CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

200656Orig1s000

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

OFFICE OF CLINICAL PHARMACOLOGY REVIEW

NDA: 200656	Submission Date(s): 11/25/2013
Brand Name	Kabiven and PeriKabiven
Generic Name	Amino acids, lipid (soybean oil), dextrose and electrolytes ((b) (4) active ingredients)
Reviewer	Sandhya Apparaju, Ph.D.
Team Leader	Sue Chih Lee, Ph.D.
OCP Division	Division of Clinical Pharmacology III
OND division	DGIEP
Sponsor	Fresenius Kabi
Relevant IND(s)	105282
Submission Type; Code	Resubmission
Formulation; Strength(s)	Three chamber bags (3CB), with dextrose solution in chamber 1, amino acids and electrolytes solution in chamber 2, and (b) (4) emulsion in chamber 3 for admixture prior to intravenous infusion;
Indication	Total Parenteral Nutrition

1 Executive Summary

1.1 Recommendation

NDA 200656 is acceptable from a Clinical Pharmacology perspective provided an agreement is reached with the sponsor with regard to labeling language.

1.2 Phase IV Commitments

None

1.3 Summary of Important Clinical Pharmacology and Biopharmaceutics Findings

NDA 200656 was originally submitted on January 28, 2011. Clinical Pharmacology review of the original submission concluded that the NDA was acceptable (see review 09/28/2011). Sponsor received a Complete Response letter on 11/21/2011 due to clinical, product quality, device performance and human factor assessment deficiencies. The resubmission attempts to address these issues. There were no outstanding issues for Clinical Pharmacology in this review cycle. Labeling has been reviewed and revisions proposed to the sponsor. See final labeling in DARRTs once approved.

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/s/

SANDHYA K APPARAJU
05/05/2014

SUE CHIH H LEE
05/05/2014

OFFICE OF CLINICAL PHARMACOLOGY REVIEW

NDA: 200656	Submission Date: January 28, 2011
Brand Names [Proposed]	Kabiven and (b) (4)
Generic Name	Amino acids, lipid (soybean oil), dextrose and electrolytes ((b) (4) active ingredients)
Reviewer	Sandhya Apparaju, Ph.D.
Team Leader	Sue Chih Lee, Ph.D.
OCP Division	Division of Clinical Pharmacology III, DCP3
OND Division	Division of Gastroenterology and Inborn Errors Products, DGIEP
Sponsor	APP Pharmaceuticals
Relevant IND(s)	105,282
Submission Type	Original NDA; Standard Review
Formulation; Strength(s)	Three chamber bags (3CB), with dextrose solution in chamber 1, amino acids and electrolytes solution in chamber 2, and (b) (4) emulsion in chamber 3 for admixture prior to intravenous infusion;
Proposed Indication	Total Parenteral Nutrition [for adults (b) (4)

An optional intra-divisional level OCP briefing for NDA 200656 was held on September 21, 2011 from 9-10 AM in conference room 3300 of WO Bldg 51. Attendees included Drs Dennis Bashaw, Hae Young Ahn, Karyn Berry, Sue Chih Lee, Dilara Jappar and Sandhya Apparaju

Table of Contents

1 Executive Summary

1.1 Recommendation

NDA 200656 is acceptable from a Clinical Pharmacology perspective. Labeling comments are pending.

1.2 Phase IV Commitments

Pediatric study requirements are under discussion.

1.3 Summary of Important Clinical Pharmacology and Biopharmaceutics Findings

Two new 3-chamber bag all-in-one formulations for total parenteral nutrition (TPN), namely Kabiven and [redacted] are proposed under NDA 200656. This is a 505b(2) submission referencing four different U.S. approved formulations for parenteral nutrition. There are currently no 3-chamber bag formulations approved in U.S. for an all-in-one, total parenteral nutrition. Individually approved 1-chamber or 2-chamber bag formulations are co-infused to provide all necessary nutrients for TPN (i.e. lipids, dextrose and amino acids, electrolytes etc). Proposed Kabiven formulations contain dextrose in chamber 1, amino acids with electrolytes in chamber 2 and soybean oil [redacted] by egg phospholipid as lipid source in the third chamber. The [redacted] formulation contains lower osmolarity ([redacted] % dextrose) compared to Kabiven formulation for central infusion ([redacted] % dextrose) and therefore is proposed for administration via central as well as peripheral vein. The formulations have been approved since 1999 in several countries.

The formulations contain sodium glycerophosphate as a proposed new source of the electrolyte phosphate, claiming its [redacted] The molecule is hydrolyzed to release phosphate in vivo by the ubiquitous phosphatases. A second source of phosphate in the formulations is claimed as the [redacted], egg phospholipids used in the lipid formulation.

To support the proposed switch from inorganic phosphate to organic phosphate source, the sponsor provided results from 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. Relative bioavailability data in serum and urine samples suggest a phosphate provision of approximately 80%, 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. 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 TPN formulation containing [redacted] 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. NDA also includes results from eleven small clinical trials that used either of the proposed formulations in patients requiring parenteral nutrition for 7 or more days, which will be further discussed in the clinical review for this NDA by Dr. Karyn Berry.

There were no other clinical pharmacology assessments in this NDA, including no dedicated specific population or drug-drug interaction studies. Sponsor has addressed these in the label using existing literature and clinical use information.

2 Summary of CPB Findings

2.1 General Attributes of the Drug

2.1.1. What are the highlights of the chemistry and physical-chemical properties of the drug substance and the formulation of the drug product as they relate to clinical pharmacology and biopharmaceutics review?

Kabiven® (b) (4) and (b) (4) (also referred to as Kabiven® and (b) (4), respectively) are admixtures for intravenous (parenteral) nutrition. Each chamber in the 3-chamber bag (3CB) presentation contains a distinct product. Chamber 1 contains a sterile, (b) (4), hypertonic solution of dextrose, USP in water for injection for fluid replenishment and caloric supply. Chamber 2 contains a sterile, (b) (4) solution of amino acids and electrolytes in water for injection. Chamber 3 contains a 20 % (b) (4) emulsion [Intralipid 20 %] as a source of calories and essential fatty acids. The chambers are separated by peelable seals. Upon opening of the seals, these three components are mixed together to form the final product for parenteral nutrition. Formulations are designed to have a prolonged shelf life (24 months) without the need for refrigeration. Please refer to the CMC review of this NDA for further information in this regard.

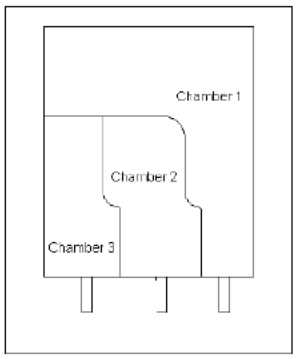


Figure 1. The three chamber bag. The smallest chamber (chamber 3) always contains lipi (b) (4) the middle chamber (chamber 2) contain the amino acid solution and the chamber next to the handle (chamber 1) the glucose solution.

The dextrose content in the (b) (4) formulation is lower ((b) (4) %) compared to Kabiven (for central infusion; (b) (4) %). This reduced osmolarity allows its administration via either a peripheral vein or a central vein. Sodium glycerophosphate is utilized in these formulations as the source of phosphate ((b) (4) %). In addition, the egg phospholipids used as (b) (4) in the intralipid formulation is also noted as a source of phosphate provision in Kabiven and (b) (4) formulations (~ (b) (4) %).

The components of the proposed formulations are listed below along with their concentrations in individual chambers as well as after mixing the contents of the three chambers:

	Kabiven	(b) (4)
Pack sizes (ml)	2566 2053 1540 1026	2400 1920 1440
Composition		
Individual Chamber (per 1000 ml)		
(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		
(b) (4)		

The following are excipients within each component of the proposed products:

Intralipid 20 %	**Function**
(b) (4)	(b) (4)
Purified egg phospholipids, (b) (4)	
Sodium hydroxide, USP	pH adjuster (b) (4)
(b) (4)	
Water for injections, USP	
Amino acid with electrolytes (b) (4)	
Acetic acid, glacial, USP	pH adjuster of amino acid solution
(b) (4)	(b) (4)
Water for injections, USP	
Glucose (b) % and (b) %	
(b) (4)	(b) (4)

2.1.2. What are the proposed mechanism(s) of action and therapeutic indication(s)?

Parenteral nutrition is the provision of nutrient requirements by the intravenous route, or in a strict sense by bypassing the passage over the gut mucosa. It is indicated for all patients irrespective of age or clinical condition in whom the absorption of nutrients by the gastrointestinal tract is either impossible or insufficient to fulfill the patients requirements.

Kabiven (b) (4) and (b) (4) (also referred to as Kabiven and (b) (4)) are indicated for (b) (4)

(b) (4)

2.1.3. What are the proposed dosage(s) and route(s) of administration?

Kabiven® is administered as an intravenous infusion via a central vein. (b) (4) is administered intravenously via a peripheral or a central vein. The products are available in different bag sizes to fit individual needs. Kabiven®: 1026, 1540, 2053, and 2566 ml bags; (b) (4): 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 (b) (4) kcals/day, (b) (4) kcals/day, (b) (4) kcals/day or (b) (4) kcals/day equivalent to a range from (b) (4) kcals/kg/day for a (b) (4) kg person if one bag is administered per day. The corresponding figures for the three bag sizes of (b) (4) are (b) (4) kcals/day, (b) (4) kcals/day and (b) (4) kcals/day. The dose should be individualized and is dependent on the patient's clinical condition, body weight and nutritional requirements. The recommended doses are as follows:

Proposed Dosing Information for Kabiven [via Central Infusion]

Mode of Administration	Central Vein
Energy Requirement	Depends on clinical condition; ofte(b) (4)cal/kg body weight/day
Dosing	(b) (4) Maximum daily dose is 40mL/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)g bw)
Recommended Infusion Period	12-24hr

Proposed Dosing Information for (b) (4) [Peripheral or Central Infusion]

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

Dose rationale: Sponsor's dosing recommendations were based upon the guidelines set by American Society for Parenteral and Enteral Nutrition (A.S.P.E.N.) and by the European Society for Parenteral and Enteral Nutrition (E.S.P.E.N.).

Range of Minimum and Maximum Daily Concentration 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) kcal/g dextrose, kcal/g lipids, and (b) kcal/g protein, and (b) (4) nitrogen/g protein. Bolded numbers are from ASPEN Guidelines (Mirtallo 2004).

(b) (4)

Electrolyte Content of 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

2.1.4 What is the relevant regulatory history for the review of this NDA?

Foreign approvals of proposed formulations: Kabiven and (b) (4) (containing the novel organic phosphate source, sodium glycerophosphate) are currently approved in Sweden

(since 1999), Australia and in more than 50 other countries in the world. A summary table of total patient exposures as provided by the sponsor is shown below:

Table 4. 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]						
No. of patients treated						
No. of countries with product sales						

U.S. regulatory history: A pre-IND sponsor meeting (105282) for the proposed products was held on August 20, 2009, with a follow-up communication on January 25, 2010. These communications discussed the 505b(2) regulatory approach for the proposed NDA, the information needed in support of the organic sodium glycerophosphate as a novel phosphate source and the rationale for the proposed ranges of electrolytes. Specifically, the sponsor was notified that a 505b(2) approach was acceptable and that both formulations can be submitted under one NDA. The sponsor was requested to demonstrate the relative bioavailability of phosphate resulting from the two different sources i.e. from the proposed products containing sodium glycerophosphate vs. the referenced products containing inorganic phosphates. Sponsor was also asked to provide additional justification for clinical review in the NDA for the proposed ranges of electrolytes that differed somewhat from the referenced products.

In a subsequent communication submitted to the agency the sponsor noted that demonstrating bioequivalence of the phosphate moiety using the complete product containing all (b) (4) components of Kabiven or (b) (4), a Total Parenteral Nutrition (TPN) solution is not possible due to physiological effects of the nutrients on phosphate metabolism. However, the requested characterization will be feasible to be performed using products that contain the phosphate component only (i.e. Sodium Glycerophosphate vs. Inorganic Phosphates). Additionally, exploration of potential interactions or matrix effects of other components of the total TPN product, on phosphate bioavailability from the novel source was proposed to be determined by a study comparing phosphate from glycerophosphate administered as part of the Kabiven and (b) (4) products versus administration of glycerophosphate (Glycophos) alone. Both these studies were to be conducted in healthy volunteers. Kabiven (for central infusion) was not to be studied as this would necessitate the insertion of a central venous catheter, a procedure that cannot be regarded ethical for the study of phosphate infusion in healthy volunteers.

2.1.5 How do the compositions of the proposed parenteral nutrition products compare to the referenced U.S. approved products in this 505b(2) regulatory submission?

The Sponsor intends to demonstrate safety and efficacy of Kabiven and (b) (4), by referencing prior findings by the FDA of safety and efficacy for approved parenteral nutrition products. Therefore, this application references 4 separate reference listed drugs (RLDs) listed below, for each corresponding component as well as the overall product:

Name of Drug Product	NDA #
Intralipid® 20%	NDA 018449 and ANDA 020248
Novamine® 11.4% Injection	NDA 017957
Clinimix® E Sulfite free with Electrolytes in Dextrose with Calcium	NDA 020678
Aminosyn® II with Electrolytes in Dextrose Injection with Calcium	NDA 019683

All four reference listed products are utilized in parenteral nutrition regimens, similar to the proposed products when the enteral route is inadvisable, inadequate or not possible. The route of administration and dosage form of the proposed drug products are the same as those of the reference listed drugs which are utilized as individual components of a parenteral nutrition regimen via the intravenous route.

Specifically, the fat component in Kabiven and (b) (4) is an emulsion for infusion identical to Intralipid® 20% (NDA 18449). The amino acid content (in solution) compares to that in Novamine 11.4 % (NDA 17957). The dextrose (in solution) is comparable to that in the approved strengths of Clinimix E sulfite free with electrolytes in dextrose with calcium (NDA 20678). The electrolyte content (in solution) in the proposed products doesn't exactly correspond to that in the referenced Aminosyn II (NDA 19683) or Clinimix. 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. Please see the clinical review for further information in this regard. In addition, to support the switch in the source of phosphate to the organic sodium glycerophosphate, the sponsor conducted relative bioavailability studies in healthy volunteers to demonstrate comparability to the phosphate bioavailability from inorganic sources used in the RLDs, when administered at equimolar doses.

A comparison of the active components in each of these referenced products against the components of the proposed Kabiven products is shown below for further detail:

- Amino acid comparison of Kabiven formulations vs. Novamine 11.4 %:

	Kabiven	(b) (4)	Intralipid® 20%	Novamine® 11.4%
Packaging: No of Chambers	3	3	1	(b) (4)
Soybean Oil	(b) (4)		20%	
Total Amino Acids			--	
Individual Amino Acids (mg/mL)				
Alanine	(b) (4)			
Arginine				
Aspartic Acid				
Glutamic Acid				
Glycine				
Histidine				
Isoleucine				
Leucine				
Lysine				
Methionine				
Phenylalanine				
Proline				
Serine				
Threonine				
Tryptophan				
Tyrosine				
Valine				

- Comparability of glucose in Kabiven formulations against Clinimix E and comparison of the electrolyte content against 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	(b) (4)	
Electrolytes (mmol/L)				
Sodium	31	22		
Potassium	23	17		
Magnesium	3.9	2.8		
Calcium	1.9	1.4		
(b) (4) phosphorous	9.7	7.5		
Chloride	45	(b) (4)		
Acetate	38	27		
Sulfate[1]	3.9	2.8		

[1] From magnesium sulfate

2.2 General Clinical Pharmacology and Biopharmaceutics

2.2.1 What are the design features of the biopharmaceutic, clinical pharmacology, and clinical studies in the NDA?

The proposed formulation is a mixture of (b) (4) different active ingredients namely glucose, 17 essential and non-essential amino acids, 5 electrolytes and fat (soybean oil) for intravenous infusion in parenteral nutrition. The products are proposed for approval under a 505b(2) regulatory approach, referencing four U.S. approved parenteral nutrition products. With the exception of the characterization of phosphate bioavailability from the novel organic source (sodium glycerophosphate), no other pharmacokinetic information is presented in the NDA.

A formal pharmacokinetic bridging for all active components was not found to be necessary. For active ingredients in solution (e.g. amino acids, dextrose and electrolytes), bioavailability/bioequivalence 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 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 3CB presentation of Kabiven and (b) (4) formulations appears to provide all-in-one parenteral nutrition without other significant changes to the treatment paradigm itself. The potential effect, if any of the new organic phosphate source on the globule size in the lipid emulsion will be addressed by the CMC discipline. Please see the chemistry discipline's review in this regard.

Biopharmaceutic assessments: The general design features of the two relative bioavailability studies in support of the novel phosphate source are summarized below:

Study ID	Type of Study	Objective(s) of the Study	Study Design/ Type of Control	Test Product(s)/ Dosage Regimen/ Route of Administration	Number of Subjects Treated	Healthy Subjects or Diagnosis of Population	Duration of Treatment	Study Status/ Type of Report
5.3.1 Reports of Biopharmaceutic Studies								
5.3.1.2 Comparative BA and Bioequivalence (BE) Study Reports								
Glyc-001-C P1	BE	BE of Phosphate from Glycero-phosphate vs Sodium Phosphates	Double-blind, randomized, 2-way crossover, active-control	Glycerophosphate (Glycophos®) Inorganic phosphate (sodium phosphates injections) Both: 20mmol/hr, 4-hr IV infusion into a peripheral vein in forearm	Total: 25	Healthy subjects	Two single infusions of 4hrs, one of test and one of reference, with a 7-day washout	Complete/ Full

Study ID	Type of Study	Objective(s) of the Study	Study Design/ Type of Control	Test Product(s)/ Dosage Regimen/ Route of Administration	Number of Subjects Treated	Healthy Subjects or Diagnosis of Population	Duration of Treatment	Study Status/ Type of Report
KABI-003-C P1	BA	Relative BA of Phosphate from (b) (4) (b) (4) vs Glycero-phosphate	Double-blind, Randomized	(b) (4) Glycerophosphate (Glycophos) diluted in 0.9 % sodium chloride (NaCl) Both 13.3mL/kg bw/8hr, 0.101mmol phosphate/kg body weight/8hr, IV infusion into peripheral vein in forearm	Total: 10	Healthy subjects	Two single infusions of 8 hours, one of test and one of reference, with an 88hr washout	Complete/ Full

Clinical efficacy and safety database: Data from eleven other completed clinical trials that employed either Kabiven or (b) (4) formulations have been included in the NDA for clinical review. These were typically seven day infusions of the products in patients requiring intravenous nutrition. Please see clinical review of this NDA for further information in this regard.

Limited trough concentration data was available for essential and non-essential amino acids, fatty acid components, other biochemicals of interest (e.g. urea, creatinine, pre-albumin, beta-hydroxybutyrate, IGG-1/IGF-BP-1, insulin, leptin, HLA-Dr and IL-6, TNF-alpha) and urinary excretion of amino acids, nitrogen, urea and creatinine in three of the clinical Studies 00-3CB4-001, 00-3CB5-001 and 01-3CB5-002. These were randomized, open-label or double-blind, parallel group, comparative, safety and efficacy trials conducted in post-operative major gastrointestinal surgery patients or other patients requiring parenteral nutrition. N = 20-21 patients were included in each of these trials under the Kabiven group. Serum and urine samples were collected on mornings of days 1, 4, 6 and directly after the last treatment ended on day 7.

2.2.2 How were the active moieties in biological samples appropriately identified and measured?

For relative bioavailability assessments, the determination of phosphate in serum and urine in the presence of Na-glycerophosphate was conducted using the Cobas 6000 / c501 method (Roche).

This method for the determination of inorganic phosphate (analyte of interest) from the two phosphate sources is based on the reaction of phosphate with ammonium molybdate to form ammonium phosphomolybdate. The concentration of phosphomolybdate formed is directly proportional to the inorganic phosphate concentration and is measured photometrically.

2.2.3 What are the results and conclusions from the two relative bioavailability studies conducted in support of the change in phosphate source and do the results in general support this switch?

Key results and conclusions from the two relative bioavailability studies comparing phosphate provision across test and reference sources are summarized below.

Study Glyc-001-C P1: This was a single-centre, double-blind, randomized, two-treatment, two-sequence, active-controlled phase-I-study to evaluate phosphate from glycerophosphate (Glycophos®; 20 mmol/h for 4 h; Fresenius Kabi, Norway) versus sodium phosphates (I-Phosphates; 20 mmol/h for 4 h; Hospira, Inc, USA) in n = 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.

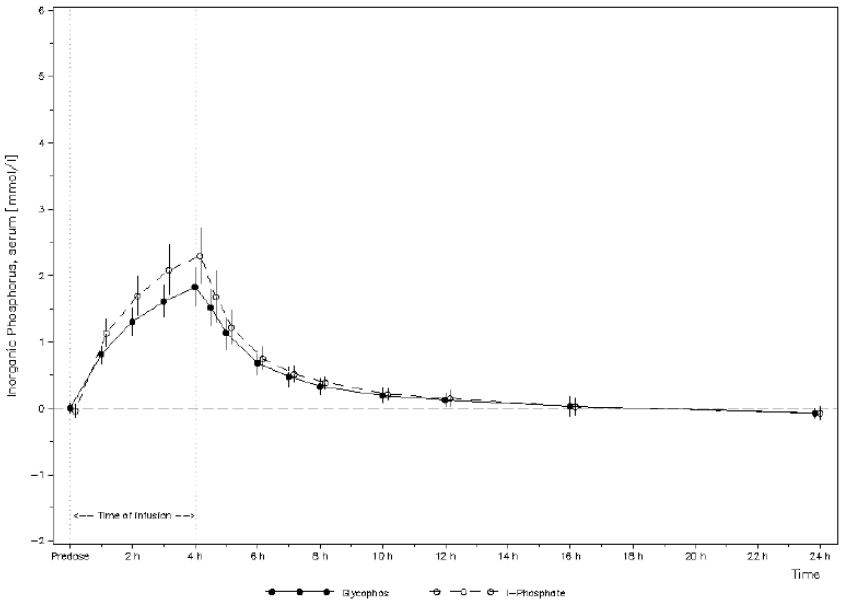
In this study the phosphate content of meals and water was standardized. No food was provided prior to and during infusion. The estimated total daily oral intake of phosphorus from food sources during this study per sponsor was ~ 1.1 g (35 mmol from lunch, snack and dinner provided at the end of infusion, 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 (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.

Study results:
Pre-dose levels of inorganic phosphate in urine and serum (days 1 and 2):

	Ae [mmol/coll]		AUC_{0-24h} [h*mmol/L]	
	Day 1	**Day 2**	**Day 1**	**Day 2**
Period 1				
Mean (SD)	26.68 (8.02)	27.23 (7.47)	28.29 (2.22)	28.10 (2.35)
Geometric mean	25.44	26.20	28.20	28.01
LL; UL (95%CI)	22.25; 29.08	23.26; 29.51	27.31; 29.12	27.07; 28.98
Period 2				
Mean (SD)	25.61 (9.63)	24.83 (8.14)	27.41 (2.39)	27.46 (2.37)
Geometric mean	23.96	23.54	27.30	27.36
LL; UL (95%CI)	20.52; 27.98	20.46; 27.08	26.29; 28.35	26.40; 28.36

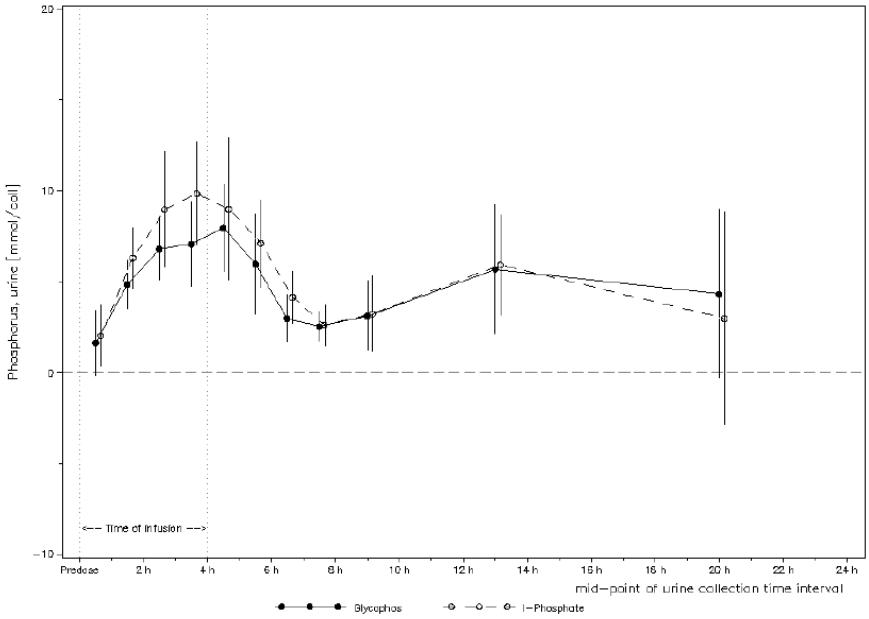
Relative Bioavailability: Serum concentrations of phosphate steadily increased during the intravenous infusion and reached a peak at the end of 4 hours. After this, concentrations decreased to baseline levels within 24 h. Within individuals, serum phosphate concentrations from the organic sodium glycerophosphate source were somewhat lower than that from the

inorganic phosphate source. Baseline-corrected serum phosphate concentrations are shown in the plot below:



In urine, the amount of excreted phosphate (baseline-corrected) increased steadily during the 4 hour infusion period after which it decreased. Overall, the amount of phosphate excreted in urine over 24 hours was somewhat smaller from the organic sodium glycerophosphate source compared to the inorganic phosphates. In the body, phosphate that is not taken up by the tissues is almost exclusively excreted into the urine.

The baseline-corrected 24-hour average urinary phosphate vs. time profiles (mid-point of urine collection interval) for the two treatment groups are shown:



Pharmacokinetic parameters for urinary excretion of phosphate and serum PK, as well as their relative bioavailability/bioequivalence assessment are shown below:

Statistical analysis of urinary phosphate excretion 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

bc: baseline corrected; Coll: collection period

Serum pharmacokinetics of phosphate:

Parameter	Glycophos® (T)	I-Phosphate (R)
$AUC_{+0-24h,\ bc}$ [h*mmol/L]	9.365 (8.557; 10.25)	11.32 (10.46; 12.25)
AUC_{0-24h} [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

Statistical analysis for serum phosphate data (BE wizard; WinNonlin 5.2):

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

bc = baseline corrected; LL: lower limit; UL: upper limit; T/R: Test to Reference ratio

The uncorrected amount excreted in urine Ae, serum AUC0-24 and Cmax values for phosphate across test and reference sources were found to be bioequivalent in this study (90 % CI for test/reference ratios within 80-125 % bounds).

For baseline-corrected data (Ae and AUC24), the two formulations did not meet the bioequivalence criteria. The lower limit of the confidence bounds fell below 80 %. The baseline phosphate data was well balanced in the two treatment periods.

Review Conclusions on relative bioavailability findings: *The demonstrated comparability of phosphate provision from the new organic sodium glycerophosphate source, to that of equimolar doses of approved inorganic phosphates is acceptable, though not strictly bioequivalent for all parameters assessed. The study allowed a direct comparison of the two sources (sodium glycerophosphate vs. I-Phosphates) in their ability to deliver phosphate to the body, in a dose setting that was not confounded by the presence of other nutrients or excipients such as those found in a complete TPN formulation. Relative bioavailability results support the incorporation of sodium glycerophosphate as a source of phosphate provision into the proposed TPN products.*

Study Results: Pharmacodynamic assessments: Changes in the following pharmacodynamic (PD) variables (in response to changes in systemic phosphate levels) were evaluated in the relative bioavailability study: amount excreted, Ae in urine for calcium, sodium and potassium over 24 h, baseline corrected; AUC0-24h, baseline corrected for serum concentrations of the above; and time matched comparisons for PTH and calcitonin.

Calcium: Serum calcium concentrations decreased gradually reaching minimum values at the end of the 4 hour infusion, after which values reverted to baseline at the end of 24 hours. The extent of decline in serum calcium was comparable for both phosphate sources. Decrease in calcium levels is an expected pharmacodynamic effect of phosphate supplementation. It didn't appear that sodium glycerophosphate had a greater effect on this decrease relative to the approved inorganic phosphate source.

Sodium: The amount of sodium excreted in urine increased steadily during and post infusion. Contribution from sodium within the two formulations (Test- Sodium glycerophosphate and Reference- Sodium phosphates) might have been a major cause for this increase in sodium load. The increase in sodium excretion was similar across the two formulations. Similarly, serum concentrations of sodium increased gradually during the infusion. Values were comparable across the two formulations and returned to baseline at 24 hours.

Potassium: Urinary excretion of potassium and serum concentrations of potassium decreased during the infusion and returned to baseline thereafter. Values were comparable across the two infusions.

Parathormone: During infusion of both phosphate sources, the mean (geometric mean) values of parathormone increased for both treatments about approximately 100%. The PD effect was same in both treatment periods.

Statistical analysis of the PD parameters was conducted by the sponsor and results suggest bioequivalence of the serum and urinary parameters as based on 90 % CI of the T/R ratio for calcium, potassium and sodium within 80-125 % range:

	PK parameter	Central value*		Point estimate (T/R)**	90% Confidence interval	
		Glycophos® (T)	I-Phosphate (R)		Lower limit	Upper limit
Calcium	$AUC_{0\text{-}24h}$ [h*mmol/l]***	52.74	52.67	1.001	0.9967	1.006
	Ae [mmol/coll]	2.610	2.892	0.9025	0.8141	1.001
Potassium	$AUC_{0\text{-}24h}$ [h*mmol/l]***	100.6	101.5	0.9912	0.9765	1.006
	Ae [mmol/coll]	62.50	61.06	1.024	0.9622	1.089
Sodium	$AUC_{0\text{-}24h}$ [h*mmol/l]***	3318	3323	0.9984	0.9959	1.001
	Ae [mmol/coll]	211.1	187.2	1.127	1.048	1.212

Abbreviation: PK= pharmacokinetic, T Test, R reference, T - Glycophos®, R – I-Phosphate, Ae = excreted amount

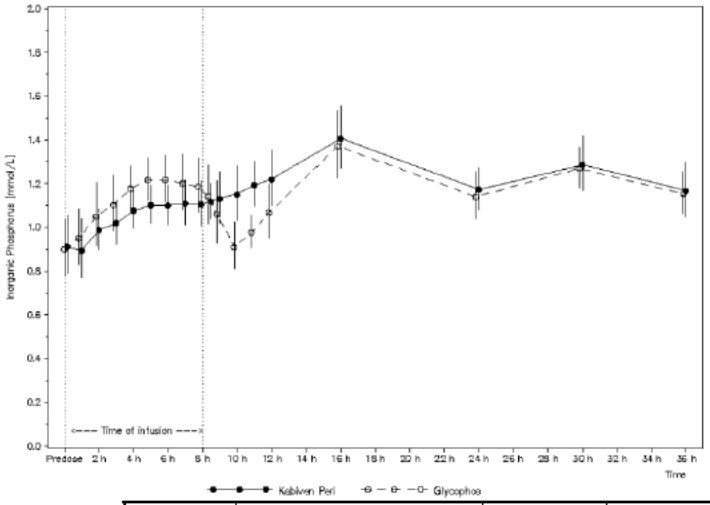
Review conclusions- PD: *The PD endpoints of interest showed an expected trend of change with exogenous phosphate administration. The extent of change in PD was comparable for the two sources. The clinical relevance of the observed magnitude of changes in PD in this study is not known, since the doses administered in the study are higher than those used therapeutically. In addition, the potential influence on PD from the additional phosphate from food sources is not understood.*

Additional comments: The dose of the phosphate source and duration of administration (20 mmol/h for 4 h) used in this study are different than that proposed for clinical use (20 mmol administered over 12-24 hours). However, due to the endogenous nature of the phosphate moiety and high phosphate provision from food intake, use of a typical dose in a healthy subject 'bioequivalence' study such as this may not assure sufficient increase in physiologic levels to allow a head-to-head product comparison. Hence reviewer finds the use of the dose and duration to be acceptable as a proof of systemic bioavailability of phosphate from the proposed new source.

In addition, in the current study sponsor didn't administer the complete test and reference TPN formulations to compare phosphate sources, but rather directly administers the two phosphate sources. Reviewer finds this acceptable as this investigation verifies the contribution of either source to systemic and urinary phosphate concentrations. As proposed by the sponsor in their rationale for choosing to administer the phosphate products instead of the complete TPN formulation in this study, it is likely that the interplay of various micro and macro nutrients (active ingredients such as amino acids, dextrose, electrolytes) in the complete parenteral nutrition formulation may or may not allow a clear identification of phosphate bioavailability from the two sources.

Study KABI-003-C P1: This was a single-centre, double-blind, randomized phase I study to evaluate the relative bioavailability of phosphate from (b) (4) formulation versus organic sodium glycerophosphate (Glycophos®) in healthy subjects. This exploratory study involved 10 healthy subjects ages 18-45 years. An equimolar amount of phosphate as provided by (b) (4) (0.101 mmol phosphate/13.3 mL (b) (4) /kg body weight/8 hours) was provided by Glycophos® diluted in 0.9 % NaCl (0.101 mmol Glycophos®/13.3 mL NaCl/kg body weight). The experimental phase consisted of one treatment period with administration of the investigational medicinal products (IMPs) on Days 3 and 7 of the treatment period and a wash-out period of 88 hours between the infusions. During the in-house period, the subjects were on standardized nutrition. In the morning of Days 3 and 7, the infusion with the IMPs started following a breakfast, which was served 2 hours before start of infusion.

Study results: Relative Bioavailability of Phosphate: Following i.v. infusion of identical phosphate doses of both test ((b) (4)) and reference (Glycophos; sodium glycerophosphate in 0.9 % NaCl) products, concentrations of phosphate in serum increased gradually over the 8 h infusion. The shape of the phosphate profile in serum for the test source ((b) (4)) was somewhat different to that from the reference source (Glycophos); Individual subject profiles demonstrated similar trend. However, the final parameters and resultant statistical analyses did not suggest significant differences in BA.



PK parameter	Central value*		Point estimate	90% Confidence interval	
	(b) (4)	Glycophos® (R)	(T/R)**	Lower limit	Upper limit
$AUC_{0\text{-}36}$ [mmol*h/L]	43.2782	42.5796	1.0164	1.0053	1.0277
C_{max} [mmol/L]	1.4147	1.3960	1.0134	0.9812	1.0467
C_{ss} [mmol/L]	1.1056	1.1860	0.9322	0.8864	0.9804
Ae*** [mmol/24 h]	19.7544	25.3066	0.7806	0.6266	0.9725

Cmax: Peak phosphate concentrations over 36 h; Css: Phosphate concentrations at the end of 8h infusion.

Review conclusions: *While, the statistical findings do not suggest significant differences in serum levels of phosphate when given as sodium glycerophosphate alone or as part of total parenteral nutrition formulation ((b) (4)), the results are potentially confounded by contribution of phosphate from food sources. The estimated total daily oral intake of phosphorous from food served during this study was 1.2 g (37.6 mmol) per the sponsor. This dose is much greater than the phosphate administered from test and reference i.v. drug sources (~7.2 mmol over a period of 8 hours). The contribution of phosphate estimated from breakfast alone (administered 2 h prior to infusion) was 6.4 mmol, which corresponds to (b) (4) % of total dose administered as part of TPN. Phosphate absorption rates when given via oral route are not known to understand the true net contributions from food sources. Thus results of this study should not be considered as conclusive evidence of phosphate provision from (b) (4) in absolute terms. No baseline measurements were available for correction.*

The differences in the shapes of the serum phosphate profile across the two sources may be due to contribution from a secondary phosphate source in the complete formulation (i.e. egg phospholipids) and/or a potential influence of the other nutritional components in the total parenteral nutrition product on the release of phosphate from Sodium Glycerophosphate. .

2.2.4 What additional Clinical Pharmacology information could be gained from the completed clinical efficacy and safety trials in patients requiring total parenteral nutrition?

Three randomized trials of safety and efficacy of kabiven in hospitalized patients requiring TPN included measures of efficacy such as amino acids, nitrogen balance, and fatty acid pattern. Results from one of these three studies, which was a double-blinded evaluation will be presented:

Study 00-3CB5-001: This was a randomized, double-blind study to evaluate the safety, tolerance and efficacy of a proposed parenteral nutritional product against Kabiven in subjects requiring parenteral nutrition. N = 21 subject were randomized to each of the two treatments. Kabiven (electrolyte modified, 2626 ml; sodium and calcium) was administered at 15 ml/kg bw/day in period 1, and 30 ml/kg bw/day in period 2,3,4,5,6,7 via central intravenous infusion.

	Baseline (period 1)	Period 4 (after 3 consecutive 24h treatments with Kabiven only)	Period 4 minus baseline	Final Examination (LOCF) (partial supplementation with oral nutrition on days 5, 6 and 7)	Final examination (LOCF) minus baseline
Essential AA	**839.79 (186.66)**			**1047.16 (174.80)**	**207.37 (196.81)**
Isoleucine (umol/L)	65.92 (26.22)	78.83 (16.14)	12.64 (24.58)	82.67 (13.77)	14.87 (28.62)
Leucine (umol/L)	137.78 (43.33)	116.32 (29.43)	-19.9 (41.35)	112.18 (28.27)	-23.84 (38.81)
Lysine (umol/L)	136.87 (33.34)	173.15 (42.21)	34.39 (45.67)	188.44 (42.50)	48.95 (48.88)
Methionine (umol/L)	26.10 (6.02)	43.36 (13.6)	16.36 (12.64)	40.6 (9.89)	13.73 (8.81)
Phenylalanine (umol/L)	62.77 (8.92)	77.6 (13.74)	13.72 (17.05)	73.91 (19.98)	10.21 (15.88)
Threonine (umol/L)	91.53 (19.53)	191.30 (63.30)	95.49 (36.20)	193.71 (37.37)	97.78 (46.21)
Tryptophan (umol/L)	26.83 (9.42)	31.61 (7.7)	4.61 (10.31)	31.74 (9.95)	4.73 (12.35)
Valine (umol/L)	230.47 (60.99)	273.06 (53.79)	41.89 (79.77)	260.79 (45.20)	30.20 (55.64)
Histidine (umol/L)	*61.51 (13.13)*	*68.14 (19.30)*	*6.13 (20.37)*	*71.47 (14.15)*	*9.30 (15.14)*
Non-essential AA	**1104.55 (172.24)**			**1444.33 (324.70)**	**339.78 (297.43)**
Arginine (umol/L)	35.31 (10.74)	73.91 (26.69)	37.24 (27.35)	87.38 (30.48)	50.07 (31.25)
Alanine (umol/L)	244.30 (51.19)	270.50 (81.19)	20.11 (79.10)	325.73 (100.37)	72.71 (80.78)
Aspartic acid					
Glutamic acid (umol/L)	54.19 (18.96)	76.15 (30.38)	20.72 (23.94)	94.15 (37.17)	33.76 (24.99)
Glycine (umol/L)	170.16 (40.65)	218.48 (69.4)	50.28 (58.72)	254.87 (87.14)	84.93 (76.52)
Proline					
Serine (umol/L)	80.99 (18.02)	98.42 (27.66)	17.57 (21.67)	109.89 (28.21)	28.49 (22.67)
Tyrosine (umol/L)	58.24 (11.63)	48.11 (9.31)	-9.70 (15.92)	49.31 (8.43)	-8.55 (12.99)
Fatty acids					
C16 (umol/L) [palmitic acid]	1213.33 (357.55)	1134.91 (408.58)	-62.84 (438.59)	1372.19 (439.05)	163.14 (448.20)
C18 (umol/L) [stearic acid]	262.40 (84.88)	268.33 (93.11)	6.93 (102.92)	299.76 (86.70)	33.15 (99.66)
C18:1 (umol/L) [oleic acid]	1548.92 (422.68)	1514.99 (478.18)	-15.72 (507.89)	1766.66 (546.13)	223.97 (585.59)
C18:2 (umol/L) [linoleic acid]	1226.87 (351.81)	2036.62 (563.64)	783.23 (535.36)	2434.00 (799.26)	1161.69 (853.92)
Other markers of					

energy utilization					
Insulin (mcU/L)	10.67 (6.0)	17.15 (8.6)	6.05 (8.76)	16.4 (9.81)	5.33 (6.7)
Leptin (mcg/L)	8.98 (9.65)	12.23 (13.37)	3.17 (6.23)	11.86 (11.79)	2.82 (4.47)
Triglyceride (mg/dL)	72.28 (29.31)	105.06 (52.16)	27.26 (51.04)	129.89 (49.63)	56.37 (58.37)
Glucose (mg/dL)	128.38 (63.72)	133.89 (41.80)	3.57 (29.45)	125.52 (36.38)	-2.86 (45.07)
Urea (mg/dL)	3.69 (1.90)	4.32 (2.63)	0.58 (1.87)	5.0 (2.69)	1.23 (1.62)
IGF-1	109.95 (45.19)	125.40 (45.09)	12.86 (27.74)	168.45 (77.76)	28.67 (37.07)
IGF BP-1	54.71 (37.11)	11.20 (7.56)	-42.52 (38.43)	11.45 (11.47)	-42.29 (36.78)

Starting day 5 of the infusion, partial oral nutrition was allowed (~ 35 % by day 7). Therefore, period 4 data is presented in the table above as until this day nutrition was solely via Kabiven.

Review comments:

Essential and non-essential amino acids demonstrated an increase over baseline with Kabiven (central vein) infusion for 7 days. Most of the individual amino acids increased over pre-treatment levels, with the exception of leucine (an essential AA) and tyrosine (a non-essential AA). Fatty acid pattern analysis suggested an increase in palmitic, stearic, oleic and linoleic acids. In addition, the levels of capric acid, C10 also increased in the kabiven group. The levels of alpha-linolenic acid were reportedly too low to detect for the majority of patients and were not evaluated. [The five major fatty acid components known to be available from soybean oil are the unsaturated fatty acids, linoleic acid C18:2 at 54 %, oleic acid, C18:1 at 24 %, alpha linolenic acid C18:3 at 7 % and the saturated fatty acids, palmitic acid C16 at 11 %, and stearic acid C18 at 4 %].

The levels of insulin, leptin and IGF-1 showed an increase over baseline. Correspondingly, the levels of IGF binding protein decreased with Kabiven therapy. The nitrogen balance [determined as a difference between nitrogen input (from protein synthesis sources included in the TPN) and output (in urinary urea)] was nearly apparent in two of the treatment periods (period 2 and 4). Deficits were noted in periods 1 and 2 where reduced infusion volumes (nitrogen input) were employed. In period 3, there was more nitrogen output (urine) compared to input via TPN thus also resulting in a relative deficit. Measurement of serum urea concentration suggests an increase over time with Kabiven therapy, suggestive of increased nutritional nitrogen intake. Amount of urea excreted in urine increased slightly with Kabiven treatment. The levels of pre-albumin (mg/L) suggestive of improved synthesis of constitutive proteins increased with treatment.

Reviewer conclusions: *Study evaluated safety, tolerability and efficacy (nutrient utilization) following Kabiven treatment. Data suggests improvement in the availability of most amino acids, fatty acids and energy utilization following Kabiven administration. The clinical relevance of observed changes is not known. Please refer to the clinical review of this NDA by Dr. Karyn Berry for further information.*

2.2.5. What are the relevant characteristics of absorption, distribution, metabolism and distribution (ADME) of the proposed products?

Each component of Kabiven™ (b) (4) has been utilized as a nutrient in clinical situations for many years and some have been studied separately.

Fat emulsion: The infused fat particles are known to be cleared from the blood stream in a manner thought to be comparable to the clearing of chylomicrons. In healthy volunteers, the maximum clearance rate of the triglycerides after fasting overnight has been found to be

equivalent to 3.8±1.5g/kg per 24 hours. Both elimination and oxidation rates are dependent on the patient's clinical condition; elimination is faster and utilization is increased in postoperative patients, in sepsis, burns and trauma, while patients with renal failure and hypertriglyceridaemia show lower utilization of exogenous fat emulsions.

Dextrose: The pharmacokinetic properties of infused glucose are essentially the same as those of glucose supplied by ordinary food. However, the peak after administration will be somewhat delayed after oral intake compared to intravenous infusion

Amino acids and electrolytes: The principal pharmacokinetic properties of the infused amino acids and electrolytes are essentially the same as for amino acids and electrolytes supplied by ordinary food. The amino acids of dietary protein first enter the portal vein and then the systemic circulation, while intravenously infused amino acids reach the systemic circulation directly.

2.3 Intrinsic and Extrinsic factors

2.3.1 What are the proposed considerations for dosing in specific populations?

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 sponsor (see labeling section below).

FDA discussions regarding the pediatric plan are pending. Sponsor's request (b) (4) pending adequate justification.

2.3.2 Are there any relevant drug-drug interactions that influence the PK and/or response (safety and efficacy) of any or all of the components of TPN products and if so, what are any considerations for dose adjustments/labeling in presence of such drugs?

No dedicated drug interaction studies have been conducted for the proposed products.. Labeling language regarding relevant DDIs has been proposed by the sponsor based on literature search (see section on labeling below).

2.4 Analytical Section

How were the active moieties identified and measured in samples during the clinical pharmacology and biopharmaceutics studies?

Determination of phosphate in serum and urine in the presence of Na-glycerophosphate using the Cobas 6000 / c501 (Roche diagnostics)

This method for the determination of inorganic phosphate (analyte of interest) from the two phosphate sources is based on the reaction of phosphate with ammonium molybdate to form ammonium phosphomolybdate. The concentration of phosphomolybdate formed is directly proportional to the inorganic phosphate concentration and is measured photometrically.

Analyses were done by (b) (4) according to their SOPs.

Internal quality controls: For serum analysis Precinorm U (PNU) and Precipath U (PPU) were used as internal quality controls, for urine analysis Bio-Rad controls Liquicheck Urine Chemistry Control Level 1 and Liquicheck Urine Chemistry Control Level 2 were used as internal quality controls.

For serum samples the limit of detection defined by the manufacturer is (b) (4) mmol/L. For urine samples the limit of detection defined by the manufacturer is (b) (4) mmol/L. For serum samples the measurement range defined by the manufacturer is (b) (4) mmol/L. For urine samples the measurement range defined by the manufacturer is (b) (4) mmol/L. Samples with values above the measurement range are diluted and reanalysed.

Interference testing: To measure the interference of glycerophosphate on the analysis of inorganic phosphate two different concentrations of urine and serum samples (spiked with glycerophosphate and unspiked) were measured on four days in five repetitions.

Validation summary:

Phosphate in serum: The Cobas 6000 method for the determination of phosphate in serum is accurate within the limits of defined accuracy in the presence of Na-glycerophosphate, showing an accuracy from 8.73% to 11.11% in spiked PNU samples and from 8.68% to 11.87% in spiked PPU samples. The percentage deviation from the mean value is within the acceptable range on both Cobas 6000 analysers used for this analysis.

The internal quality controls met the acceptance criteria according to the manufacturers specification. The coefficient of variation (precision) was between 0.79 to 2.40% for the PNU control and between 1.37 to 2.76% for the PPU control on both Cobas 6000 analysers.
Phosphate in urine: The Cobas 6000 method for phosphate in urine is accurate within the limits of defined accuracy in the presence of Na-glycerophosphate, showing an accuracy from 2.53% to 7.35% in spiked Liquicheck Urine Chemistry Control level 1 and from -0.99% to 4.97% in spiked Liquicheck Urine Chemistry Control level 2. The percentage deviations from the mean value are within the acceptable ranges on both Cobas 6000 analysers.
The internal quality controls met the acceptance criteria according to the manufacturers specification. The coefficient of variation was between 1.23 to 2.47% for the Liquicheck Urine Chemistry Control 2. The standard deviation was between 0.14 to 0.27mmol/L for the Liquicheck Urine Chemistry Control 1.

The method is within the acceptance limits for accuracy and precision and is suitable for the determination of phosphate in human serum and urine. No interference was detected.

Material	Acceptance criteria	Range of measured values
Precinorm U	Inter-day precision (CV) < (b) (4)%	(b) (4)%
Precipath U	Inter-day precision (CV) < (b) (4)%	(b) (4)%
Liquicheck Urine Chemistry Control 1	Inter-day precision (SD) < (b) (4) nmol/L	(b) (4) nmol/L
Liquicheck Urine Chemistry Control 2	Inter-day precision (CV) < (b) (4)%	(b) (4)%
Glycerophosphate spiked serum samples	Accuracy ± (b) (4)%	(b) (4)%
Glycerophosphate spiked urine samples	Accuracy ± (b) (4)%	(b) (4)%
External quality assurance	Certificate: yes	yes

Inspection issues: Following a request from the review division and DCP3, the Division of Bioequivalence and GLP compliance, DBGC inspected the clinical (Parexel International GmbH, Germany) and bioanalytical sites ((b) (4)) for the relative bioavailability study Glyc-001-C P1. 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 date 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. While we acknowledge that the sponsor did not demonstrate linearity of the assay over a wider concentration range through a typical multi-point calibration and use of QC samples that encompass such a standard curve during the study sample assay, the manufacturer of the commercial instrument used in the phosphate assay (cobas series by Roche diagnostics) has previously established linearity up to a concentration range that encompasses the test and reference sample concentrations encountered during this study. Specifically, linearity was established for the assay up to 6.46 mmol/L in serum and up to 92 mmol/L in urine. Urinary samples that exceeded the linear range were diluted during the study sample analysis. Thus while not optimally performed per regulatory standards, it appears that the analytical facility followed the manufacturer's recommendations during the assay. As error in the analytical methodology is likely to affect both test and reference samples in a somewhat similar manner, the data generated from this study would still provide a rough estimate of relative bioavailability. In addition, relative bioavailability estimates from the serum and urine concentrations which varied widely with respect to phosphate levels were similar in this study.

While such a deficiency may become an issue for a single entity drug product, particularly one that is intended for oral route, because the proposed formulations are large volume parenteral formulations intended for intravenous use, with adequate monitoring of the patients, it appears reasonable to not recommend additional data to address this issue. The

proposed labeling indicates [redacted] (b) (4)

The sponsor also notes in their response to IR dated August 18, 2011 that "the amounts of electrolytes in the formulations are aimed to provide basic requirements and in clinical practice the clinicians in general may supplement electrolytes based on the clinical situation determined by constant monitoring of the blood levels".

The proposed new phosphate source, organic sodium glycerophosphate has also been approved and used safely for several years in countries around the world. It is documented in literature that phosphatases which are ubiquitous in the human body are instrumental in hydrolyzing organic esters of phosphate including sodium glycerophosphate in order to release phosphate in its inorganic form. In addition, the proposed formulations contain a second source of phosphate contributing to ~ [redacted] (b) (4) % of total phosphate concentrations (egg phospholipids from intralipid). Therefore, potential impact of any differences in bioavailability across the organic and inorganic phosphate sources is made even smaller from an overall formulation standpoint.

3 Labeling

Detailed labeling language review and comments are pending. Relevant sections of the labeling are shown below.

7.0 DRUG INTERACTIONS

[redacted] (b) (4)

8.0 SPECIFIC POPULATIONS

Renal impairment: [redacted] (b) (4)

(b) (4)

Hepatic impairment: In patients with impaired liver function Kabiven (b) (4) should be administrated with caution. (b) (4) Frequent clinical evaluation and laboratory tests to monitor liver function such as bilirubin, (b) (4) (b) (4) should be conducted. (b) (4)

Geriatric Use: Clinical studies of Kabiven™ (b) (4) did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from other younger (b) (4) Other reported clinical experience has not identified differences in responses between the elderly and younger patients. In general, dose selection for an elderly patient should be cautious, usually starting at the low end of the dosing range, reflecting the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or drug therapy.

Pregnancy: Pregnancy Category C. Animal reproduction studies have not been conducted with Kabiven™ (b) (4). It is (b) (4) not known whether Kabiven (b) (4) can cause fetal harm when administered to a pregnant woman (b) (4). Kabiven (b) (4) should be given to a pregnant woman only if clearly needed.

Nursing Mothers: Caution should be exercised when Kabiven (b) (4) is administered to a nursing woman.

Pediatric use: (b) (4)

(b) (4)

4 Appendices

4.1 Consult Reviews

DSI (see attached)

4.2 Cover Sheet and OCP Filing Memo

GRMP Filing review (see attached)

MEMORANDUM **DEPARTMENT OF HEALTH AND HUMAN SERVICES**
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE: August 14, 2011

TO: Donna Griebel, M.D.
Director
Division of Gastroenterology Products (DGP)
Office of Drug Evaluation III

Dennis Bashaw, Pharm.D.
Director, Division of Clinical Pharmacology 3 (DCP3)

FROM: Xikui Chen, Ph.D., Chemist
Division of Bioequivalence and GLP Compliance (DBGC)
Office of Scientific Investigations (OSI)

THROUGH: Sam H. Haidar, Ph.D., R.Ph.
Chief, Bioequivalence Investigations Branch
Division of Bioequivalence and GLP Compliance
Office of Scientific Investigations

Martin K. Yau, Ph.D.
Acting Team Leader - Bioequivalence
Division of Bioequivalence and GLP Compliance
Office of Scientific Investigations

SUBJECT: Review of EIRs Covering NDA 200-656, Kabiven™ ((b) (4) (b) (4)) and ((b) (4) (b) (4)), Sponsored by APP Pharmaceuticals, LLC

At the request of the Division of Gastroenterology Products (DGP), and the Division of Clinical Pharmacology 3, DBGC audited the clinical and analytical portions of the following study:

Study Number: Glyc-001-C P1

Study 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"

The clinical portion of Study Glyc-001-C P1 was conducted at PAREXEL International GmbH, Early Phase Clinical Unit - Berlin, Haus 18, Spandauer Damm 130, 14050 Berlin, Germany. Following inspection of the clinical site (July 28, and August 1 to 5, 2011), no Form FDA-483 was issued.

Audit of the analytical portion of study Glyc-001-C P1 was conducted at [redacted] Following inspection at the analytical site ([redacted]), Form FDA-483 was issued (Attachment 1). DBGC received the [redacted] written h email to the inspectional finding on [redacted] (Attachment 2). The FDA-483 observation, n response, and our evaluation are as follows:

1. 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 quality control samples (QCs) at approximately 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.

During the inspection, we observed that one calibrator at 1.67 mmol/L phosphate was utilized to calibrate the Cobas 1 instrument on July 14, 2010, and November 4, 2010, and Cobas 2 on August 19, 2010, and November 3, 2010, respectively. The study serum samples were analyzed from September 7 to 29, 2010, and urine samples were analyzed from September 1 to 28, 2010, on Cobas 1 or Cobas 2. By using one calibrator and deionized water, the measuring range on Cobas is 0.10-6.46 mmol/L phosphate in serum and 1.1-92 mmol/L phosphate in urine samples according to the Cobas PHOS2 insert. The calibrator was not used during the period of analyses of study samples. Two quality control samples (QCs) at approximately 1.3 mmol/L phosphate in Precinorm U (PNU) and 2.1 mmol/L phosphate in Precipath U (PPU) were used for serum samples, and two QCs at 8.3

mmol/L phosphorus in Liquichek Urine Control 1 and 16.1 mmol/L phosphorus in Liquichek Urine Control 2 were used for urine samples. The two quality controls (1.3 and 2.1 mmol/L) employed in the serum samples during the study did not meet the recommendations in FDA guidance for three concentrations in the range of study samples to demonstrate the accuracy of a method. The maximum observed phosphate concentrations for serum samples were 3.38 mmol/L after the test product, and 4.20 mmol/L after the reference, respectively. The two quality controls (8.3 and 16.3 mmol/L) utilized in the urine samples during the study were not representative of study urine sample concentrations, since approximately 164 urine samples were re-analyzed due to their concentration above the measuring upper limit 92 mmol/L.

In the response from [redacted] (b) (4), the firm provided calibration standards in the appendix 6 and 7. The firm also provided 2 external quality assurances for serum samples and 2 external quality assurances for urine samples in appendix 10, and stated that external quality assurance samples cover the study samples.

Concentration of the four external quality assurances could not be located in the appendix 10. However, the concentrations of external quality assurances listed in the analytical report (study No.: Glyc-001-C P1) ranged 0.959 to 2.48 mmol/L in serum and 4.61 to 18.8 mmol/L in urine. The concentrations in external quality assurances were the same as used in internal quality controls. The quality control samples were not representative of the study samples, and the analytical method was insufficiently demonstrated to be accurate during the study.

Conclusion:

Following the above inspections, DBGC recommends that the phosphate data from study **Glyc-001-C P1** should **not** be accepted for Agency review, because the quality control samples did not represent the study samples, and the analytical method was insufficiently demonstrated to be accurate during the study for the purposes of this bioequivalence assessment.

After you have reviewed this transmittal memo, please append it to the original NDA submission.

Xikui Chen, Ph.D.

Final Classification:

Clinical

PAREXEL International GmbH, Early Phase Clinical Unit – Berlin, Haus 18, Spandauer Damm 130, 14050 Berlin, Germany – NAI

Analytical

[redacted] (b) (4) – VAI

cc: DARRTS
OSI/Ball
DBGC/Salewski/Haidar//Yau/Viswanathan/Skelly/Chen/Djernett/Mathews/CF
OND/DGP/Donna Griebel/Frances Fahnbulleh
OTS/OCP/DCPIII/Dennis Bashaw
HFR-CE350/Jonee Mearns

Draft: XC 8/12/11
Edit: MFS 8/12/11

DSI: File BE6200; O:\BE\EIRCover\200656app.pho.doc
FACTS 1283377

cc: email
CDER DSI PM TRACK

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS FILING FORM/CHECKLIST FOR NDA 200656

Office of Clinical Pharmacology

New Drug Application Filing and Review Form

General Information about the Submission

	Information		Information
NDA Number	200656	**Brand Name**	Kabiven and [redacted] (b) (4)
OCP Division (I, II, III, IV, V)	DCPIII	**Generic Name**	Mixture of [redacted] (b) (4) drug substances: Amino acids, lipids (soybean oil), dextrose and electrolytes
Medical Division	DGP	**Drug Class**	Solutions for Parenteral Nutrition
OCP Reviewer	Sandhya Apparaju	**Indication(s)**	Total Parenteral Nutrition [for adults [redacted] (b) (4)]
OCP Team Leader	Sue Chih Lee	**Dosage Form**	[redacted] (b) (4) intravenous infusion after mixing
Pharmacometrics Reviewer	N/A	**Dosing Regimen**	Dose: The daily dose varies with the clinical condition of the patient (e.g. [redacted] (b) (4)). Infusion period: 12-24 h Infusion rates Kabiven: NMT 2.6 mL/kg BW/hr [redacted] (b) (4): NMT 3.7 mL/kg BW/hr
Date of Submission	01/28/2011	**Route of Administration**	Intravenous Kabiven Via Central Vein only; [redacted] (b) (4) Via Peripheral or Central Vein
Estimated Due Date of OCP Review	09/28/2011	**Sponsor**	APP Pharmaceuticals
Medical Division Due Date	10/24/2011	**Priority Classification**	Standard
PDUFA Due Date	11/28/2011		

Clinical Pharmacology and Biopharmaceutics Information

	"X" if included at filing	Number of studies submitted	Number of studies reviewed	Critical Comments If any
STUDY TYPE				
Table of Contents present and sufficient to locate reports, tables, data, etc.	X			
Tabular Listing of All Human Studies	X			

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS FILING FORM/CHECKLIST FOR NDA 200656

HPK Summary	X			
Labeling	X			
Reference Bioanalytical and Analytical Methods	X			
I. Clinical Pharmacology				
Mass balance:				
Isozyme characterization:				
Blood/plasma ratio:				
Plasma protein binding:				
Pharmacokinetics (e.g., Phase I) -	X			Phosphate levels (see relative BA)
Healthy Volunteers-				
single dose:				
multiple dose:				
Patients-				
single dose:				
multiple dose:	X	3		Three completed clinical trials included limited assessment of amino acid and fatty acid levels via standard lab methods
Dose proportionality -				
fasting / non-fasting single dose:				
fasting / non-fasting multiple dose:				
Drug-drug interaction studies -				
In-vivo effects on primary drug:				
In-vivo effects of primary drug:				
In-vitro:				
Subpopulation studies -				
ethnicity:				
gender:				
pediatrics:				The formulations lack Cysteine. (b) (4) [redacted]
geriatrics:				
renal impairment:				No specific population study; label recommends caution in RI; Proposed (b) (4) [redacted]
hepatic impairment:				No specific population study; Proposed (b) (4) [redacted]
PD -				

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS FILING FORM/CHECKLIST FOR NDA 200656

Phase 1:	X			PD data (serum calcium, sodium, potassium, PTH and calcitonin) available from one of the relative BA studies Glyc-001-C P1
Phase 2:				
Phase 3:	X			Limited PD information available from phase 3 studies 00-3CB4-001, 00-3CB5-001 and 01-3CB5-002 (serum urea, creatinine, pre-albumin etc)
PK/PD -				
Phase 1 and/or 2, proof of concept:				
Phase 3 clinical trial:				
Population Analyses -				
Data rich:				
Data sparse:				
II. Biopharmaceutics				
Absolute bioavailability				
Relative bioavailability -				
solution as reference:				
alternate formulation as reference:	X	2		Relative BA studies (Glyc-001-C P1, KABI-003-C P1) to compare the systemic phosphate levels following Sodium glycerophosphate (current formulation) vs. inorganic phosphates (approved)
Bioequivalence studies -				
traditional design; single / multi dose:				
replicate design; single / multi dose:				
Food-drug interaction studies				
Bio-waiver request based on BCS				
BCS class				
Dissolution study to evaluate alcohol induced dose-dumping				
III. Other CPB Studies				
Genotype/phenotype studies				
Chronopharmacokinetics				
Pediatric development plan				Pediatric waiver proposed
Literature References				
Total Number of Studies	X	5		2 Relative BA studies and 3 phase 3 trials containing limited pharmacological information

On **initial** review of the NDA/BLA application for filing:

	Content Parameter	Yes	No	N/A	Comment
Criteria for Refusal to File (RTF)					
1	Has the applicant submitted bioequivalence data comparing to-be-marketed product(s) and those used in the pivotal clinical trials?			X	

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS FILING FORM/CHECKLIST FOR NDA 200656

2	Has the applicant provided metabolism and drug-drug interaction information?		X		Section 7.0 is not included in the proposed labeling; sponsor will be asked to include observed or predicted DDI or lab-drug interaction data as section 7.0.
3	Has the sponsor submitted bioavailability data satisfying the CFR requirements?	X			Limited information for systemic phosphate levels is submitted following (b) (4); Waiver for systemic BA could be granted in accordance with 21CFR§320.22(e)
4	Did the sponsor submit data to allow the evaluation of the validity of the analytical assay?	X			Yes; Methods employed in assessing serum phosphate during the two relative BA studies
5	Has a rationale for dose selection been submitted?	X			Based on standards set by American and European parenteral nutritional societies (ASPEN and ESPEN); qualitative and quantitative comparison of individual components to reference listed drugs approved for parenteral nutrition either as single chamber or 2-chamber i.v. formulations (intralipid 20 %, Novamine 11.4 %, Clinimix E, and Aminosyn II); Information to justify differences in electrolyte levels in the proposed vs. approved formulations has been included in the submission per agency's request
6	Is the clinical pharmacology and biopharmaceutics section of the NDA organized, indexed and paginated in a manner to allow substantive review to begin?	x			
7	Is the clinical pharmacology and biopharmaceutics section of the NDA legible so that a substantive review can begin?	X			
8	Is the electronic submission searchable, does it have appropriate hyperlinks and do the hyperlinks work?	X			
Criteria for Assessing Quality of an NDA (Preliminary Assessment of Quality)					
	Data				
9	Are the data sets, as requested during pre-submission discussions, submitted in the appropriate format (e.g., CDISC)?	X			Electronic datasets for drug concentrations, patient demographics, PK parameters etc could be located in the NDA submission
10	If applicable, are the pharmacogenomic data sets submitted in the appropriate format?			X	
	Studies and Analyses				
11	Is the appropriate pharmacokinetic information submitted?	X			Some PK information submitted per agency's request; In general, a waiver of BA information for this parenteral formulation could be justified based on 21CFR320.22(e)
12	Has the applicant made an appropriate attempt to determine reasonable dose individualization strategies for this product (i.e., appropriately designed and analyzed dose-ranging or pivotal studies)?	X			Formulation is available in three different sizes; the dose is individualized depending on the patient's clinical condition (e.g. (b) (4))
13	Are the appropriate exposure-response (for desired and undesired effects) analyses conducted and submitted as described in the Exposure-Response guidance?		x		Parenteral nutrition is a well known area and the amounts of nutrients are based on standards set by ASPEN and ESPEN in this regard and based on prior approved formulations
14	Is there an adequate attempt by the applicant to use exposure-response relationships in order to assess the need for dose adjustments for intrinsic/extrinsic factors that might affect the pharmacokinetic or pharmacodynamics?		X		
15	Are the pediatric exclusivity studies			X	

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS FILING FORM/CHECKLIST FOR NDA 200656

	adequately designed to demonstrate effectiveness, if the drug is indeed effective?				
16	Did the applicant submit all the pediatric exclusivity data, as described in the WR?			X	(b) (4) [redacted]
17	Is there adequate information on the pharmacokinetics and exposure-response in the clinical pharmacology section of the label?		X		Separate labels are proposed for Kabiven and for (b) (4) [redacted] to avoid dosing errors related to the use of central or peripheral vein. Limited general clinical pharmacology information is included in these labels. Due to the absence of dedicated studies evaluating PK, no information in this regard has been included; There is no section 7.0 included for drug-drug interactions; there are no subsections for renal or hepatic impairment under section 8.0; No specific population or DDI studies have been conducted. However, label will be reviewed and changes will be proposed if necessary.
	General				
18	Are the clinical pharmacology and biopharmaceutics studies of appropriate design and breadth of investigation to meet basic requirements for approvability of this product?	X			
19	Was the translation (of study reports or other study information) from another language needed and provided in this submission?			X	

IS THE CLINICAL PHARMACOLOGY SECTION OF THE APPLICATION FILEABLE? *YES*

Comments for the sponsor (for inclusion in the 74-day letter):

- **Proposed PLR labeling should include a DRUG INTERACTIONS Section 7.0. Include any observed or predicted drug-drug (prescription or OTC) or drug-laboratory interactions in this section. Provide mechanisms of interaction if available, as well as practical instructions for preventing or managing these interactions. You should perform a literature search in this regard and provide the findings with references in your response.**
- **Proposed labeling should include subsections for Renal Impairment and Hepatic Impairment under the Use in Specific Populations Section 8.0. Include all information relevant to use and dosing in these specific subpopulations. A literature search in this regard is recommended.**
- **Organize the Clinical Pharmacology Section 12.0 of the proposed labeling into Mechanism of action (12.1), (b) (4) [redacted] and Pharmacokinetics (12.3).**

Sandhya Apparaju, Ph.D.

Reviewing Clinical Pharmacologist Date

Sue Chih Lee, Ph.D.

Team Leader/Supervisor Date

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/s/

SANDHYA K APPARAJU
03/24/2011

SUE CHIH H LEE
03/24/2011

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

SANDHYA K APPARAJU
09/28/2011

SUE CHIH H LEE
09/28/2011

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CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS FILING FORM/CHECKLIST FOR NDA 200656

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CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS FILING FORM/CHECKLIST FOR NDA 200656

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CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS FILING FORM/CHECKLIST FOR NDA 200656

	adequately designed to demonstrate effectiveness, if the drug is indeed effective?				
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	General				
18	Are the clinical pharmacology and biopharmaceutics studies of appropriate design and breadth of investigation to meet basic requirements for approvability of this product?	X			
19	Was the translation (of study reports or other study information) from another language needed and provided in this submission?			X	

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Sandhya Apparaju, Ph.D.

Reviewing Clinical Pharmacologist Date

Sue Chih Lee, Ph.D.

Team Leader/Supervisor Date

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

SANDHYA K APPARAJU
03/24/2011

SUE CHIH H LEE
03/24/2011