

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

200656Orig1s000

CROSS DISCIPLINE TEAM LEADER REVIEW

Cross-Discipline Team Leader Review

Date	8/14/2014
From	Ruyi He, MD
Subject	Cross-Discipline Team Leader Review
NDA/BLA # Supplement#	NDA 200656 (SEQ-0025) Responses to complete response and general advice letters
Applicant	Fresenius Kabi USA, LLC
Date of Submission	11/25/2013
PDUFA Goal Date	8/25/2014
Therapeutic Class	Large Volume Emulsion: as a source of calories, protein and essential fatty acids
Proprietary Name / Established (USAN) names	Kabiven and Perikabive (Lipid Injectable Emulsion with Amino Acids and Electrolytes and Dextrose)
Proposed Indication(s)	Kabiven and Perikabiven are indicated for intravenous infusion as a source of calories, protein and essential fatty acids for • Patients requiring parenteral nutrition • Prevention of essential fatty acid deficiency • (b) (4) treatment of negative nitrogen balance
Proposed Dosage forms / Strength	Three chamber bag, with each individual chamber containing dextrose solution, amino acid and electrolyte solution, and fat emulsion, respectively.
Recommended:	I recommend that NDA 200656 for Kabiven and Perikabiven be approved for intravenous infusion as a source of calories, protein and essential fatty acids.

1. Introduction

Parenteral nutrition (PN) is the provision of intravenous nutrients to patients whose gastrointestinal (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, and sterile water for injection, electrolytes, vitamins and minerals, administered intravenously. 3-in-1 or all-in-one formulations contain IVFE in the same container with dextrose, amino acids, sterile water for injection, electrolytes, vitamins and minerals.

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.

The sponsor submitted a 505(b)(2) New Drug Application (NDA) 200656 for KABIVEN and PERIKABIVEN on 28 January 2011. The agency issued a Complete Response Letter to the sponsor on 21 November 2011. In this submission, the sponsor submitted responses to the complete response letter and addressed the issues listed on the complete response letter.

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

The sponsor stated that Kabiven and PeriKabiven are products that are designed to provide “all in one” total nutrient admixtures for PN. The potential advantages of this product 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 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

2. Background

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 and would be indicated for the prevention of essential fatty acid deficiency (b) (4) treat negative nitrogen balance in patients (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 doses delivered would be individualized and would depend on the patient's clinical condition, body weight and nutritional requirements.

The agency issued a Complete Response Letter to the sponsor on 21 November 2011 with following deficiencies:

CLINICAL

1. Information to [REDACTED] (b) (4)

PRODUCT QUALITY

2. Information on the amount of heavy metals in each compartment of the three chamber bag and the total amount of heavy metals in each product is inadequate. The presence of heavy metals in these products may have significant adverse effects on organs and tissues such as nephropathy, neurotoxicity, and hepatotoxicity.

3. Adequate controls for the levels of heavy metals specified in Item #2 in each of the compartments have not been provided. Due to the large volume to be infused into patients, develop specifications and adequate acceptance criteria to control the amount of daily intake of these heavy metals. .

4. You revised the proposed expiration dating period to (b) (4) months because you observed precipitation in your product when it is stored at the proposed storage conditions for longer than that time period.

5. DMF # (b) (4) has been reviewed in support of NDA200656 and found to contain deficiencies.

6. Confirm that the (b) (4) meets (b) (4)

DEVICE PERFORMANCE

7. You 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 testing regimen.



9. You 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 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.

HUMAN FACTORS ASSESSMENT

10. Although the (b) (4) bag will be utilized by health care providers, after evaluating the packaging sample provided, we found it very cumbersome to manipulate. Therefore, to ensure that use-related hazards associated with using the (b) (4) bag have been successfully identified and mitigated, you should 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 iv bags.

LABELING

11. 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

During recent inspections of the manufacturing facilities for this application, our field investigator conveyed deficiencies to the representatives of some facilities. Satisfactory resolution of these deficiencies is required before this application may be approved.

In this review, I will focus the evaluations on the deficiencies listed above.

3. CMC/Device

CMC

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. CMC team has no PMR/PMC recommendation.

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), cadmium (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 confirmed to meet (b) (4) as safe food contact materials.

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

5. A new supplier for (b) (4) was proposed for Kabivan and Perikabivan, and based on the review for DMF (b) (4) it is deemed adequate for these drug products.
6. The ONDQA Precedence Committee held on May 13, 2014 had decided that there are no active moiety which could be designated as an NME in the drug product of this NDA. However, organic glycerol phosphate (Sodium Glycerophosphate) used as an active ingredient to supply phosphate will be consider new active ingredient.

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

On June 10, 2014, Dr. Tarun indicated that "Based on the revised labels for the immediate container/closures as well as conformance of the storage temperature in the "How Supplied" section of PI to the USP format, this NDA is now recommended for **APPROVAL** from the ONDQA perspective with an expiration dating period of 24 months. Dr. Tarun provided following labeling recommendations and I concur.

1. Font size of the established name should be enlarged.
2. Lot number and expiration dating period are missing.
3. Regarding PI Labeling:
Storage temperature in How Supplied section should follow the USP format.

CDRH

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.

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 3-chamber parenteral nutritional bag.

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 complete review dated April 22, 2014.

As part of the current pre-approval drug inspection, the Center for Devices and Radiological Health requested an abbreviated device inspection covering Design Controls and CAPA for the device component.

During this inspection the following Quality System violation was observed: Failure to establish and maintain design control procedures for Kabiven/ (b) (4) combination product (NDA 200-656). (21 CFR 820.30)

CDRH has reviewed the EIR and exhibits and concluded that the deficiency listed does not qualify as major at this time. CDRH recommends that this inspection be classified as VAI and approval of NDA 200-656. Please see Francisco Vicenty's review dated May 20, 2014 in detail.

4. Nonclinical Pharmacology/Toxicology

Dr. Emmanuel Akinshola, is the reviewer and Dr. Sushanta Chakder is the team leader for this NDA and they concluded in the review that from a nonclinical standpoint, this NDA is recommended for approval and has no recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps.

Based on the Dr. Akinshola's review, the Applicant has submitted a complete safety assessment of leachables/extractables from the 3-CB (b) (4) packaging system. Safety assessment of the potential leachables from the 3-CB packaging system was performed following (b) (4) and storage of the 3-CB (b) (4) bags with components of the drug product (lipid, glucose and amino acid), or treatments with comparable solvents, such as saline, water or 13 % ethanol stored in the (b) (4) container for extended period at different temperatures after (b) (4) to allow leaching of the migrants from the container into the liquids. The levels of leachables and extractables and their degradation products were measured, analyzed, and an assessment of the safety was performed. For some components, for which the levels were not detectable because of insolubility or for some other reason, the safety assessment of that component was performed based on the assumption that 100% of it will be released into the IV fluid.

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. Thus, there are no safety concerns for the potential leachables/extractables from the (b) (4) 3-CB packaging system into Kabiven/Perikabiven IV fluids.

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

5. Clinical Pharmacology/Biopharmaceutics

Dr. Sandhya Apparaju, is the Clinical Pharmacology reviewer for this NDA and Dr. Sue Chih Lee is the Team Leader. They concluded that this NDA is recommended for approval and has

no recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps.

Clinical Pharmacology review of the original submission concluded that the NDA was acceptable (see review 09/28/2011).

6. Clinical Microbiology

NA

7. Clinical/Statistical- Efficacy

No new efficacy data was submitted during this review cycle.

8. Safety

The Applicant reported that no additional nonclinical or 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.

Please refer to Dr. Berry's complete review.

9. Advisory Committee Meeting

NA

10. Pediatrics

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.

In this complete response re-submission the Applicant [REDACTED] (b) (4)
[REDACTED] and a deferral for trials in pediatric patients ages 2 to 16 years. [REDACTED] (b) (4)

The Applicant also proposed [REDACTED] (b) (4)

Pediatric patients < 2 years of age generally require specific, individually compounded PN. Based on the nutritional calculations, PMHS review team and the Division agrees 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 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).

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

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 $\geq$ 2 years of age. 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.

11. Other Relevant Regulatory Issues

Proprietary Names

Office of Medication Error Prevention and Risk Management has reviewed the proposed proprietary names and has concluded that Kabiven (for the central formula), and Perikabiven (for the central/peripheral formula) are acceptable. Office of Medication Error Prevention and Risk Management has noted the sponsor this conclusion on 1/27/2014.

12. Labeling

DMEPA concluded that the proposed container label and prescribing information acceptable.

Meeta Patel, PharmD from Office of Prescription Drug Promotion (OPDP) provided a labeling review and recommended providing information regarding serious warnings and precautions regarding sepsis (5.3) and metabolic effects (5.4) in the Highlights section for completeness. I concur with this recommendation. Please see her review dated on April 30, 2014 in details.

I concur with labeling recommendations provided by the review team.

13. Recommendations/Risk Benefit Assessment

- Recommended Regulatory Action

I concur with Dr. Berry's recommendation that NDA 200656 for Kabiven and Perikabive be approved for the indication for intravenous infusion as a source of calories, protein and essential fatty acids for

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

All deficiencies listed in the CR letter have been resolved.

- Recommendation for other Postmarketing Requirements and Commitments

One safety study in pediatric patients aged 2 to 16 years.

The timelines are:

- Protocol Submission: Final clinical study protocol submission to FDA will be made within 6 months from date of approval. Expected date February 2015
- 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: August 2107
- Submission of final clinical study report: approximately 6 - 12 months after study end (last patient last visit). Expected date of submission: August 2018

I concur with the timeline.

- Recommended Comments to Applicant

None.

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/s/

RUYI HE
08/14/2014