

UNITED STATES PUBLIC HEALTH SERVICE
CENTER FOR BIOLOGICS EVALUATION AND RESEARCH

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INTERNAL MEMORANDUM

DATE: Jan 31, 2011

FROM: Jan Simak, Ph.D.
Visiting Scientist, Laboratory of Cellular Hematology

THROUGH: Jaroslav Vostal, M.D., Ph.D.
Chief, Laboratory of Cellular Hematology

TO: Iliana Valencia
Regulatory Project Manager

SUBJECT: Midcycle memorandum – revision of the original memo of Nov 8, 2010

Submission type: NDA
BN 090067

Product Name: Isoplate Solution in the 500 mL EXCEL Container

Applicant/Manufacturing Site: B. Braun Medical Inc., Irvine, CA

CBER Rec. Date: July 14, 2010

Conclusion and Recommendation:

Following comments and comments from other review team members (CDER consult CMC review, OBRR pharm/tox review, labeling review, stat. review) should be communicated in the CR letter to the sponsor. No PMR study request should be communicated at this time.

Letter Ready Comments:

Product Development Rationale

1) You stated in the paragraph 2.5.1. that advantages of storing hyperconcentrated platelets in PAS include reduced adverse transfusion reactions, facilitated ABO- incompatible transfusions, and availability of additional plasma for other purposes. Please provide all available specific clinical data to support the first two claims.

Protocol II: In Vitro Platelet Quality Study

2) The Protocol II in vitro study met its primary endpoint of pH > 6.2, but failed in one secondary endpoint: the surface P-selectin expression, which is more than 20% higher in the test group (22± 15.4 %) compared to control (15.1±9.1%).

FDA believes that high P-selectin expression (> 20% higher compared to control) on 5 day Isoplate stored platelets is a significant finding that may have clinical consequences. Please comment.

3) The Individual Study Information (1.13.8) of your IND13684/27 Annual Report shows that high numbers of subjects did not complete the study in Protocol II ,(e.g. at Hoxworth site 12 subjects of 25 enrolled (48%) did not complete the study). With such high rate of subjects not completing the study, validity of submitted results is highly compromised. Please explain the discrepancy in the rate of subjects not completing the study between participating study sites and provide detailed justification for each individual case which did not complete the Protocol II study.

Protocol III: In Vivo Platelet Study

4) FDA has a serious concern about validity of your results from the Protocol III In Vivo Platelet Study. In the paragraph 5.3.5.1.16.2.1 Discontinued Subjects, you stated that fifteen subjects from the Yale site were excluded from analysis in Protocol III: *In Vivo* Platelet Study. For 11 evaluated subjects at the Yale clinical site 28 subjects were enrolled, 2 of them did not meet the inclusion criteria and 15 subjects were excluded from evaluation for variety of reasons. In some cases, the justification for exclusion like “low day 5 pH for test platelets” –(b)(6)-, “radiolabel anomalies” -----(b)(6)-----, or “isotope not received” (b)(6), are not acceptable. In contrast, there was no subject exclusion from analysis at the Dartmouth clinical site, which reported only 3 volunteer screening failures. The extremely high exclusion rate at the Yale clinical site is not acceptable. Dramatic difference in exclusion rate between Yale and Dartmouth clinical sites demonstrates that the study quality was not equivalent at these two sites. In addition, exclusion of 15 subjects at the Yale site may represent a bias in statistical evaluation of results. Please provide additional data on a group of 12 donors evaluated with the In Vivo Platelet Study with the same design as in the Protocol III and performed at a third independent clinical site.

Trima device modification

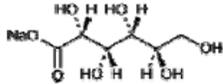
5) Please note that the eventual NDA approval will also depend on the concurrent clearance of the 510(k) submission for modification of the Trima device (Caridian) for the collection of hyperconcentrated platelets.

Background & Summary

The Isoplate Solution is identical to the Isolyte[®] S, pH 7.4 (Multi-Electrolyte Injection) is a FDA approved sterile, nonpyrogenic intravenous injection packaged in B. Braun's EXCEL[®] Container and approved, as of September 29, 1989 (ANDA 19-696), for the following indication: For use in adults as a source of electrolytes and water for hydration, and as an alkalinizing agent.

The company performed in vitro and in vivo studies under IND 13684. So far 28 Amendments of this IND were reviewed and FDA comments communicated to the sponsor. See the review memos for IND 13684 for detailed information. The new indication of the Isolyte is as follows: Platelet additive solution for the storage of hyperconcentrated platelets. The sponsor submitted a new proprietary name of the product "Isoplate".

Isolyte S has the following approved formulation:

Ingredients	Formula	Amount (Each 100 mL contains)
ACTIVE INGREDIENTS (electrolytes)		
Sodium Chloride USP	NaCl	0.53g
Sodium Acetate Trihydrate USP	C ₂ H ₃ NaO ₂ ·3H ₂ O	0.37g
Potassium Chloride USP	KCl	0.037g
Magnesium Chloride Hexahydrate USP	MgCl ₂ ·6H ₂ O	0.03g
Dibasic Sodium Phosphate Heptahydrate USP	Na ₂ HPO ₄ ·7H ₂ O	0.012g
Monobasic Potassium Phosphate NF	K ₂ HPO ₄	0.00082g
Sodium Gluconate USP		0.5g
INACTIVE INGREDIENTS		
Water for Injection USP	H ₂ O	q.s.
Glacial Acetic Acid USP	C ₂ H ₄ O ₂	adjustment for pH
Sodium Hydroxide NF	NaCl	adjustment for pH

Isoplate Solution Indication for Use

Indicated as a platelet additive solution for the storage of leukoreduced hyperconcentrated apheresis platelets.

Clinical Studies

The *In Vivo* platelet survival/recovery study of Isoplate stored platelets (Protocol III) showed satisfactory results, however, the study had extremely high exclusion rate (see the

FDA comments). Based on the stated insufficiencies of your Protocol III In Vivo Platelet Study, with continuing concern on recovery and survival of the Isoplate stored platelets, FDA may request evaluation of CCI as a part of the required postmarked study.

The *In Vitro* platelet quality study (Protocol II) met the primary endpoint of pH > 6.2, but failed in one secondary endpoint, the surface P-selectin expression, which is more than 20% higher in the test group (22± 15.4 %) compared to control (15.1± 9.1%). We believe that high P-selectin expression (> 20% higher compared to control) on 5 day Isolyte stored platelets is a significant finding that may have clinical consequences. Therefore, we have informed the sponsor (CRMTS #7147, Sept. 9, 2009) that to assure clinical safety of the product, a postmarket study focused on platelet transfusion adverse events may be required. The Individual Study Information (1.13.8) of your IND13684/27 Annual Report shows high numbers of subjects not completing the study in Protocol II, e.g. at Hoxworth site 12 subjects of 25 enrolled (48% !) did not complete the study. With such high rate of subjects not completing the study, validity of submitted results is highly compromised.

NDA review team

Review Discipline	Reviewer Name
Regulatory	Iliana Valencia (OBRR/DBA/RPMB)
Clinical	Jan Simak (OBRR/DH/LCH)
Pharmacology	Yolanda Branch (OBRR/DH/
Statistical	Chinying Wang (OBE/DB/TEB)
CMC/CDER	Minerva Hughes (OPS/ONDQA/NDQAII/Branch IV)
DMPQ	Nawab Siddiqui (OCBQ/DMPQ/BII)
Labeling	Lore Fields (OBRR/DBA/BPB)
BIMO	Anthony Hopkins (OCBQ/DIS/BMB)
Epidemiology	Faith Barash (OBE/DE/TBSB)
PNR Review	Catherine Miller (OCBQ/DCM/APLB)

Review progress

Fileability: Yes, the application was found sufficiently complete to permit a substantive review. The review classification for this application is Standard. Therefore, the user fee goal date is April 14, 2011.

PREA: No, this application similarly to BN080041 does not trigger PREA (21 U.S.C. 355c) requirements because it does not include new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration. (email from Nisha Jain of 6/29/2010)

BIMO: Clinical Investigator Inspections of two sites (Drs. Dumont, Snyder) requested (8/24/2010) The Bioresearch Monitoring Branch issued inspection requests on August 24, 2010 covering two Protocol III (*In vivo* Platelet Study) clinical investigators and study sites: Lebanon, New Hampshire - 15 Subjects; New Haven, Connecticut - 28 subjects - inspection scheduled to begin during week of November 8-12, 2010. The above inspections are pending completion. The requested completion date for each inspection was November 22, 2010. The two BIMO inspections both concluded. No Form FDA 483, *Inspectional Observations*, was issued to either of the inspected clinical investigators. Both of the inspection reports are under review (Antony Hawkins Memo 11/8/10, email Jan 21, 2011).

DMPQ: The production facility has been recently inspected. Whether additional inspection is required will be decided by DMPQ reviewer. No outstanding DMPQ issue identified (Nawab Siddiqui email 11/8/10)

PNR: Proposed proprietary name was reviewed and found acceptable (memo from Catherine Miller of 8/11/2010)

CDER consult CMC review: Initial quality assessment performed, comments included the filing letter (memo from Minerva Hughes of 8/6/2010). Midcycle review memo of Nov 10, 2010 provided with comments to sponsor.

Pharm./tox review: Comments included in the filing letter (memo from Yolanda Branch of 8/9/2010). Midcycle review memo provided (11/10/2010) repeating comments communicated in the filing letter.

Epidemiology: Midcycle review memo provided (11/18/2010) with comments concerning PMR study.

Labeling : Midcycle review memo with comments provided by Lore Fields on 01/18/2011

Stat. review:

For both studies conducted under Protocols II and III, sponsor should provide the computed confidence intervals to determine if the acceptable criteria are met. In addition, sponsor should include the computer programs and datasets used in your analyses (Jean Wang Memo 11/5/10)

Clinical/ Scientific lead review

See the letter ready comments above.

FDA comments included in the filing letter (from CMC and pharm/tox. reviewers):

1. DMF letter of authorizations should reference the DMF number, the specific item being referenced, and the date of the submission for that item. Provide revised DMF letter of authorizations for the ---(b)(4)-- Sodium Chloride USP and Potassium Chloride USP drug substances. The Agency is unable to review the referenced DMFs in support of your NDA in the absence of an adequate letter of authorization.
2. It is noted that B. Braun Medical Inc. conducted the chemical, biological and physical functional testing on the Excel® plastic container in accordance with the USP requirements and additional B. Braun tests. The product's proposed indication is for platelet storage in the following ratio: 65% Isoplate solution and 35% plasma. It is stated in the label that Isoplate solution will not be used for direct infusion. However, please note Isoplate will be directly infused into patients as a component of apheresis platelet products. This is of concern because there can be an accumulation of extractable/leachable beyond the acceptable range with multiple use (doses) of product. The levels of each extractable/leachable need to be assessed at the maximum daily dose of the combination product to ensure safety. Please see the comments below:
 - a. Please note the toxicological evaluation of leachables/extractables from the plastic should be based on animal studies that defined a toxic dose of an IV administered compound and on the anticipated clinical application of the product. Please identify each extractable/leachable and calculate their levels at the maximum clinical dose, to ensure that it is within an acceptable range.
 - b. Please electronically submit all preclinical (toxicological) studies that are cross referenced in order to complete the file.