DEPARTMENT OF HEALTH AND HUMAN SERVICES Public Health Service

Food and Drug Administration
Center for Biologics Evaluation and Research
Office of Biostatistics and Epidemiology
Division of Biostatistics

STATISTICAL REVIEW AND EVALUATION
BLA

Date: April 28, 2011

BLA/Supplement Number:	125384/0
Product Name:	Kedbumin – Albumin (Human) 25% solution
Indication(s):	Hypervolemia; Hypoalbuminemia; Cirrhotic Ascites; OHSS; ARDS; Burns; Hymodialysis; Cardiopulm; Bypass
Applicant:	Kedrion, S.p.A.
Date(s):	CBER receipt date: 8/3/2010, 2/22/2011; PDUFA date: 6/3/2011
Review Priority:	Standard (10-month)
Statistical Branch:	CBER/OBE/DB/TEB (HFM-219)
Primary Statistical Reviewer:	Shiowjen Lee, Ph.D.
Concurring Reviewer (1):	Jessica Kim, Ph.D., Team Leader/ Acting Chief Therapeutics Evaluation Branch (HFM-219)
Medical Office/Division:	CBER/OBRR/DH/CRB
Clinical Reviewer(s):	Larry Landow, MD (HFM-392)
Project Manager:	Crystal Allard (HFM-380)

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1. EXECUTIVE SUMMARY

Sponsor's proposed product is Kedbumin which is manufactured from albumin paste supplied ----------(b)(4)----------. The raw material is obtained from Source Plasma that is collected in licensed U.S. plasmapheresis centers. The proposed product intends to treat conditions including hypovolemia, hypoalbuminemia, prevention of central volume depletion, ovarian hyperstimulation syndrome (OHSS), adult respiratory distress syndrome (ARDS), burns, hemodialysis, and as priming fluids in cardiopulmonary bypass procedures. The route of administration is intravenous (IV). Since the proposed product is made from albumin paste supplied ----------(b)(4)----------, the sponsor provides facility information and validation results in the current Biologic License Application (BLA). There are no new clinical trials conducted for this BLA.

This reviewer has been requested by CMC (Chemistry, Manufacturing and Control) reviewer to review the analytical procedure applied for the comparison of two of the main international standards used to test for the quantitative determination of the ----------(b)(4)----------. From statistical perspective, sponsor's way of equivalence evaluation is inappropriate for the following reasons:

- The two standards are compared based on general hypotheses of H_o: two standards are not different vs. H_1: two standards are different.
- A p-value greater than 0.05 (or fail to reject H_o) does not imply that the two standards are equivalent. Failing to reject H_o could be due to a large variation resulting from a sloppy conduct of testing or could be due to an inadequate data size.

To demonstrate the equivalence of two standards, a properly pre-specified error margin (or equivalence margin) should be used for the assessment. Though sponsor's way of equivalence evaluation of the two standards is inappropriate from statistical perspective, the final determination ultimately depends on the assessment from CMC's perspective.

1.1 Conclusions and Recommendations

This reviewer defers to the product/CMC reviewer and reviewer from Office of Compliance and Biologic Quality (OCBQ) for comments on the evaluation regarding facility issues; while to the clinical reviewer for comments on any clinically relevant safety assessment on the submitted post-marketing datasets which are summarized in this review memo.

1.2 Brief Overview of Clinical Studies

There are no new clinical trials conducted for this submission.

1.3 Major Statistical Issues and Findings

There are no new clinical trials conducted for this submission. No statistical issues have been identified.

2. INTRODUCTION

2.1 Overview

The proposed product is Kedbumin which is manufactured by the sponsor from albumin paste supplied ----------(b)(4)----------. The raw material is obtained from Source Plasma that is collected in licensed U.S. plasmapheresis centers. Albumin plays a role in stabilizing extracellular fluid volume and it is a carrier protein for steroids, fatty acids hormones, enzymes, drugs and toxins. The proposed product intends to treat conditions including hypovolemia, hypoalbuminemia, prevention of central volume depletion, ovarian hyperstimulation syndrome (OHSS), adult respiratory distress syndrome (ARDS), burns, hemodialysis, and as priming fluids in cardiopulmonary bypass procedures. The route of administration is intravenous (IV).

The following gives a summary of chronological order of communications between the FDA and the sponsor regarding the proposed product.

- A Pre-IND meeting was held on 3/26/2009.
  a. The sponsor (meeting question #3) did not plan to conduct new clinical trials prior to filing the BLA, as the intention for the licensing of the product is to be based on
     - The documented safety history of use of albumin (from 1 January 2002 to 30 June 2008, ---(b)(4)--- were distributed in Europe; assuming an average dose of 40 g, approximately --(b)(4)-- doses were administered during the reference period) and
     - Medical literature that supports the clinical safety of albumin for the indication proposed by the sponsor.

     The FDA concurred at the pre-IND meeting that no new clinical trials are needed with the caveat that the sponsor submits its post-marketing safety database at the time of filing. The FDA indicated however new data from adequate and well-controlled clinical trials would be required if the sponsor proposes indications other than those approved for licensed albumin products.

  b. Since the proposed product is manufactured from albumin paste supplied ----------(b)(4)----------, a number of facility issues were discussed. Additionally, FDA encouraged the sponsor to request a Pre-BLA meeting with Office of Compliance and Biologic Quality (OCBQ) to discuss the issues raised at the Pre-IND meeting.

- A Pre-BLA meeting was held on 9/14/2009. The sponsor discussed facility issues and validation approaches with the FDA reviewers from CMC and OCBQ.

As a result, sponsor's BLA submission (STN125384/0) includes information regarding facility issues and validation results for CMC and OCBQ; summary of safety and efficacy results from literatures regarding albumin and post-marketing safety data sets.

2.2 Data Sources

Data sources include sponsor's submission (STN125384/0) in papers, electronic post-marketing SAS datasets and sponsor's responses to FDA requests (BLA125384/0/8, receipt dated 2/22/2011).

3. STATISTICAL EVALUATION

There are no new clinical trials conducted for this BLA.

3.1 Evaluation of Efficacy

Not applicable.

Study Design and Endpoints

Not applicable.

Patient Disposition, Demographic and Baseline Characteristics

Not applicable.

Statistical Methodologies

Not applicable.

Results and Conclusions

Not applicable.

3.2 Evaluation of Safety

There are no new clinical trials conducted for the BLA. The sponsor in the BLA submitted post-marketing data of Uman Albumin that has been marketed by the sponsor in Italy and several other countries. The reported post-marketing data cover the period from January 1, 2002 to March 31, 2010. The adverse event listing extracted from the submitted SAS dataset is in Appendix 1 of this review. The following gives a descriptive summary of the data:

- A total of 13 patients (9 males and 4 females) reported 26 adverse event reactions. The age of patients ranged from 8 to 84 years old with an average of 60 years.
- One death occurred. The sponsor evaluated that the events occurred to the patient were unlikely related to Uman Albumin.
- Among the 26 adverse events, a total of 20 events (77%) were classified as possibly or probably related to the drug product; 5 (19%) were classified as unlikely related; and 1 (4%) was unclassifiable.
- Of the 20 events possibly or probably related to the drug product, 7 were classified as serious, 12 as non-serious, and 1 as not-defined.

This reviewer defers to the clinical reviewer for comments on any clinically relevant safety assessment on the submitted post-marketing datasets.

3.3 Gender, Race, Age and Other Special/Subgroup Populations

Not applicable.

3.4 Drug Product Review

This reviewer has been requested by CMC reviewer, Dr. Wayne Hicks, to review the analytical procedure applied for the comparison of two of the main international standards used to test for the

quantitative determination of the ----------(b)(4)----------. The sponsor Kedrion uses the ----------(b)(4)----------. The standard towards which the sponsor intends to compare is the "Reference ----------(b)(4)----------" provided by (b)(4). The CMC reviewer's question is whether the two standards are *equivalent* based on the data summary submitted in Module 3.2.P.

----------(b)(4)----------

- ----------(b)(4)----------.
- ----------(b)(4)----------.

----------(b)(4)----------

According to the sponsor, the concentration of (b)(4) in the sample is calculated by the comparison with the reference preparation, titred in IU/mL, using linear regression. The two standards were compared during three independent analytical sessions. Sponsor's summary of the regression analysis for the comparison of the two standards is listed in their Table P.5-21 (page 42 of 83 of Module 3.2.P) and is shown in the following:

Parameter	**Acceptance criteria**	**Results**		
Slope comparison	$p \geq 0.05$	1st	2nd	3rd
		p = 0.460	p = 0.754	p = 0.647
y-intercept comparison	$p \geq 0.05$	1st	2nd	3rd
		p = 0.126	p = 0.903	p = 0.680
Global test of comparison	$p \geq 0.05$	1st	2nd	3rd
		p = 0.209	p = 0.927	p = 0.408
Sponsor's Table P.5-21 on page 42 of 83, Module 2.3.P.				

As the resulting p values are all greater than 0.05, the sponsor concludes that the EDQM and CBER standards are equivalent and therefore they can be used without distinction for the measurement of (b)(4).

This reviewer disagree sponsor's equivalence assessment from statistical perspective for the following reasons:

- The results shown in the table appear to compare the two standards with general hypotheses of H_o: two standards are not different vs. H_1: two standards are different.
- A p-value greater than 0.05 (or fail to reject H_o) does not imply that the two standards are equivalent. Failing to reject H_o could be due to a large variation resulting from a sloppy conduct of testing or could be due to an inadequate data size.

From a statistical perspective, a properly pre-specified error margin (or equivalence margin) should be used for the equivalence assessment of the two standards.

The FDA requested the sponsor to provide a pre-specified margin for the equivalence testing (dated 1/20/2011). The sponsor's response (BLA125384/0/8, receipt dated 2/22/2011) indicates that they did not pre-specify an equivalence margin for the assessment. They cite three references and state that their assessment based on the comparison of regression lines is a common practice. The overall test for coincidence reported in Table P.5-21 does not allow rejecting the null hypothesis of coincidence between the two regression lines based on the two standards. They state that the two regression lines do not differ significantly and therefore can be accepted to be coincidence of the two standards.

This reviewer disagree sponsor's assessment due to reasons stated previously from statistical perspective. Having said that, however, whether the two standards are equivalent or not ultimately depend on the assessment from CMC's perspective. The CBER CMC reviewer decided to accept that the two standards are considered to be equivalent from their experiences (see attached e-mail in Appendix 2).

4. SUMMARY AND CONCLUSIONS

4.1 Statistical Issues and Collective Evidence

This reviewer has been requested by CMC reviewer to review the analytical procedure applied for the comparison of two of the main international standards used to test for the quantitative determination of the ----------(b)(4)----------. From statistical perspective, sponsor's way of equivalence evaluation is inappropriate for the following reasons:

- The two standards are compared based on general hypotheses of H_o: two standards are not different vs. H_1: two standards are different.
- A p-value greater than 0.05 (or fail to reject H_o) does not imply that the two standards are equivalent. Failing to reject H_o could be due to a large variation resulting from a sloppy conduct of testing or could be due to an inadequate data size.

To demonstrate the equivalence of two standards, a properly pre-specified error margin (or equivalence margin) should be used for the assessment.

4.2 Conclusions and Recommendations

Though sponsor's way of equivalence evaluation of the two standards is inappropriate from statistical perspective, the final determination ultimately depends on the assessment from CMC's perspective. This reviewer defers to the CMC reviewer for the final decision.

APPENDICES

Appendix 1. Adverse Event Listing based on Post-Marketing Data from January 1, 2002 to March 31, 2010

Identification Number	Country	Sex/Age	Reaction Descrip.	Onset Date	Admin. Date start	Outcome	Causality Assessment at the Time of Reporting	Causality Assessment after Revision
IT-KEDRION-2002009	Italy	M/45	Hypotonia	06/26/2002	06/26/2002	Recovered	Non serious, Unexpected, Possibly related	Non serious, Unexpected, Possibly related
IT-KEDRION-2002010	Italy	M/61	Pyrexia	10/18/2002	10/18/2002	Recovered	Serious, Expected	Serious, Expected, Unclassifiable
IT-KEDRION-2003004	Italy	F/77	Erythema diff.	02/10/2003	02/10/2003	Recovered	Not defined, Expected	Not defined, Unexpected, Probably related
IT-KEDRION-2004013	Italy	F/77	Dyspnoea	06/11/2004	06/09/2004	Fatal	Serious	Serious, Unexpected, Unlikely related
IT-KEDRION-2004013	Italy	F/77	Hypoxia	06/11/2004	06/09/2004	Fatal	Serious	Serious, Unexpected, Unlikely related
IT-KEDRION-2004013	Italy	F/77	Multi-organ fail	06/11/2004	06/09/2004	Fatal	Serious	Serious, Unexpected, Unlikely related
IT-KEDRION-2004013	Italy	F/77	Leukocytosis	06/11/2004	06/09/2004	Fatal	Serious	Serious, Unexpected, Unlikely related
IT-KEDRION-2004013	Italy	F/77	Acute renal fail	06/11/2004	06/09/2004	Fatal	Serious	Serious, Unexpected, Unlikely related
IT-KEDRION-2006002	Italy	F/80	Urticaria	01/16/2006	01/16/2006	Recovered	Non serious	Non serious, Expected, Probably related
IT-KEDRION-2006002	Italy	F/80	Face Oedema	01/16/2006	01/16/2006	Recovered	Non serious	Non serious, Unexpected, Possibly related
IT-KEDRION-2006002	Italy	F/80	Palatal Oedema	01/16/2006	01/16/2006	Recovered	Non serious	Non serious, Unexpected, Possibly related
IT-KEDRION- 2006008	Italy	M/8	Cough	06/15/2006	06/15/2006	Recovered	Non serious, Unexpected	Non serious, Unexpected, Possibly related
IT-KEDRION- 2006008	Italy	M/8	Inj. site urticaria	06/15/2006	06/15/2006	Recovered	Non serious, Unexpected	Non serious, Expected, Probably related
IT-KEDRION- 2007029	Italy	M/48	Lip Oedema	08/28/2007	08/28/2007	Unknown	Non serious, Unexpected	Non serious, Unexpected, Possibly related
IT-KEDRION- 2007029	Italy	M/48	Pruritus	08/28/2007	08/28/2007	Unknown	Non serious, Unexpected	Non serious, Expected, Possibly related
IT-KEDRION- 2007033	Italy	F/82	Cyanosis	11/12/2007	10/16/2007	Recovered	Serious, Unexpected	Serious, Unexpected, Probably related
IT-KEDRION- 2007033	Italy	F/82	Pyrexia	11/12/2007	10/16/2007	Recovered	Serious, Unexpected	Serious, Expected, Probably related
IT-KEDRION- 2007033	Italy	F/82	Stridor	11/12/2007	10/16/2007	Recovered	Serious, Unexpected	Serious, Unexpected, Probably related
IT-KEDRION- 2007033	Italy	F/82	Tremor	11/12/2007	10/16/2007	Recovered	Serious, Unexpected	Serious, Unexpected, Probably related
IT-KEDRION-2008005	Italy	M/43	Urticaria	02/18/2008	02/18/2008	Recovered	Non serious	Non serious, Expected, Possibly related
IT-KEDRION- 2008007	Italy	M/43	Urticaria	03/04/2008	03/04/2008	Recovered	Non serious	Non serious, Expected, Possibly related
IT-KEDRION- 2008009	Italy	M/66	Chills	08/08/2009	08/08/2009	Recovered	Non serious	Non serious, Unexpected, Possibly related
IT-KEDRION- 2008009	Italy	M/66	Pyrexia	08/08/2009	08/08/2009	Recovered	Non serious	Non serious, Expected, Probably related
IT-KEDRION-2009012	Italy	M/71	Anaphylactic	08/31/2009	08/31/2009	Recovered	Serious, Expected	Serious, Expected, Probably related
IT-KEDRION-2009044	Italy	M/84	Malaise	11/14/2009	11/14/2009	Unknown	Serious	Serious, Unexpected, Probably related
IT-KEDRION-2009044	Italy	M/84	Tremor	11/14/2009	11/14/2009	Unknown	Serious	Serious, Unexpected, Probably related

Appendix 2.

From: Hicks, Wayne
Sent: Tuesday, April 26, 2011 10:18 AM
To: Lee, Shiowjen
Subject: RE: Kedrion (b)(4) (BLA125384) - Equivalence of two standards

Hi Shiojen,
Thanks for getting back to me. You know there are some things to learn as a new reviewer, which I am. I learned from Yiping that finding a new standard to replace ----(b)(4)---- standard has been going on for ~15 years. A conversation with a previous, now retired CMC albumin reviewer who had worked on this issue for ~7 years let me know that I could accept these two standards as equivalent. and led me to some references.
I have decided to accept their use of the ------(b)(4)------ as an equivalent.

Thanks again,
Wayne

From: Lee, Shiowjen
Sent: Tuesday, April 26, 2011 9:04 AM
To: Hicks, Wayne
Cc: Kim, Jessica; Jia, Yiping; Allard, Crystal
Subject: Kedrion (b)(4) (BLA125384) - Equivalence of two standards

Just to check back with you if the sponsor gets back to us regarding results of their equivalence claim of two standards (i.e., (b)(4) standard and their in-house standard).
Per Crystal, the deadline of final review memo to EDR is 5/13. I plan to complete the final review and send it for supervisor's concurrence next two weeks.
Please let me know once you hear from the sponsor.

Thanks much. Shiowjen

From: Hicks, Wayne
Sent: Monday, April 04, 2011 2:23 PM
To: Lee, Shiowjen
Subject: RE: Kedrion (b)(4)

Hi Shiowjen,
Thanks for the quick response.
----(b)(4)---- and -----(b)(4)---- are the (b)(4) standard and the (b)(4) standard respectively.

Wayne

From: Lee, Shiowjen
Sent: Monday, April 04, 2011 1:54 PM
To: Hicks, Wayne
Subject: RE: Kedrion (b)(4)

1. Regarding "----*(b)(4)*----, *and* -----*(b)(4)*-----" in the draft question to the sponsor, I am not sure what these are. Are they the "standards"?
2. Regarding the question you asked "*If the sponsor returns the requested data and it is determined that there is a sufficient discrepancy between the (b)(4) standard and the (b)(4) standard, do you have a suggested course of action?*" - I don't have a suggested course of action. If there is a sufficient discrepancy between the two standards from CMC's perspective, the sponsor should be asked to address the issue. Please let me know if I need to be involved in a discussion.

Thanks.

From: Hicks, Wayne
Sent: Monday, April 04, 2011 1:26 PM
To: Lee, Shiowjen
Subject: Kedrion (b)(4)

Hi Shiowjen,
I have pasted below the question regarding equivalence testing of the (b)(4) standards below. Please let me know if the phrasing accurately reflect your meaning. I also have a question for you. If the sponsor returns the requested data and it is determined that there is a sufficient discrepancy between the (b)(4) standard and the (b)(4) standard, do you have a suggested course of action?

The statistical hypotheses that the sponsor is testing is different from the "equivalence" concept. Additional data will need to be provided to establish equivalence between the (b)(4) standard and the (b)(4) standard. Please provide plots of the two standards, ----(b)(4)----, and -----(b)(4)----- on the same graph. A 95% confidence interval for the difference of the two linear regression plots should be obtained.

Thanks,
Wayne

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