF; 132.95–49.40mg/dL); the concentration of triglycerides in the Kabiven group at the final examination (LOCF) was 153.77–57.52mg/dL).

Urea-serum
Measurement of the urea concentration in the serum provides information about the nutritional nitrogen intake. Mean serum urea concentration increased modestly during the study. Serum urea levels in the Kabiven group increased at each period from Period 1 through the final examination, with arithmetic means of 2.998–1.487mmol/L at Period 1, 3.340±1.680mmol/dL at Period 4 (LOCF), 3.888±1.973mmol/dL at Period 6 (LOCF), and 5.192±4.920mmol/dL at the final examination (LOCF).

Creatinine
The levels of serum creatinine stayed relatively constant during the study. Mean serum creatinine concentration decreased modestly from Period 1 (75.591±16.525mmol/L) to Period 4 (LOCF; 62.377±16.113mmol/dL), remained relatively stable at Period 6 (LOCF; 62.650±15.495mmol/dL), and were close to the Period 1 level at the final examination

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(LOCF; 73.041±27.339mmol/dL at the final examination) in the Kabiven group.

Pre-albumin
After a slight decrease in the median from Period 1 to Period 4 (LOCF), serum pre-albumin concentration increased modestly through the final examination (LOCF) in the Kabiven group. The mean concentrations were 0.139±0.043g/L at Period 1, 0.115±0.050g/L at Period 4 (LOCF), 0.139±0.056g/L at Period 6 (LOCF), and 0.151±0.063g/L at the final examination (LOCF).

6.1.5 Analysis of Secondary Endpoints(s)

N/A

6.1.6 Other Endpoints

N/A

6.1.7 Subpopulations

Per the Clinical Pharmacology reviewer, no dedicated PK or safety studies are available in specific subpopulations. However, language relevant to safety and dosing in subpopulations including renal, hepatic and geriatric patients has been included in the proposed labeling by the Applicant.

See section 7.6.3 regarding the pediatric plan.

6.1.8 Analysis of Clinical Information Relevant to Dosing Recommendations

N/A

6.1.9 Discussion of Persistence of Efficacy and/or Tolerance Effects

N/A

6.1.10 Additional Efficacy Issues/Analyses

N/A

7 Review of Safety

Safety Summary

A total of 145 subjects received Kabiven, 93 subjects received [redacted] (b) (4) and ten (10) healthy subjects received [redacted] (b) (4). Three (3) deaths occurred in the Kabiven pool treatment group and 4 deaths in the comparator group. Two deaths were reported in both the [redacted] (b) (4) treatment group and the comparator group. None of the deaths in the Kabiven or [redacted] (b) (4) treatment groups were attributed to the drugs. Adverse events observed in the clinical trials were similar to AEs listed in the Package Inserts of the RLDs, such as nausea, vomiting and pyrexia. The incidence of AEs was similar between treatment groups in both the Kabiven and [redacted] (b) (4) trials. Abnormal electrolyte shifts were seen in both Kabiven and [redacted] (b) (4). The electrolyte shifts in the Kabiven subjects was similar to that observed in the comparator group. The electrolyte shifts for potassium, magnesium and phosphate were greater in the [redacted] (b) (4) group than in the comparators. Close laboratory monitoring of electrolytes and supplementation will be necessary for both Kabiven and [redacted] (b) (4).

The Applicant has proposed the use of [redacted] (b) (4) for peripheral or central intravenous administration. The Applicant did not submit clinical trial data for [redacted] (b) (4) administered via central vein administration. It is unclear to this reviewer the benefit of giving [redacted] (b) (4) through a central vein when [redacted] (b) (4) has a lower electrolyte content. Kabiven would be a more appropriate PN product since its content is intended for central use.

7.1 Methods

7.1.1 Studies/Clinical Trials Used to Evaluate Safety

Safety data were reviewed from seven (7) Kabiven clinical trials, four (4) [redacted] (b) (4) [redacted] (b) (4) clinical trials and two (2) pharmacology studies. A total of 145 subjects received Kabiven and 93 subjects received [redacted] (b) (4). Safety analyses were based on TEAEs, laboratory assessments and vital signs.

7.1.2 Categorization of Adverse Events

The Applicant reported that all AEs were re-coded using MedDRA version 13.0. Treatment emergent adverse events (TEAE) were defined as any event that occurred after initiation of the first infusion of trial treatment and/or that worsened after initiation of the first infusion of trial treatment.

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7.1.3 Pooling of Data Across Studies/Clinical Trials to Estimate and Compare Incidence

Safety data was pooled from all 7 Kabiven clinical trials and safety data was pooled from all 4 [redacted] (b) (4) clinical trials. The 2 pharmacology studies were reviewed separately.

7.2 Adequacy of Safety Assessments

7.2.1 Overall Exposure at Appropriate Doses/Durations and Demographics of Target Populations

Kabiven Clinical Trials

The mean actual infusion volume for Kabiven at each period was at least 95% of the prescribed volume. The mean actual infusion volume for the comparator group at each period was at least 97% of the prescribed volume. The mean actual overall infusion volumes were 95% and 93% of the prescribed volumes in the Kabiven and comparator group. In the Kabiven pool, the mean infusion duration ranged from 20.94 to 21.60 hours through Period 6 with a mean total infusion duration of 143.56 hours. In the comparator pool, the mean infusion duration ranged from 21.04 to 21.77 hours through Period 6 with a mean total infusion duration of 144.60 hours.

In the Kabiven pooled trials, subjects who received Kabiven had a mean age of 59 years (range of 25 to 87 years); 40% were at least 65 years of age and 14% were at least 75 years of age. A total of 60% of subjects were male and all subjects were white except for 1 Black/African American subject.

Table 19: Kabiven Trials Pooled Demographics and Baseline Characteristics

Parameter	Kabiven Pooled N=145	Comparator Pooled N=144
Age (years)		
Mean (SD)	59.2 (13.9)	60.3 (13.1)
Median (min, max)	61.0 (25, 87)	62.0 (28, 85)
Age group (years), n (%)		
<65	87 (60.0)	84 (58.3)
≥65	58 (40.0)	60 (41.7)
≥75	20 (13.8)	20 (13.9)
Gender, n (%)		
Female	51 (35.2)	57 (39.6)
Male	94 (64.8)	87 (60.4)
Race, n (%)		
White	144 (99.3)	144 (100.0)
Black or African American	1 (0.7)	0 (0.0)
Body Mass Index (kg/m^2)	N=140	N=143
Mean (SD)	24.1 (4.0)	24.3 (4.3)
Median (min, max)	24.0 (15.0, 32.0)	24.0 (15.0, 34.0)
Weight (kg)	N=144	N=144
Mean (SD)	70.3 (13.9)	70.0 (13.6)
Median (min, max)	72.5 (35.0, 98.0)	70.0 (35.0, 101.0)

Medical Reviewer's comments: The demographic make-up was adequate for the Kabiven clinical trials. There were no major demographic differences between treatment groups.

(b) (4) Clinical Trials

Exposure to the study drug, 7 subjects received 2 to 3 days and 7 subjects received ≤ 1 day. Most subjects (N=73) received ≥ 80% of their target mean daily exposure; 18 subjects received 51% to 79% and only 2 subjects received ≤ 50%.

Table 20: (b) (4) Trials Pooled Demographics and Baseline Characteristics

Parameter	(b) (4) Pooled N=93	Comparator Pooled N=91
Age (years)		
Mean	57.3 (16.7)	57.2 (17.3)
Median (min, max)	60.0 (18, 87)	61.0 (20, 82)
Age group (years), n (%)		
<65	56 (60.2)	52 (57.1)
≥65	37 (39.8)	39 (42.9)
≥75	11 (11.8)	16 (17.6)
Gender, n (%)		
Female	45 (48.4)	43 (47.3)
Male	48 (51.6)	48 (52.7)
Race, n (%)		
White	68 (73.1)	65 (71.4)
Asian	1 (1.1)	3 (3.3)
Other	1 (1.1)	1 (1.1)
Not Collected	23 (24.7)	22 (24.2)
Body Mass Index (kg/m^2)	N=91	N=88
Mean	22.6 (4.8)	22.3 (4.7)
Median	23.0 (12.6, 40.1)	22.2 (13.2, 37.9)
Weight (kg)	N=91	N=89
Mean (SD)	63.6 (14.8)	63.1 (14.1)
Median (min, max)	64.0 (30.0, 99.0)	62.0 (39.0, 100.0)

BMI=body mass index, max=maximum, min=minimum, SD=standard deviation
Age is calculated as the closest lower integer result of (date of informed consent - date of birth)/365.25.
Weight, height, and body mass index (BMI) reported at enrollment. BMI was calculated for Studies 98-3CB2-001, 98-3CB2-002, 03-3CB8-001 using the formula weight in kg/(height in meters)^2.
Percentages are based on the number of subjects in the safety population within treatment group.

Medical Reviewer's comments: The demographic make-up was adequate for the (b) (4) clinical trials. There were no major demographic differences between treatment groups.

7.2.2 Explorations for Dose Response

No explorations for dose response was performed.

7.2.3 Special Animal and/or In Vitro Testing

The animal and/or in vitro testing data submitted by the Applicant as a part of the application was considered adequate by the Pharmacology/Toxicology Reviewer.

7.2.4 Routine Clinical Testing

The protocol defined clinical testing and safety assessments were adequate.

7.2.5 Metabolic, Clearance, and Interaction Workup

N/A

7.2.6 Evaluation for Potential Adverse Events for Similar Drugs in Drug Class

7.3 Major Safety Results

7.3.1 Deaths

Kabiven clinical trials
The Applicant reported that a total of 3 (2%) of the 145 patients in the Kabiven pool and 4 (2.8%) of the 144 patients in the comparator pool died post treatment. Of the deaths of the Kabiven patients, 1 occurred after 4 days of trial treatment and the other 2 occurred 6 and 20 days after the last infusion of the trial treatment.

The Applicant did not consider any of the deaths related to the trial treatment. See Table 21 for causes of death.

Table 21: Deaths in Kabiven Pooled Trials

Trial/Subject	Treatment	Adverse event (Preferred Term)
00-3CB4-001/001	Kabiven	Gastrointestinal hemorrhage Cardiac arrest
97-3CB1-001/027	Kabiven	Respiratory failure
97-3CB1-001/042	Kabiven	Cardiac failure
00-3CB4-001/012	Comparator (StructoKabiven)	Respiratory failure
00-3CB4-001/016	Comparator (StructoKabiven)	Pancreatitis
97-3CB1-001/019	Comparator (Kabimix 14)	Pancreatitis necrotizing Renal failure acute
98-3CB1-002/004	Comparator (Kabimix 14)	Bronchopneumonia Multi-organ failure Hypercoagulation

Reference ID: 3044686

[redacted] (b) (4) Clinical Trials

The Applicant reported that 2 subjects (2%) in each treatment group died post treatment. Of the 2 deaths in the [redacted] (b) (4) group, one was the day after the last infusion of TPN treatment and one was 18 days after the last infusion.

The Applicant regarded these deaths as not related or unlikely related to [redacted] (b) (4). See Table 22 for causes of death.

Table 22: Deaths in [redacted] (b) (4) Pooled Trials

Trial/Subject	Treatment	Adverse event (Preferred Term)
03-3CB8-001/001	[redacted] (b) (4)	Post-procedural sepsis/post-operative sepsis with multi-organ failure Bronchopulmonary aspergillosis/nosocomial pneumonia
98-3CB2-002/015	[redacted] (b) (4)	Cholecystitis/AST, ALT, ALP & GGT increase; fever; hypotension; septic shock
01-3CB6-001/018	Comparator (StructoKabiven Peripheral)	Aortic aneurysm/leaking aortic aneurysm
03-3CB8-001/099	Comparator (SMOFKabiven Peripheral)	Hepatitic necrosis with bleeding and suspected liver abscess, sepsis, progressive LV failure

Medical Reviewer's comments: There were no deaths attributed to Kabiven or [redacted] (b) (4). *In this patient population it is very likely that death may be related to underlying medical conditions/complications.*

7.3.2 Nonfatal Serious Adverse Events

Kabiven Clinical Trials

8 (6%) of the 145 subjects who received Kabiven experienced a non-fatal serious TEAE. 12 (8%) of the 144 subjects in the comparator pool had non fatal TEAEs. None of the SAEs were considered by the Applicant to be related to Kabiven.

Table 23: Kabiven Clinical Trials – Non-fatal SAEs

Study Subject ID	Trial treatment	SAE (Preferred Term)	Intensity	Relationship	Outcome
00-3CB5-001 020	Kabiven	Renal injury (pt removed percutaneous catheter himself and injured parts of kidney)	Severe	Unlikely	Recovered w/sequelae
01-3CB5-002 009	Kabiven	Cholecystitis Gastric fistula	Moderate Moderate	Unlikely Unlikely	Rec w/seq Recovered
01-3CB5-002 043	Kabiven	Gastrointestinal hemorrhage	Severe	Unlikely	Recovered
03-3CB7-001 015	Kabiven	Intestinal anastomosis complication	Severe	Unlikely	Rec w/seq
03-3CB7-001 053	Kabiven	Gastric hemorrhage	Moderate	Unlikely	Recovered
97-3CB1-001 020	Kabiven	Peritonitis	Moderate	Not related	Ongoing
98-3CB1-003 017	Kabiven	Pneumonia Pulmonary edema	Severe Severe	Not related Not related	Recovered Recovered
98-3CB1-003 039	Kabiven	Subclavian vein thrombosis	Severe	Not related	Rec w/seq
00-3CB5-001 001	AOI StructoQ EL	Cerebrovascular accident	Mild	Unlikely	Rec w/seq
00-3CB5-001 037	AOI StructoQ EL	Intestinal anastomosis complication	Severe	Unlikely	Rec w/seq
00-3CB5-001 039	AOI StructoQ EL	Abdominal wound dehiscence	Severe	Unlikely	Rec w/seq
01-3CB5-002 013	StructoKabiven	Pulmonary embolism	Severe	Unlikely	Recovered
01-3CB5-002 040	StructoKabiven	Brainstem infarction	Severe	Unlikely	Rec w/seq
03-3CB7-001 005	SmofKabiven	Ileus paralytic Resp failure Septic shock Staphylococcal infection	Severe Severe Severe Severe	Unlikely Unlikely Unlikely Unlikely	Recovered Recovered Recovered Recovered
03-3CB7-001 008	SmofKabiven	Intestinal anastomosis complication	Severe	Unlikely	Rec w/seq
03-3CB7-001 035	SmofKabiven	Pancreaticojejunostomy	Moderate	Unlikely	Recovered
03-3CB7-001 036	SmofKabiven	Pneumonia	Severe	Unlikely	Recovered
03-3CB7-001 039	SmofKabiven	Post procedural bile leak	Moderate	Unlikely	Recovered
98-3CB1-002 004	Kabimix 14	Hypercoagulation	Severe	Not related	Unknown
98-3CB1-003 047	Pharmacy Compound Bag	Wound infection	Moderate	Not related	Rec w/seq

Modified Applicant's table ISS, p.75

[redacted] (b) (4) Clinical Trials
One (1%) of the 93 subjects who received [redacted] (b) (4) and 3 (3%) of the subjects in the comparator pool experienced a non-fatal SAE. The SAE in the [redacted] (b) (4) group was considered by the Applicant to be unlikely related. See Table 24.

Table 24: [redacted] (b) (4) Non-fatal SAEs

Study Subject ID	Trial treatment	SAE (Preferred Term)	Intensity	Relationship	Outcome
01-3CB6-001 019	[redacted] (b) (4)	Anastomotic leak	Severe	Unlikely	Recovered
98-3CB2-002 021	Clinomel N4-550	Pneumonia aspiration Cardiogenic schock	Severe Severe	Not related Not related	Recovered Recovered
98-3CB2-002	Clinomel N4-550	Subarachnoid hemorrhage	Severe	Not related	Recovered
98-3CB2-002 037	Clinomel N4-550	Acute pulmonary edema	Severe	Related	Recovered

Modified applicant's table, ISS p. 138

7.3.3 Dropouts and/or Discontinuations

[redacted] (b) (4) Clinical Trials
A total of 12 subjects (8%) in the Kabiven pool and 12 subjects (8%) in the comparator pool discontinued study treatment as the result of a TEAE. Most TEAEs by preferred term resulted in discontinuation of a single subject. TEAEs that resulted in discontinuation of more than 1 subject in the Kabiven pool were pyrexia (4 subjects, 3%) and nausea (2 subjects, 1%). These 4 TEAEs of pyrexia and 1 event of "central venous catheterization" in the Kabiven pool, as well as 3 events of "device related infection" and 1 event of pyrexia in the comparator pool (all resulting in discontinuation), were described by the Applicant as being related to an infected central catheter.

[redacted] (b) (4) Clinical Trials
A total of 4 (4%) subjects in each pool discontinued study treatment as the result of a TEAE. TEAEs that resulted in withdrawal from the [redacted] (b) (4) group were jaundice (severe- possible related), phlebitis (severe-probable related), cytolytic hepatitis (moderate- related), and lymphangitis (mild-related)

7.3.4 Significant Adverse Events

Kabiven Clinical Trials
A total of 102 subjects (70%) who received Kabiven experienced at least 1 TEAE and 107 subjects (74.3%) in the comparator pool experienced at least 1 TEAE. Most TEAEs were of mild or moderate intensity; 16 subjects (11%) who received Kabiven experienced a severe TEAE and 16 subjects (11.1%) of subjects in the comparator pool experienced a severe TEAE. 31 subjects (21.4%) had TEAEs that were considered by

the Applicant to be related to the use of Kabiven and 39 subjects (27.1%) in the comparator pool had a TEAE that was considered to be related to a comparator treatment .

Table 25: Overview of TEAEs in Kabiven Trials

	Kabiven Pooled N=145 n (%)	**Comparator Pooled N=144 n (%)**
Subjects with at least 1 TEAE	102 (70.3)	107 (74.3%)
Subjects with at least 1 severe TEAE	16 (11%)	16 (11.1%)
Subjects with at least 1 related TEAE	31 (21.4%)	39 (27.1%)
Subjects with at least 1 TEAE resulting in death	3 (2.1%)	4 (2.8%)
Subjects with at least 1 serious TEAE	10 (6.9%)	15 (10.4%)
Subjects with at least 1 serious related TEAE	0	0
Subjects with at least 1 resulting in discontinuation of study drug	12 (8.3%)	12 (8.3%)

Applicant's table ISS, p. 71

Medical Reviewer's comments: Most TEAEs were considered by the investigator to be unrelated to study medication;

[redacted] (b) (4) Clinical Trials

A total of 40 (43%) subjects who received [redacted] (b) (4) experienced at leat 1 TEAE. 38 (41.8%) subjects in the comparator pool experienced at least 1 TEAE. 7% of subjects who received [redacted] (b) (4) experienced a severe TEAE. 15% of [redacted] (b) (4) subjects had TEAEs that were considered by the Applicant to be at least possibly related to the use of the treatment.

Table 26: [redacted] (b) (4) - Overview of TEAEs

	[redacted] (b) (4) Pooled N=93 n (%)	Comparator Pooled N=91 n (%)
Subjects with at least 1 TEAE	40 (43.0)	38 (41.8)
Subjects with at least 1 severe TEAE	6 (6.5)	7 (7.7)
Subjects with at least 1 related TEAE	14 (15.1)	12 (13.2)
Subjects with at least 1 TEAE resulting in death	2 (2.2)	2 (2.2)
Subjects with at least 1 serious TEAE	3 (3.2)	5 (5.5)
Subjects with at least 1 serious related TEAE	0	1 (1.1)
Subjects with at least 1 resulting in discontinuation of study drug	4 (4.3)	4 (4.4)

Applicant's table, ISS p.134

7.3.5 Submission Specific Primary Safety Concerns

Thrombophlebitis is a specific safety concern for [redacted] (b) (4). Thrombophlebitis may occur if peripheral veins are used for infusion of solutions that are hypertonic to body fluids. Several factors may contribute to thrombophlebitits including the type of cannula used and its diameter and length, the duration of the infusion, pH and osmolality of the infusion, infection and the number of manipulations.

In the clinical studies of [redacted] (b) (4), the Applicant stated that local tolerance of the vein punctured for study drug infusion was rated according to the "Modified Maddox scoring system".[15] See Table 27 for the Modified Maddox Scale.

Table 27: Modified Maddox Scale

Grade	Criteria
0	No pain at IV site, no erythema, no swelling, no induration, no palpable venous cord
1	Painful IV site, no erythema, no swelling, no induration, no palpable venous cord
2	No pain at IV site, erythema or some degree of swelling, or infusion stopped spontaneously
3	Painful IV site with erythema or some degree of swelling or both, no induration, no palpable cord
4	Painful IV site, erythema, swelling and with induration or palpable venous cord less than 3 inches above IV site
5	Painful IV site, erythema, swelling, induration, and palpable venous cord greater than 3 inches above IV site
6	Frank vein thrombosis along with all signs of 4, IV may have stopped running due to thrombosis

In Studies 98-3CB2-001, 01-3CB6-001, and 03-3CB8-001, the Applicant states that 3 visual inspections of the infusion site were performed every trial treatment period: the first within 4 hours after initiation of trial treatment, the second on completion of trial treatment and the third approximately 24 hour after initiation of trial treatment. In Study 98-3CB2-002, at least 2 visual inspections of the infusion site were to be performed every trial treatment period: the first within 2 hours after initiation of daily trial treatment, the second approximately 7 hours after initiation of daily trial treatment. In case of local venous intolerance in connection with the peripheral infusion (catheter /cannula withdrawal), an additional visual inspection was to be performed immediately.

The Applicant stated that injection site reaction was assessed as Maddox grade 0 in nearly all patients at all assessment times throughout the study. Table 28 summarizes the number of subjects with maximum modified Maddox scores of 4, 5, or 6.

Table 28: Subjects with a maximum Modified Maddox Scores of 4, 5, or 6

Modified Maddox Score	[redacted] (b) (4) Pooled N=93 n(%)	Comparator Pooled N=91 n(%)
4	4 (4.3)	4 (4.4)
5	2 (2.2)	1 (1.1)
6	1 (1.1)	0

Applicant's table, 2.7.4 Summary of Clinical Safety

Medical Reviewer's comments: Thrombophlebitis/phlebitis are potential complications of PPN. The majority of injection site reactions were reported by the Applicant as mild. The incidence of observed injection site reactions were similar among the two treatment groups.

7.4 Supportive Safety Results

7.4.1 Common Adverse Events

Kabiven Clinical Trials

A total of 70% of subjects in the Kabiven pool and 74% of subjects in the comparator pool had at least 1 TEAE during the clinical studies (Table 30). The TEAEs that occurred in at least 5% of subjects who received Kabiven were nausea (15%), pyrexia (9%), hypertension (8%), and vomiting and hemoglobin decreased (6% each).

Table 29: Treatment Emergent AEs (≥ 3%) by System Organ Class and Preferred Term

	Kabiven Pooled N=145		Comparator Pooled N=144	
Number (%) of subjects with at least one AE	102 (70.3)		107 (74.3)	
Number (%) of subjects	n	%	n	%
System organ class Preferred term				
Blood and lymphatic system disorders				
Anemia	5	3.4	7	4.9
Gastrointestinal disorders				
Nausea	22	15.2	20	13.9
Vomiting	8	5.5	10	6.9
Flatulence	4	2.8	9	6.3
Dyspepsia	4	2.8	6	4.2
General disorders and administration site conditions				
Pyrexia	13	9.0	13	9.0
Investigations				
Hemoglobin decreased	8	5.5	10	6.9
Total protein decreased	6	4.1	11	7.6
Blood potassium decreased	6	4.1	7	4.9
GGT increased	6	4.1	3	2.1
Metabolism and nutrition disorders				
Hyperglycemia	3	2.1	5	3.5
Hypokalemia	6	4.1	5	3.5
Vascular disorders				
Hypertension	12	8.3	14	9.7

Medical Reviewer's comments: The incidence of observed TEAEs were similar among treatment groups.

(b) (4) Clinical Trials

A total of 43% of subjects treated with (b) (4) and 42% of subjects treated with a comparator had at least 1 TEAE during the clinical studies. Hyperglycemia occurred in 5% of subjects receiving (b) (4). The next most common TEAEs were pyrexia and hypokalemia (4% each).

Table 30: (b) (4) Clinical Trials Treatment Emergent AEs (≥ 2%) by System Organ Class and Preferred Term

	(b) (4) Pooled N=93		Comparator Pooled N=91	
Number (%) of subjects with at least one AE	40 (43)		38 (41.8)	
Number (%) of subjects	n	%	n	%
System organ class Preferred term				
Blood and lymphatic system disorders				
Anemia	2	2.2	0	0
Gastrointestinal disorders				
Nausea	2	2.2	3	3.3
General disorders and administration site conditions				
Pyrexia	4	4.3	0	0
Investigations				
GGT increased	2	2.2	3	3.3
Blood alkaline phosphatase increased	2	2.2	0	0
Alanine aminotransferase Increased	2	2.2	1	1.1
Blood glucose increased	2	2.2	0	0
Blood triglycerides Increased	3	3.2	0	0
C-reactive protein increased	2	2.2	1	1.1
Blood urea increased	2	2.2	0	0
Metabolism and nutrition disorders				
Hyperglycemia	5	5.4	4	4.4
Hypokalemia	4	4.3	1	1.1
Hypoalbuminemia	2	2.2	0	0
Psychiatric disorders				
Insomnia	2	2.2	0	0
Vascular disorders				
Hypotension	2	2.2	0	0
Phlebitis	2	2.2	0	0
Skin & subcutaneous tissue disorders				
Pruritus	2	2.2	0	0

Applicant's table

7.4.2 Laboratory Findings

Laboratory assessments for Kabiven and [redacted] (b) (4) and their respective comparator pools that were reviewed included the following: electrolytes, complete blood count and glucose for both Kabiven and [redacted] (b) (4) and their respective comparator pools during the clinical program. The Applicant submitted data on shifts in laboratory values from baseline to all post-infusion assessments by period.

Kabiven Clinical Trials

Hemoglobin
No clinically meaningful differences in the worsening of post-treatment hemoglobin were identified between Kabiven and comparator treated subjects. Most subjects had low hemoglobin values at baseline and for at least 1 post-treatment assessment, Kabiven 69%; comparator pool, 71%. 23 Kabiven subjects (16%) and 19 comparator subjects (13%) had shifts from normal at baseline to low at any post-treatment time point. One additional Kabiven subject (1%) shifted from normal at baseline to low alert post treatment. Eight Kabiven subjects (6%) and 9 comparator subjects (6%) who were low at baseline shifted to low alert concentrations (<8g/dL) post treatment. One additional subject (1%) in the comparator pool shifted from below the normal range for hemoglobin at baseline to above the normal range post treatment.

Leukocytes
Approximately one third of subjects had normal leucocyte counts at baseline and throughout the study (Kabiven 35%, comparator 38%), while 24% of Kabiven subjects were high at baseline and remained high post treatment compared to 27% of comparators. 14.5% of Kabiven subjects and 9.7% of comparator subjects had shifts from normal at baseline to high at any post-treatment time point. 4.8% of Kabiven subjects and 2.8% of comparator subjects had shifts from normal at baseline to low at any post-treatment period.

Platelets
Worsening of platelet count during the study was comparable in subjects treated with Kabiven or comparator drugs. 52% of the Kabiven subjects and 55% of the comparators had normal platelet counts at baseline and throughout the study. Platelet concentrations shifted from normal at baseline to high in 9% of Kabiven subjects and 8.4% of comparator subjects and shifted from baseline of normal to low in 4.8% of Kabiven subjects and 3.5% of comparator pool subjects.

Sodium
A majority of subjects in each pool had sodium values within the normal range at baseline and throughout the study Kabiven subjects, 64% and comparator subjects, 64%. A total of 18 Kabiven subjects (13%) and 13 comparator subjects (9%) shifted from normal sodium values at baseline to low values post treatment; 2 additional

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comparator subjects (1%) shifted from normal to low alert (<130mmol/L) values. Four additional Kabiven subjects (3%) shifted from low to low alert values. Six subjects in the Kabiven pool (4%) and 7 subjects in the comparator pool (5%) shifted from normal sodium values at baseline to high post-treatment values. No subject had a high alert (>155mmol/L) value during the study.

Potassium
54% of Kabiven subjects and 45% of comparator subjects had normal potassium levels at baseline and throughout the trial. Potassium values shifted from normal at baseline to low (17.6%) or low alert (1.4%; <3.0mmol/L) in Kabiven subjects and also in the comparator subjects (24% and 5%, respectively). Twelve percent of Kabiven subjects and 9.2% of comparator subjects also shifted from normal to high with respect to potassium.

Table 31: Shifts in Potassium Values from Baseline to Worst Post-treatment assessments

Shift from baseline to post-treatment time point	Kabiven pooled N=145 n (%)	Comparator Pool N=144 n (%)
Number of subjects	142	141
Normal to low alert	2 (1.4)	7 (5.0)
Low to low alert	1 (0.7)	0
Normal to low	25 (17.6)	34 (24.1)
High to low	3 (2.1)	1 (0.7)
Normal to high	17 (12.0)	13 (9.2)
Low to high	0	3 (2.1)

Calcium
55% of Kabiven subjects and 42% of comparator pool subjects had low calcium values at baseline and remained low throughout the trial. Of Kabiven subjects with normal calcium values at baseline, 5.3% shifted to low, 0.76% shifted to low alert (<1.75mmol/L) and 0.76% shifted to high during the trial as compared to the comparator pool in which 5.4% of subjects who were normal at baseline shifted to low and 3.1% shifted to high. No subject had a high alert (> 3 mmol/L) value during the trial.

Table 32: Shifts in Calcium Values from Baseline to Worst Post-treatment assessments

Shift from baseline to post-treatment time point	Kabiven pooled N=145 n (%)	Comparator Pool N=144 n (%)
Number of subjects	132	130
Normal to low alert	1 (0.76)	0
Low to low alert	2 (1.5)	4 (3.1)
Normal to low	7 (5.3)	7 (5.4)
High to low	0	0

Normal to high	1 (0.76)	4 (3.1)
Low alert to high	0	0
High to low alert	0	0

Magnesium
74% of Kabiven subjects and 65% of comparator pool subjects had normal magnesium values at baseline and throughout the trial. Of Kabiven subjects with normal magnesium concentrations at baseline 1.6% shifted to low and 8.7% shifted to high; of comparator subjects that were normal at baseline, 7.1% shifted to low, 5.6% shifted to high and 0.8% shifted to high alert (>1.2mmol/L) post treatment. One additional comparator subject (0.8%) who had a low value at baseline shifted to a high value during the study.

Table 33: Shifts in Magnesium Values from Baseline to Worst Post-treatment assessments

Shift from baseline to post-treatment time point	Kabiven pooled N=145 n (%)	Comparator Pool N=144 n (%)
Number of subjects	127	126
Normal to high alert	0	1 (0.8)
Normal to low	2 (1.6)	9 (7.1)
Normal to high	11 (8.7)	7 (5.6)
Low to high	0	1 (0.8)

Phosphate
55% of Kabiven subjects and 38% of comparator pool subjects had normal phosphate values and baseline and throughout the trial. Phosphate concentrations shifted from normal at baseline to low (8.5%) or low alert (5.1%; <0.6mmol/L) in Kabiven subjects and also in the comparator subjects (13.1% and 6.5%, respectively). A total of 9.4% of subjects in the Kabiven pool and 17.8% of subjects in the comparator pool shifted from normal to high with respect to phosphate. No subject had a high alert (>2.5mmol/L) value during the study.

Table 34: Shifts in Phosphate Values from Baseline to Worst Post-treatment assessments

Shift from baseline to post-treatment time point	Kabiven pooled N=145 n (%)	Comparator Pool N=144 n (%)
Number of subjects	117	107
Normal to low alert	6 (5.1)	7 (6.5)
Low to low alert	1 (0.9)	0
Normal to low	10 (8.5)	14 (13.1)
High to low	2 (1.7)	1 (0.9)

Normal to high	11 (9.4)	19 (17.8)
Low alert to high	1 (0.9)	0
High to low alert	0	1 (0.9)

Glucose
41% of Kabiven subjects and 36% of comparator subjects had high baseline glucose values that remained high post-treatment. 36.2% of Kabiven subjects had glucose values that shifted from a normal baseline to high and 1.4% had values that shifted to high alert. 333.8% of the comparator subjects had normal baseline glucose values that shifted to high and 2.3% shifted to high alert.

Table 35: Shifts in Glucose Values from Baseline to Worst Post-treatment assessments

Shift from baseline to post-treatment time point	Kabiven pooled N=145 n (%)	Comparator Pool N=144 n (%)
Number of subjects	138	130
Normal to low alert	1 (0,7)	0
Low to high	2 (1.4)	2 (1.5)
Normal to low	1 (0.7)	0
High to low	1 (0.7)	0
Normal to high	50 (36.2)	44 (33.8)
Normal to high alert	2 (1.4)	3 (2.3)
Low alert to high	1 (0.7)	0
High to low alert	0	1 (0.8)
High to high alert	3 (2.2)	7 (5.4)

[redacted] (b) (4) Clinical Trials

Hemoglobin
43% of [redacted] (b) (4) subjects and 43% of comparator pool subjects were low at baseline and remained low at post-treatment assessments. 29% of [redacted] (b) (4) subject and 13% of comparator subjects had shifts from normal at baseline to low at any post-treatment time point.

Leukocyte
34% of [redacted] (b) (4) subjects and 35% of comparator subject had normal leukocyte counts at baseline and thoughout the trials. 26% of [redacted] (b) (4) subjects and 18% of comparators were high at baseline and remained high throughout the trials.

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Platelets
The majority of subjects in each pool had normal platelet counts at baseline and throughout the study ([redacted] (b) (4) 53%, comparator 67%). Platelet values shifted from normal at baseline to both high and low levels in <10% of subjects in both the [redacted] (b) (4) and comparator pools. One additional subject in each pool (1% each pool) had low levels at baseline and low alert levels post treatment and 1 additional [redacted] (b) (4) subject shifted from normal to low alert levels. Two additional comparator subjects (2%) had low alert (≤75x10⁹/L) values at baseline and at least 1 post-treatment assessment. A total of 15 additional subjects in the Kabiven pool (17%) and 8 additional subjects in the comparator pool (9%) had high alert (≥500x10⁹/L) assessments at baseline and at least 1 post-treatment assessment.

Sodium
51% of [redacted] (b) (4) subjects and 45% of comparator subjects had sodium values within the normal range at baseline and throughout the trials. A total of 12 [redacted] (b) (4) subjects (14%) and 18 comparator subjects (21%) shifted from normal sodium values at baseline to low values post-treatment; 4 additional [redacted] (b) (4) subjects (5%) and 5 additional comparator subjects (6%) shifted from normal to low alert (<130mmol/L) values. Five additional subjects in the [redacted] (b) (4) pool (6%) and 3 additional subjects in the comparator pool (4%) shifted from low to low alert values. Four subjects in the [redacted] (b) (4) pool (5%) and 1 subject in the comparator pool (1%) shifted from normal sodium concentrations at baseline to high post-treatment values. No subject had a high alert (>155mmol/L) value for sodium during the study.

Potassium
52% of [redacted] (b) (4) subjects and 65% of comparator subjects had potassium values within the normal range at baseline and throughout the trials. Potassium values shifted from normal at baseline to low (15%) or alert low (6%; <3.0mmol/L) in [redacted] (b) (4) subjects and also in the comparator subjects (8% and 1%, respectively). 8% of [redacted] (b) (4) subjects and 5.8% of [redacted] (b) (4) subjects shifted from normal to high with respect to potassium.

Table 36: Shifts in Potassium Values from Baseline to Worst Post-treatment assessments

Shift from baseline to post-treatment time point	[redacted] (b) (4) pooled N=93 n (%)	Comparator Pool N=91 n (%)
Number of subjects	88	86
Normal to low alert	5 (5.7)	1 (1.2)
Low to low alert	1 (1.1)	3 (3.5)
Normal to low	13 (14.8)	7 (8.1)
High to low	1 (1.1)	0

Normal to high	7 (8.0)	5 (5.8)
Low alert to high	1 (1.1)	1 (1.2)
Normal to high alert	0	1 (1.2)

Calcium
60% of [redacted] (b) (4) subjects and 60% of comparator subjects had normal calcium concentrations at baseline and throughout the study. 24% of [redacted] (b) (4) subjects and 22% of comparator subjects had low calcium values at baseline and post-treatment. Of [redacted] (b) (4) subjects with normal calcium concentrations at baseline, 2 (3%) shifted to low, and 3 (4%) shifted to high during the study; comparator subjects that were normal at baseline shifted to low (6 subjects, 8%) and high (3 subjects, 4%). One additional [redacted] (b) (4) subject shifted from low calcium at baseline to high calcium post-treatment and 1 additional comparator subject shifted from high calcium at baseline to low calcium post treatment. No subject had a high alert (>3mmol/L) value during the study.

Table 37: Shifts in Calcium Values from Baseline to Worst Post-treatment assessments

Shift from baseline to post-treatment time point	[redacted] (b) (4) pooled N=93 n (%)	Comparator Pool N=91 n (%)
Number of subjects	74	79
Normal to low alert	0	0
Low to low alert	0	0
Normal to low	2 (2.7)	6 (7.6)
High to low	0	1 (1.3)
Normal to high	3 (4.1)	3 (3.8)
Low alert to high	0	0
High to low alert	0	0

Magnesium
78% of the [redacted] (b) (4) subjects and 76% of the comparators had normal magnesium values at baseline and throughout the study. Of [redacted] (b) (4) subjects with normal magnesium concentrations at baseline, 1 (2%) shifted to low and 7 (13%) shifted to high; of comparator subjects that were normal at baseline, 5 shifted to high (9%), and 1 shifted to high alert (2%; >1.2mmol/L) values. No subjects had low alert (<0.4mmol/L) at any time during the study.

Table 38: Shifts in Magnesium Values from Baseline to Worst Post-treatment assessments

Shift from baseline to post-treatment time point	[redacted] (b) (4) pooled N=93 n (%)	Comparator Pool N=91 n (%)
Number of subjects	55	55
Normal to high alert	0	1 (1.8)
Normal to low	1 (1.8)	0
Normal to high	7 (12.7)	5 (9.1)

Phosphate
52% of [redacted] (b) (4) subjects and 65% of comparator subjects had normal phosphate values at baseline and throughout the study. Phosphate values shifted from normal at baseline to low (10%) or low alert (10%; <0.6mmol/L) in [redacted] (b) (4) subjects and also in the comparator subjects (8% and 1%, respectively). Phosphate values shifted from normal at baseline to high in [redacted] (b) (4) subjects (4%) and comparator subjects (7%). No subjects had high alert (>2.5mmol/L) values for phosphate at any time during the study.

Table 39: Shifts in Phosphate Values from Baseline to Worst Post-treatment assessments

Shift from baseline to post-treatment time point	[redacted] (b) (4) pooled N=93 n (%)	Comparator Pool N=91 n (%)
Number of subjects	69	75
Normal to low alert	7 (10.1)	1 (1.3)
Low to low alert	1 (1.4)	0
Normal to low	7 (10.1)	6 (8.0)
Normal to high	3 (4.3)	5 (6.7)
Low alert to high	1 (1.4)	1 (1.3)

Glucose
25% of [redacted] (b) (4) subject and 41% of comparator subjects had glucose baseline and post treatment values. 33% of [redacted] (b) (4) subjects and 23% of comparator subjects were normal at baseline and shifted to high. No subjects had low alert (<2.2mmol/L) values for glucose at any time during the study.

Table 40: Shifts in Glucose Values from Baseline to Worst Post-treatment assessments

Shift from baseline to post-treatment time point	[redacted] (b) (4) pooled N=93 n (%)	Comparator Pool N=91 n (%)
Number of subjects	61	71
Low to high	0	1 (1.4)
Normal to low	0	1 (1.4)
Normal to high	20 (32.8)	16 (22.5)
Low alert to high	2 (3.3)	0
High to high alert	4 (6.6)	3 (4.2)

Medical Reviewer's comments: Shifts in electrolyte and glucose values for the Kabiven subjects and comparator subjects were generally similar between both groups. Electrolyte, particularly potassium, phosphate, magnesium and glucose shift were greater in the [redacted] (b) (4) *group than in the comparator groups.* [redacted] (b) (4) [redacted] *patients may require electrolyte supplementation. Electrolyte requirements vary with different clinical conditions and careful monitoring of electrolye balance is required in all patients receiving PN.*

7.4.3 Vital Signs

The Applicant reported that overall, there were no clinically significant trends in heart rate, blood pressure, respiratory rate, termperature or weight with either Kabiven and its comparator pool and [redacted] (b) (4) and its comparator pool.

7.4.4 Electrocardiograms (ECGs)

N/A

7.4.5 Special Safety Studies/Clinical Trials

See section 7.3.5

7.4.6 Immunogenicity

N/A

7.5 Other Safety Explorations

7.5.1 Dose Dependency for Adverse Events

N/A

7.5.2 Time Dependency for Adverse Events

N/A

7.5.3 Drug-Demographic Interactions

N/A

7.5.4 Drug-Disease Interactions

No drug disease interaction studies were conducted

7.5.5 Drug-Drug Interactions

No drug interaction studies were conducted for the proposed products.

7.6 Additional Safety Evaluations

7.6.1 Human Carcinogenicity

N/A

7.6.2 Human Reproduction and Pregnancy Data

N/A

7.6.3 Pediatrics and Assessment of Effects on Growth

The Applicant submitted (b) (4)

A consult was requested from the Pediatrics and Maternal Health Staff to address the following questions:

1) The Applicant is requesting (b) (4)

2) The Applicant is requesting a waiver for use in children < 2 yrs of age, (b) (4) Is this acceptable?

(b) (4)

A letter was sent to the Applicant on September 8, 2011 denying their request (b) (4)

The Applicant submitted a Pediatric Plan on October 21, 2011. The Pediatric Plan will be reviewed during the second review cycle.

7.6.4 Overdose, Drug Abuse Potential, Withdrawal and Rebound

Nausea and vomiting and sweating have been observed during the infusion of amino acids at rates exceeding the recommended maximum rate. Overdose of Kabiven and/or (b) (4) may cause fluid overload, electrolyte imbalances, hyperglycemia and hyperosmolarity.

An impaired capacity to eliminate fat may lead to the fat overload syndrome as a result of overdosage. This syndrome though may also occur at recommended rates of infusion in association with a sudden change in the patient's clinical status, such as renal function impairment or a severe infection. The fat overload syndrome is characterized by hyperlipidemia, fever, fat infiltration and disorders in various organs. These symptoms are usually reversible if the infusion is discontinued, but may require hemodialysis or hemofiltration in rare cases.

No drug abuse potential or withdrawal has been reported.

7.7 Additional Submissions / Safety Issues

Safety data from the Clinical Pharmacology studies:

Glyc-001-C P1
All but 2 subjects (subject 006 and 009) received the doses of Glycophos and I-phosphate

A total of 15 (60%) subjects reported at least one TEAE. A total of 28 TEAEs were reported during and following administration of the drug products. Nine (36%) subjects reported 12 TEAEs for the treatment with Glycophos® and 11 (44%) subjects reported 16 TEAEs for the treatment with I-phosphate. For Glycophos®, 10 TEAEs were considered by the Investigator to be of mild and 2 of moderate intensity, for I-Phosphate all TEAEs were considered by the Investigator to be mild. Regarding the relationship to the IMP, the Investigator considered 6 TEAEs reported by 4 subjects as related to Glycophos®, and 10 TEAEs, reported by 5 (20%) subjects as related to I-Phosphate. For the pre-treatment days a total of 3 AEs were reported of which one (supraventricular extrasystoles) caused premature withdrawal of the subjects. All episodes of hypocalcaemia were considered by the Investigator to be of mild intensity and the only TEAE considered to be related to the drug product. No severe TEAE occurred. None of the subjects died, no serious and no significant AE occurred, and none of the subjects were withdrawn due to a TEAE.

Table 41: TEAEs by subject, system organ class/preferred term, safety population

	Glycophos N=25		**I-Phosphate N=25**	
Number (%) of subjects with at least one AE	9 (36.0)		11 (44.0)	
Number (%) of subjects	n	%	n	%
System organ class Preferred term				
Gastrointestinal disorders				
Dry mouth	1	4.0	0	0
Nausea	0	0	1	4.0

Infections and infestations				
Nasopharyngitis	0	0	1	4.0
Oral herpes	1	4.0	1	4.0
Investigations				
Hemoglobin decreased	0	0	1	4.0
Neutrophil count decreased	1	4.0	1	4.0
Metabolism and nutrition disorders				
Hypocalcemia	4	16.0	5	20.0
Muscuoloskeletal and connective tissue disorders				
Back pain	1	4.0	0	0
Nervous system disorders				
Headache	2	8.0	0	0
Reproductive system and breast disorders				
Dysmenorrhea	0	0	1	4.0

Applicant's table, ISS

KABI-003-C P1

A total of 3 (30%) subjects experienced one TEAE during the study. All TEAEs were reported for the treatment with Glycophos® and none for the treatment with [redacted] (b) (4) All TEAEs reported were considered by the Investigator to be of mild intensity and one TEAE, headache, was considered by the Investigator to be related to the IMP. No moderate or severe TEAE occurred. None of the subjects died, no serious and no significant, unknown or unexpected AE occurred, and none of the subjects were withdrawn due to a TEAE. All AEs were resolved at the end of the study, none were to be followed up.

Overall, organic phosphate infusion, alone (Glycophos®) or together with nutrients ([redacted] (b) (4)) caused an increase of inorganic phosphate in serum, which was not outside the physiological ranges. All serum phosphate concentration measured in this study were within physiological ranges of 0.8 to 1.5 mmol/L. The mean serum concentration-time profile of inorganic phosphate were comparable over time for both treatments.

Medical Reviewer's comments: Overall, no significant AEs were observed with organic phosphate infusion.

8 Postmarket Experience

Kabiven is approved for PN for adult patients and children above 2 years of age. Kabiven was first registered in Sweden on March 12, 1999 and the product is registered in 58 countries. Kabiven has been administered to approximately [redacted] (b) (4) patients worldwide since 1999.

(b) (4) is approved for PN for adult patients and children above 2 years of age. (b) (4) was first registered in Sweden on December 29, 1999 and the product is registered in (b) (4) countries. (b) (4) has been administered to approximately (b) (4) million patients worldwide since 1999.

Table 42 : Patient exposure to Kabiven and (b) (4)

Year	2000	2002	2004	2006	2008	1999-2009
Kabiven (b) (4) (units)						(b) (4)
(b) (4) (units)						
Total Kabiven (units)						
Number of Patients Treated						
Number of Countries with Product Sales						

Applicant's table, ISS

In July 2003, the European Commission's branch handling pharmaceuticals provided a notice to applicants that pointed out the risk of cross-allergy reactions between peanut and soybean oils. As a result, Kabiven products, which contain soybean oil, include the following information in the Summary of Product Characteristics:

• Section 4.3 Contraindications: "Hypersensitivity to egg, soy, or peanut protein or to any of the active substances or excipients"

• Section 4.4 Special warnings and special precautions for use: "This medicinal product contains soybean oil and egg phospholipids, which may rarely cause allergic reactions. Cross allergic reaction has been observed between soybean and peanut."

<u>Kabiven</u>

Reported post marketing adverse drug reactions (ADRs) for Kabiven from March 1999 through October 2010 include 17 subjects who experienced 27 ADR as reported spontaneously, from regulatory authorities, in the literature and other sources. Twelve of these subjects experienced 19 SAEs. The relationship of the majority of AEs were reported as possible or probable related to the drug product. These AEs included pyrexia, injection site reaction, dyspnea, erythema multiforme, hypersensitivity, pruritus, hyperlipidemia, thrombocytopenia, , leukopenia, liver disorder, abdominal pain, and vomiting.

Table 43: Tabulation of Subjects (events) reported postmarketing for Kabiven

PSUR period	ADRs: Spontaneous/Regulatory authority reports	ADRs Literature reports	SAEs: Spontaneous/Regulatory authority reports	SAEs: Literature reports
March 1999-Sep 2003	6 (8)	0	4 (5)	0
Oct 2003-Jan 2008	5 (9)	1 (1)	5 (9)	0
Feb 2008-Oct 2010	5 (9)	0	3 (5)	0
Total	**16 (26)**	**1 (1)**	**12 (19)**	

Table 44: ADRs from sources other than clinical trials for Kabiven

Country/ Source	Age (years) /Sex/Other Diseases	Adverse Event (*=serious)	Relationship: Reporter/Company	Outcome
France, Spontaneous, Case 0001420	54/Male/-	Pyrexia, injection site inflammation	Possible (source not specified)	Recovered
France, Health Authority, Case 0002394	52/Male/cancer	*Hyperkalemia	Not assessable (but likely due to administration of potassium-containing solutions)	Death (due to underlying disease)
France, Health Authority, Case 0002395	54/Female/major abdominal surgery	*Pyrexia	Not assessable (but unlikely)	Normalized after 7 weeks while under continuous therapy.
France, Health Authority, Case 0002490	-/-/-	*Prolonged hospitalization, family stress	Not assessable (broken seal on the Kabiven bag)	Unknown
France, Health Authority, Case 0002511	81/Female/-	*Macrocytic anemia (possibly a consequence of fat overload)	None/possible	Death
Italy, Spontaneous, Case 0002536	16/Male/-	Dyspnea	Probable (source not specified)	Recovered
Sweden, Spontaneous, Case 20040110	71/Female/ clostridial infection, diarrhea, gastroenteritis, hypertension	*Erythema multiform	Possible/probable	Recovered
Spain, Literature, Case 2005110277	55/Male/ gastric adenocarcinoma, Billroth's operation II, partical gastrectomy	Hypersensitivity (pruritic rash)	Probable (source not specified; cernevit was a suspect drug)	Recovered
France, Health Authority, Case 2007010010	82/Male/ hemorrhagic pancreatitis, sigmoidectomy	*Pruritus	Unlikely/possible	Recovered
France, Health Authority, Case 2007010023	46/Male/abdominal pain, diarrhea, gastrointestinal hemorrhage, pancolitis, proctorrhagia, tobacco abuse	*Hyponatremia	Unlikely (source not specified; cymevan probable cause)	Recovered

Country/ Source	Age (years) /Sex/Other Diseases	Adverse Event (*=serious)	Relationship: Reporter/Company	Outcome
France, Health Authority, Case 2007020130	44/Female/atypical mycobaceriosis, HIV infection, esophageal and oral candidiasis, visceral leishmaniasis	*Hyperlipidemia (pancytopenia, hyperthermia), asthenia, upper abdominal pain, liver disorder	Possible/probable	Recovered
France, Health Authority, Case 2007090591	70/Male/-	*Thrombocytopenia, leukopenia	Possible (source not specified)	Recovered
Phillipines, Spontaneous, Case 2008030058	73/Male/cancer	Pyrexia, chills, wheezing	Probable (source not specified)	Recovered
Malaysia, Spontaneous, Case 2008100337	66/Male/-	Hypersensitivity (chills, increased body temperature, rash, pruritus)	Probable (source not specified)	Recovered
France, Health Authority, Case 2008120454	47/Male/ pancreatic adenocarcinoma, anorexia, liver metastases, weight loss	*Extravasation (swelling, injection site extravasation)	Possible/probable	Recovered
Sweden, Health Authority, Case 2009110617	63/Female/ fibromyalgia, hypertension, thyroid lobectomy, lung adenocarcinoma	*Liver disorder (jaundice)	Possible/possible	Recovered
France, Health Authority, Case CV20100399	55/male/ nephrectomy, renal cancer	*Abdominal pain, vomiting, hyperthermia (tremor)	Probable/possible	Recovered

(b) (4)

Reported post marketing adverse drug reaction (ADR) for (b) (4) from December 1999 through November 2010 include 18 subjects who have experienced 29 ADRs as reported spontaneously, from regulatory authorities, in the literature and other sources. Sixteen of these subjects experienced 25 SAEs. The relationship of the majority of AEs were reported as possible or probable related to the drug product. These AEs included anaphylactoid reaction, Candidiasis, pyrexia, injection site reaction, bronchospasm/dyspnea, hypersensitivity, pruritus, hyperlipidemia, leukopenia, hepatitis, renal failure, vomiting, septicemia, hypertriglyceridemia, cholestasis and hypotension.

Table 45: Tabulation of Subjects (events) reported postmarketing for [redacted] (b) (4)

PSUR period	ADRs: Spontaneous/Regulatory authority reports	ADRs Literature reports	SAEs: Spontaneous/Regulatory authority reports	SAEs: Literature reports
Dec 1999-Sep 2003	2 (5)	0	1 (3)	0
Oct 2003-Jan 2008	11 (17)	0	11 (16)	0
Feb 2008-Oct 2010	8 (14)	0	7 (11)	0
Total	**18 (29)**	**0**	**16 (25)**	0

Table 46: ADRs from Sources other than clinical trials for [redacted] (b) (4)

Country/ Source	Age (years) /Sex/ Other Diseases	Adverse Event (*=serious)	Relationship: Reporter/Company	Outcome
Poland, Spontaneous, Case 0002482	69/Male/Renal insufficiency	*Hypotension, decreased oxygen saturation, tachycardia	Possible (source not specified)	Death
Poland, Spontaneous, Case 0002483	63/Female/colon cancer with infiltration of the abdominal wall	Bronchospasm, dyspnea	Probable (source not specified)	Recovered
Italy, Spontaneous, Case 20031105	81/Male/pancreatic cancer	*Vomiting	Probable (source not specified; oxygen absorber [iron] was suspended with the solution and administered IV to the patient – clear handling mistake)	Recovered
France, Health Authority, Case 20040819	70/Male/chronic lymphatic leukemia, hypogamma-globulinemia, infection, pneumonitis, pneumonopathy	*Anaphylactoid reaction (hypotension, bronchospasm, pyrexia, chills, vomiting)	Not assessed/ Unlikely (symptoms probably caused by Tegeline.)	Unknown
United Kingdom, Spontaneous, Case 2005040007	60/Female/-	*Anaphylactoid reaction (hypersensitivity, pruritus, gastroesophageal reflux disease)	Probable/possible	Recovered
United Kingdom, Spontaneous, Case 2005040008	45/Male/allergy, diverticular disease, hypertension, psoriasis	*Anaphylactoid reaction (flushing, pyrexia, pruritus)	Possible (source not specified)	Recovered
Greece, Spontaneous, Case 2006040055	86/Female/breast cancer, diabetes mellitus, hypertension	*Candiasis (pyrexia, sepsis, hypotension)	Possible (source not specified)	Fatal
Greece, Spontaneous, Case 2006040060	76/Male/pancreatic cancer, Whipple's operation	*Candidiasis (fever)	Possible (source not specified)	Recovered
Greece, Spontaneous, Case 2006070322	63/Male/-	*Candidiasis (fever)	Possible (source not specified)	Recovered

Country/ Source	Age (years) /Sex/ Other Diseases	Adverse Event (*=serious)	Relationship: Reporter/Company	Outcome
Greece, Spontaneous, Case 2006100445	21/Male/acute lymphoblastic leukemia, blood culture positive, fever, mucositis, secondary pancytopenia	*Lung disorder (abnormal lung biopsy, pneumonitis, pulmonary fibrosis, pneumonia, pleurisy, pulmonary vascular disorder, lung infiltration), pyrexia, abnormal liver scan, abnormal bone marrow aspiration, reticuloendothelial system stimulated, hypophosphatemia	Unlikely/unlikely (according to PSUR Feb2008-Dec2009)	Recovering
Phillipines, Spontaneous, Case 2006010004	80/Male/ Postoperative adhesion	Phlebitis *Candidiasis	Probable Unlikely (sources not specified)	Recovered
France, Spontaneous, Case 2007020060	92/Female/ conductive keratoplasty, glaucoma, hip arthroplasty, knee arthroplasty	*Injection site inflammation (lymphangitis, pyrexia)	Possible (source not specified)	Recovered
Indonesia, Spontaneous, Case 2007050305	70/Female/ choledochojejunostomy, gastro-jejunostomy, intestinal adenocarcinoma, obstructive jaundice	*Renal failure	Possible/Possible	Recovered
Poland, Health Authority, Case 2008100348	17/Female/-	*Hypovolemic shock, decreased blood pressure, anuria	Probable/possible	Recovered
France, Health Authority, Case 2009030050	82/Female/ colostomy, hysterectomy, rectal cancer, small bowel resection	*Hepatitis	Possible/possible	Not recovered
France, Health Authority, Case 2009050165	19/Male/Aphthous ulcer, Crohn's disease, enterectomy, fever of unknown origin	*Leukopenia (lymphopenia)	Possible/possible	Not recovered
France, Health Authority, Case 2009090501	47/Male/alcohol abuse HIV positive, hepatitis C, smoker	*Pancreatitis	Possible/possible	Recovered
Germany, Health Authority, Case 2009100519	76/Male/-	Injection site edema	Probable/probable	Unknown
Turkey, Spontaneous, Case CV20100180	43/Female/-	Fever, hyperglycemia	Possible/possible	Recovering

Country/ Source	Age (years) /Sex/ Other Diseases	Adverse Event (*=serious)	Relationship: Reporter/Company	Outcome
Singapore, Spontaneous, Case CV20100305	Adult/male/cancer	*Septicemia, dyspnea	Probable/possible	Unknown
Spain, Health Authority, CV20100230	57/Male/caustic injury	*Hypertriglyceridemia, cholestasis	Possible/possible	Recovering
Sweden, Health Authority, Case CV20100555	14/Male/ulcerative colitis	*Deep vein thrombosis	Possible/possible	Not recovered

Applicant's table, ISS

Per the Applicant, sodium glycerophosphate containing products manufactured by Fresenius Kabi have been administered to approximately [redacted] (b) (4) people over the last 10 years in [redacted] (b) (4) countries worldwide. Between March 1999 and March 2009 over [redacted] (b) (4) units of sodium glycerophosphate containing products were sold.

Medical Reviewer's comments: Patients who receive PN often have multiple co-morbidities and it is possible that some of these ADRs could be related to underlying medical conditions. Many of the ADRs listed in the PSURs of both Kabiven and [redacted] (b) (4), such as hypertriglyceridemia, phlebitis, infection and fever are similar to AEs listed in the PI of the RLDs..

Appendices

9.1 Literature Review/References

A.S.P.E.N. Aluminum Task Force. A.S.P.E.N. statement on aluminum in parenteral nutrition solutions. Nutrition in Clinical Practice 2004; 19: 416-417.

A.S.P.E.N. Parenteral Nutrition Handbook, The American Society for Parenteral and Enteral Nutrition, 2009.

A.S.P.E.N., Safe Practices for Parenteral Nutrition, Task Force for Revision of Safe Practices for Parenteral Nutrtition. Journal of Parenteral and Enteral Nutrition 2004; 28(6).

A.S.P.E.N., Statement on Parenteral Nutrition Standardization, Journal of Parenteral and Enteral Nutrition 2007; 31(5):441-448

Berner Y, Shuler TR, Nielsen FH. Selected ultatrace elements in total parenteral nutrition solutions. America Journal of Clinical Nutrition 1989;50:1079-83.

Bouchoud L, Fonzo-Christe, Sadeghipour F, Bonnabry P. Maximizing calcium and phosphate content in neonatal parenteral nutrition solutions using organic calcium and phosphate salts. Journal of Parenteral and Enteral Nutrition, 2010; 34(5):543-545

Buchman, A, Neely M, Grossie B, Truong L. Organ heavy metal accumulation during parenteral nutrition is associated with pathologic abnormalities in rats. Nutrition 17: 600-606, 2001.

Costello I, Powell C, Williams AF. Sodium glycerophosphate in the treatment of neonatal hypophosphatemia, Archives of Diseases in Childhood 1995; 73:F44-F45.

Culebras JM, Martin-Pena, G, Garcia-de-Lorenzo A, Zarazaga A, Rodriguez-Montes, JA. Practical aspects of peripheral parenteral nutrition. 2004 Lippincott William & Wilkins, 1363-1950.

Department of Health and Human Services, Food and Drug Administration. Aluminum in large and small volume parenterals used in total parenteral nutrition. 21 CFR Part 201, 2002 Vol 67, No. 228

Department of Health and Human Services, Food and Drug Administration Safety Alert: Hazards of Precipitation Associated with Parenteral Nutrition, April 1994.

Greene HL, Hambridge KM, Schanler R, Tsang RC. Guidelines for the use of vitamins, trace elements, calcium, magnesium, and phosphorous in infants and children receiving total parenteral nutrition: report of the Subcommittee on Pediatric Parenteral Nutrient Requirements from the Committee on Clinical Practice Issues of the American Society for Clinical Nutrition. American Journal of Clinical Nutrition 1988; 48:1324-42.

Hauer EC, Kaminski MV. Trace metal profile of parenteral nutrition solutions. The American Journal of Clinical Nutrition 1978;31:264-8.

Howard L, Ashley C, Lyon D, Shenkin A. Autopsy tissue trace elements in 8 long term parenteral nutrition patients who received the current US Food and Drug Administration formulation. Journal of Parenteral and Enteral Nutrition 2007;31(5):388-396.

Leung F. Trace elements in parenteral micronutrition. Clinical Biochemistry 1995; 28(6):561-566.

Leung F, Grace M, Alfieri M, Bradley C. Abnormal trace elements in a patient on total parenteral nutrition with normal renal function. Clinical Biochemistry 1995; 28(3):297-302.

Maddox RR, Rush DR, Rapp RP, Foster TS, Mazella V, Mckean HE. Double-blind study to investigate methods to prevent cephalothin-induced phlebitis. American Journal of Hospital Pharmacy, 1977, 34:29-34.

Peguero Monforte G. Multicenter, prospective, parallel, double blind, randomized study to evaluate the clinical effectiveness and tolerance of disodium glycerophosphate in pediatric patients requiring TPN (total parenteral nutrition). Pharmacia & Upjohn; Clinical Trial No. 91-114, Document No. 98000143;1998.

Pluhator-Murton MM, Fedorak RN, Audette RJ, Marriage BJ. Trace element contamination of total parenteral nutrition 2. Effect of storage duration and temperature. Journal of Parenteral and Enteral Nutrition 1999;23 (4):228-232.

Ukleja A, Romano MM. Complications of Parenteral Nutrition. Gastroenterology Clinics of North America 36 (2007) 23-46.

http://dailymed.nlm.nih.gov/dailymed/about.cfm- Accessed April 2011-October 2011.

9.2 Labeling Recommendations

There are no labeling recommendations this review cycle.

9.3 Advisory Committee Meeting

There was no advisory committee meeting for this application.

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[1] Buchman, A, Neely M, Grossie B, Truong L. Organ heavy metal accumulation during parenteral nutrition is associated with pathologic abnormalities in rats. Nutrition 17: 600-606, 2001.

[2] Leung F. Trace elements in parenteral micronutrition. Clinical Biochemistry 1995; 28(6):561-566.

[3] Greene HL, Hambridge KM, Schanler R, Tsang RC. Guidelines for the use of vitamins, trace elements, calcium, magnesium, and phosphorous in infants and children receiving total parenteral nutrition: report of the Subcommittee on Pediatric Parenteral Nutrient Requirements from the Committee on Clinical Practice Issues of the American Society for Clinical Nutrition. American Journal of Clinical Nutrition 1988; 48:1324-42.

[4] Berner Y, Shuler TR, Nielsen FH. Selected ultatrace elements in total parenteral nutrition solutions. America Journal of Clinical Nutrition 1989;50:1079-83.

[5] A.S.P.E.N. Parenteral Nutrition Handbook, The American Society for Parenteral and Enteral Nutrition, 2009.

[6] Department of Health and Human Services, Food and Drug Administration Safety Alert: Hazards of Precipitation Associated with Parenteral Nutrition, April 1994.

[7] Bouchoud L, Fonzo-Christe, Sadeghipour F, Bonnabry P. Maximizing calcium and phosphate content in neonatal parenteral nutrition solutions using organic calcium and phosphate salts. Journal of Parenteral and Enteral Nutrition, 2010; 34(5):543-545

[8] Costello I, Powell C, Williams AF. Sodium glycerophosphate in the treatment of neonatal hypophosphatemia, Archives of Diseases in Childhood 1995; 73:F44-F45.

[9] A.S.P.E.N., Safe Practices for Parenteral Nutrition, Task Force for Revision of Safe Practices for Parenteral Nutrtition. Journal of Parenteral and Enteral Nutrition 2004; 28(6).

[10] Ukleja A, Romano MM. Complications of Parenteral Nutrition. Gastroenterology Clinics of North America, 36 (2007) 23-46.

[11] A.S.P.E.N. Aluminum Task Force. A.S.P.E.N. statement on aluminum in parenteral nutrition solutions. Nutrition in Clinical Practice 2004; 19: 416-417.

[12] Department of Health and Human Services, Food and Drug Administration. Aluminum in large and small volume parenterals used in total parenteral nutrition. 21 CFR Part 201, 2002 Vol 67, No. 228

[13] International Conference of Harmonisation of Technical Requirement for Registration of Pharmaceuticals for Human Use. Final Concept Paper-Q3D: Impurities: Guidelines for Metal Impurities, July 2009

[14] http://dailymed.nlm.nih.gov/dailymed/about.cfm

[15] Maddox RR, Rush DR, Rapp RP, Foster TS, Mazella V, Mckean HE. Double-blind study to investigate methods to prevent cephalothin-induced phlebitis. American Journal of Hospital Pharmacy, 1977, 34:29-34.

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/s/

KARYN L BERRY
11/15/2011

RUYI HE
11/15/2011
I concur with Dr. Berry's conclusion and recommendations

CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

NDA/BLA Number: 200-656 **Applicant: APP Pharmaceuticals** **Stamp Date: 01/28/2011**

Drug Name: Kabiven and (b) (4) **NDA/BLA Type: Standard**

On initial overview of the NDA/BLA application for filing:

	Content Parameter	Yes	No	NA	Comment
FORMAT/ORGANIZATION/LEGIBILITY					
1.	Identify the general format that has been used for this application, e.g. electronic CTD.	X			eCTD
2.	On its face, is the clinical section organized in a manner to allow substantive review to begin?	X			
3.	Is the clinical section indexed (using a table of contents) and paginated in a manner to allow substantive review to begin?	X			
4.	For an electronic submission, is it possible to navigate the application in order to allow a substantive review to begin (*e.g.*, are the bookmarks adequate)?	X			
5.	Are all documents submitted in English or are English translations provided when necessary?	X			
6.	Is the clinical section legible so that substantive review can begin?	X			
LABELING					
7.	Has the applicant submitted the design of the development package and draft labeling in electronic format consistent with current regulation, divisional, and Center policies?	X			
SUMMARIES					
8.	Has the applicant submitted all the required discipline summaries (*i.e.*, Module 2 summaries)?	X			
9.	Has the applicant submitted the integrated summary of safety (ISS)?	X			
10.	Has the applicant submitted the integrated summary of efficacy (ISE)?	X			
11.	Has the applicant submitted a benefit-risk analysis for the product?	X			
12.	Indicate if the Application is a 505(b)(1) or a 505(b)(2). If Application is a 505(b)(2) and if appropriate, what is the reference drug?				505(b)(2) Dextrose, Amino Acids, Intralipid
DOSE					
13.	If needed, has the applicant made an appropriate attempt to determine the correct dosage and schedule for this product (*i.e.*, appropriately designed dose-ranging studies)? Study Number: Study Title: Sample Size: Arms: Location in submission:				BA/BE studies
EFFICACY					
14.	Do there appear to be the requisite number of adequate and well-controlled studies in the application? Pivotal Study #1			X	Applicant has submitted 1 randomized, DB clinical trial, safety

File name: 5_Clinical Filing Checklist for NDA_BLA or Supplement 010908

Reference ID: 2923885

CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

	Content Parameter	Yes	No	NA	Comment
	Indication: Pivotal Study #2 Indication:				trials and the literature as supportive evidence
15.	Do all pivotal efficacy studies appear to be adequate and well-controlled within current divisional policies (or to the extent agreed to previously with the applicant by the Division) for approvability of this product based on proposed draft labeling?			X	No pivotal clinical trials
16.	Do the endpoints in the pivotal studies conform to previous Agency commitments/agreements? Indicate if there were not previous Agency agreements regarding primary/secondary endpoints.			X	No pivotal clinical trials
17.	Has the application submitted a rationale for assuming the applicability of foreign data to U.S. population/practice of medicine in the submission?	X			
SAFETY					
18.	Has the applicant presented the safety data in a manner consistent with Center guidelines and/or in a manner previously requested by the Division?	X			
19.	Has the applicant submitted adequate information to assess the arythmogenic potential of the product (*e.g.*, QT interval studies, if needed)?			X	
20.	Has the applicant presented a safety assessment based on all current worldwide knowledge regarding this product?	X			
21.	For chronically administered drugs, have an adequate number of patients (based on ICH guidelines for exposure[1]) been exposed at the dose (or dose range) believed to be efficacious?			X	
22.	For drugs not chronically administered (intermittent or short course), have the requisite number of patients been exposed as requested by the Division?			X	
23.	Has the applicant submitted the coding dictionary[2] used for mapping investigator verbatim terms to preferred terms?	X			
24.	Has the applicant adequately evaluated the safety issues that are known to occur with the drugs in the class to which the new drug belongs?	X			
25.	Have narrative summaries been submitted for all deaths and adverse dropouts (and serious adverse events if requested	X			

[1] For chronically administered drugs, the ICH guidelines recommend 1500 patients overall, 300-600 patients for six months, and 100 patients for one year. These exposures MUST occur at the dose or dose range believed to be efficacious.

[2] The "coding dictionary" consists of a list of all investigator verbatim terms and the preferred terms to which they were mapped. It is most helpful if this comes in as a SAS transport file so that it can be sorted as needed; however, if it is submitted as a PDF document, it should be submitted in both directions (verbatim -> preferred and preferred -> verbatim).

CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

	Content Parameter	Yes	No	NA	Comment
	by the Division)?				
OTHER STUDIES					
26.	Has the applicant submitted all special studies/data requested by the Division during pre-submission discussions?	X			
27.	For Rx-to-OTC switch and direct-to-OTC applications, are the necessary consumer behavioral studies included (*e.g.*, label comprehension, self selection and/or actual use)?			X	
PEDIATRIC USE					
28.	Has the applicant submitted the pediatric assessment, or provided documentation for a waiver and/or deferral?	X			
ABUSE LIABILITY					
29.	If relevant, has the applicant submitted information to assess the abuse liability of the product?			X	
FOREIGN STUDIES					
30.	Has the applicant submitted a rationale for assuming the applicability of foreign data in the submission to the U.S. population?	X			
DATASETS					
31.	Has the applicant submitted datasets in a format to allow reasonable review of the patient data?	X			
32.	Has the applicant submitted datasets in the format agreed to previously by the Division?	X			
33.	Are all datasets for pivotal efficacy studies available and complete for all indications requested?	X			
34.	Are all datasets to support the critical safety analyses available and complete?	X			
35.	For the major derived or composite endpoints, are all of the raw data needed to derive these endpoints included?			X	
CASE REPORT FORMS					
36.	Has the applicant submitted all required Case Report Forms in a legible format (deaths, serious adverse events, and adverse dropouts)?	X			
37.	Has the applicant submitted all additional Case Report Forms (beyond deaths, serious adverse events, and adverse drop-outs) as previously requested by the Division?		X		
FINANCIAL DISCLOSURE					
38.	Has the applicant submitted the required Financial Disclosure information?	X			
GOOD CLINICAL PRACTICE					
39.	Is there a statement of Good Clinical Practice; that all clinical studies were conducted under the supervision of an IRB and with adequate informed consent procedures?	X			

IS THE CLINICAL SECTION OF THE APPLICATION FILEABLE? _X__Yes_____

If the Application is not fileable from the clinical perspective, state the reasons and provide comments to be sent to the Applicant.

CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

Please identify and list any potential review issues to be forwarded to the Applicant for the 74-day letter.

None

Reviewing Medical Officer Date

Clinical Team Leader Date

Reference ID: 2923885

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

KARYN L BERRY
03/25/2011

RUYI HE
03/25/2011