

UNITED STATES PUBLIC HEALTH SERVICE
CENTER FOR BIOLOGICS EVALUATION AND RESEARCH

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INTERNAL MEMORANDUM

DATE: Feb 15, 2012

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

Submission type: NDA
BN 090067/0011 Amendment- Response to Non-
Approval Letter dated Feb 4, 2011.

Product Name: Isoplate Solution in the 500 mL EXCEL Container

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

CBER Rec. Date: 11/10/2011

Conclusion and Recommendation:

Comments from all discipline reviewers should be communicated to the sponsor.

Letter ready comments to the response to clinical questions.

1. Response is satisfactory

2. Response is not satisfactory. FDA considers the high P-selectin expression (> 20% higher compared to control) on five day Isoplate stored platelets as a significant finding which could have clinical consequences. Possible adverse effects of Isoplate stored platelets may only be investigated in a large scale clinical study. Therefore you will be

required to conduct a post-market clinical study to assess potential adverse effects of Isoplate stored platelets.

3. Response is satisfactory

4. Response is satisfactory

5. Response is satisfactory, please submit the 510(k) submission for Trima Accel system for the collection of hyperconcentrated platelets. Please note that the NDA approval is dependent on 510(k) clearance of Trima Accel system for the collection of hyperconcentrated platelets.

Background Summary:

CBER issued a Non-Approval Letter of BN 090067 on Feb. 4, 2011.

CBER received on November 10, 2011, resubmission of the NDA and considers this a complete, class 2 response to February 4, 2011, Action Letter. Therefore, the goal date is May 11, 2012.

Submission Content:

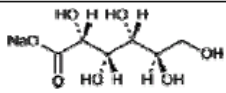
In support of the complete response, the following information is enclosed:

1. In Module 1 are enclosed- the 356h form, cover letter, and response to non-approval letter, and FDA non-approval letter dated February 4, 2011.
2. In Module 2, 2.7.6 Synopses of Individual Studies.
3. In Module 1.14.1, the revised container label and amended Physician's Labeling Reference (PLR).
4. In Module 3.2.S.6, details on the container closure system (i.e., materials of composition, suitability, and quality control) for the following drug substances: sodium chloride, sodium acetate trihydrate, potassium chloride, magnesium chloride, sodium phosphate dibasic heptahydrate, and monobasic potassium phosphate.
5. In Module 5.3.5.1 are enclosed Protocol II and III Clinical Report and statistical calculations.
6. In Module 5.3.5.1.25.3 are enclosed the raw data and calculations for Protocol II and III Clinical Report in SAS, .xpt, and Excel format.

Drug description

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.

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.

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)

Review Discipline	Reviewer Name
BIMO	Anthony Hawkins (OCBQ/DIS/BMB)
Epidemiology	Faith Barash (OBE/DE/TBSB)
PNR Review	Dana Martin (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 May 11, 2012. NO OUTSTANDING ISSUE

PREA: No, as assessed for the original submission, 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)
NO OUTSTANDING ISSUE

BIMO: Clinical Investigator Inspection of the additional clinical site Dr. Cancelas-Perez, Hoxworth Blood Center was performed, final report is pending, however, preliminary results indicate no action required. Midcycle memo from Anthony Hawkins received 2/15/2012. NO OUTSTANDING ISSUE

DMPQ: Company should submit the Categorical exclusion under 21 CFR 25.31(a). They have submitted Categorical exclusion under 21 CFR 25.31(J). This does not apply to this NDA. No other issues for the response to CR letter. (email from Nawab Siddiqui 11/18/2011)

Epidemiology: Pharmacovigilance Plan will be requested (memo with letter ready comments from Faith Barash 1/30/12), Sponsor requested type B meeting on Feb 8/2012 to discuss this issue.

CDER consult CMC review: The Applicant's response is complete for filing from the CMC (i.e., CDER consulted CMC) perspective. Of note, all review comments regarding labeling from the CDER consult final discipline review were not conveyed to the applicant in the CR letter (email from Minerva Hughes of 2/1/2012). Outstanding labeling issues will be resolved by DBA labeling reviewer. **Midcycle memo pending**

Pharm./tox review: The nonclinical responses to CR letter were sufficient.
Midcycle memo received from Yolanda Branch 2/15/2012. NO OUTSTANDING ISSUE

Labeling: **Midcycle memo pending**

Satistics: Response to stat comment (item 6) is satisfactory. Midcycle memo from Chinying Wang received on 2/15/2012. NO OUTSTANDING ISSUE

PNR: PNR reevaluation will be performed within 90 days of approval.

Review of the sponsor's responses to clinical comments

Product Development Rationale:

FDA comment:

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.

Sponsor's response:

The language in paragraph 2.5.1 referenced by FDA above was provided as 'Scientific Background' supported by literature. The literature referenced indicates that PAS stored platelets may lower febrile transfusion reactions and allergic reactions. B. Braun and CaridianBCT do not intend to make marketing claims about Isoplate stored platelets related to reduced adverse reactions unless there is clinical (post market data) that supports the direct claim at which time this information will be added to the labeling.

Reviewer's comment: Response is satisfactory

Protocol II: In Vitro Platelet Quality Study:

FDA comment:

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 the control group (15.1 ± 9.1 %). FDA is concerned regarding high P-selectin expression (> 20% higher compared to control) on five day Isoplate stored platelets. This finding could have clinical consequences. Please comment.

Sponsor's response:

As discussed with the Agency in the meeting CRMTS #8012 on June 30, 2011 there is no indication from the literature that the P-selectin levels in the range measured for Isoplate-

stored platelets have negative clinical consequences. Data from the literature was provided in CRMTS #8012 and shows that P-selectin values for Isoplate-stored platelets were in range of commonly transfused platelet products. Subsequent to the June 30, 2011 meeting, analysis of the *in vivo* data demonstrates no correlation between P-selectin and clinical outcomes. The *in vivo* radio label recovery and survival data for Isoplate-stored platelets met the acceptance criteria indicating that this product is acceptable for transfusion. There was no correlation between radiolabel recovery and survival and P-selectin in the *in vivo* study. The R2 values for recovery and survival in comparison to P-selectin were 0.016 and 0.028, respectively. The R2 values were less than 0.1 indicating that there is a no correlation. Please see the clinical report for Protocol III in Module 5.3.5.1 for details. B. Braun added a table of secondary outcomes in the Isoplate Physician's Labeling Reference (PLR), which is similar to Fenwal's Intersol labeling, as a means of public awareness around secondary endpoints that did not meet the 20% non-inferiority margin. The amended PLR is enclosed in Module 1.14.1.3.

Reviewer's comment: Response is not satisfactory. FDA considers the high P-selectin expression (> 20% higher compared to control) on five day Isoplate stored platelets as a significant finding which could have clinical consequences. To study adverse effects, very large sample size is needed and that is not feasible in premarket setting. Possible adverse effects of Isoplate stored platelets may only be investigated in a large scale postmarket study. Therefore FDA should issue PMR for this product. Another argument supporting requirement of a postmarket study is that this is a new type of product.

FDA comment:

3. The Individual Study Information (1.13.8) of your IND 13684/27 Annual Report shows that high numbers of subjects did not complete the study in Protocol II, (at the Hoxworth site 12 subjects of 25 enrolled (48%) did not complete the study). 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.

Sponsor's response:

The circumstances surrounding the subjects excluded from analysis at Hoxworth (HOX), Blood Center of Wisconsin (BCW), and American Red Cross (ARC) were due to common and anticipated issues. The same software version and disposable lots numbers were utilized at all three study sites therefore there were no differences in test articles. HOX assigned subject identification numbers for screen failures; whereas ARC and BCW did not, this accounted for 4 of the 12 exclusions. Screen failures are defined as subjects who signed the informed consent but did not meet the inclusion criteria, disqualifying them from study participation. Screen failures are outside of HOX's control and can vary from site to site and study to study. In addition, HOX experienced a larger number (5 out of 12 of the exclusions) of "incomplete apheresis procedure due to hematoma or infiltration". Hematomas and infiltrations can occur during any apheresis or whole blood donation; they are not unique to the investigational Trima Accel system. Because subjects underwent two apheresis procedures in one day, subjects were connected to the disposable tubing sets via needle stick. Therefore, there was greater potential for more venous access issues such as hematoma or infiltration. These adverse

events could be due to poor phlebotomy, but more likely due to subjects with small or poor veins for the two apheresis procedures. In a normal donation setting, a donor would not donate twice in one day therefore this is an artifact of the study environment only and not the normal use environment.

Table 1 provides a summary of subject enrollment and primary reasons for exclusion. The reasons for exclusion have been organized into common categories.

Table 1 – Protocol II: 100 subjects were enrolled to achieve 66 evaluable paired collections.

Enrollment	HOX	ARC	BCW	Totals
Consented	25	28	47	100
Included Subjects	13	20	33	66
Excluded Subjects	12	8	14	34
Reasons for Excluding Subjects	HOX	ARC	BCW	Totals
1. Signed Consent but failed to show	0	0	8	8
2. Failed to qualify for 1 st apheresis procedure	4	1	4	9
3. Failed to qualify for 2 nd apheresis procedure	1	2	0	3
4. Protocol Deviations resulting in exclusions	1	1	0	2
5. Incomplete apheresis procedure due to operator mis-loading disposable tubing set	1	0	0	1
6. Incomplete apheresis procedure due to draw pressure too low	0	1	0	1
7. Incomplete apheresis procedure due to hematoma or infiltration	5	3	2	10

Reviewer's comment: Response is satisfactory.

Sponsor justified all exclusions. The exclusion rate is very high may be a source of bias in the in vitro study. We would, however, not learn any new significant information from the new study if ordered to repeat. The original 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 the control group (15.1±9.1 %). The way to address this potentially significant finding is to order PMR as specified in the previous comment.

Protocol III: In Vivo Platelet Study:

FDA comment:

4. FDA has a serious concern about 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 II evaluated subjects at the Yale clinical site 28 subjects were enrolled, two of them did not meet the inclusion criteria and 15 subjects were excluded from evaluation for various reasons. The "low day 5 pH for test platelets" (b)(6) should be regarded as a product failure. The frequency of exclusion such as "radiolabel anomalies" ----(b)(6)-----, or "isotope not received" (b)(6), were much higher than those seen in comparable studies. In contrast, there was no subject exclusion from analysis at the Dartmouth clinical site, which reported only three volunteer screening failures. The marked difference in exclusion rates between Yale and Dartmouth clinical sites demonstrates that the study quality was not equivalent at these two sites. The exclusion of 15 subjects at the Yale site may represent a bias in a 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.

Sponsor's response:

In communication from the Agency dated February 4, 2011, FDA requested that the clinical data collected at the Yale study site be excluded from analysis. This study was repeated at a third study site, Hoxworth Blood Center (HOX), to collect an additional N=12 data points for inclusion in analysis. Consequently, all data collected at Yale was excluded from analysis.

The new results met the FDA's acceptance criteria that:

- Test minus 66% Control is equal to or greater than zero with one-sided 97.5% confidence limit for recovery.
- Test minus 58% Control is equal to or greater than zero with one-sided 97.5% confidence limit for survival. Please see the revised clinical report for Protocol III enclosed in Module 5.3.5.1 for details.

Reviewer's comment: Response is satisfactory. The additional in vivo study was performed at HOX site. There were 4 exclusion including 2 screen failures, 1 incomplete collection, and 1 protocol deviation. This is still high exclusion rate but comparable with other clinical sites and therefore the results are acceptable.

FDA comment:

5. Ultimately the NDA approval will also depend on the concurrent clearance of a 510(k) submission for modification of the Trima device (Caridian) for the collection of hyper concentrated platelets.

Sponsor's response: B. Braun and CaridianBCT acknowledge that the NDA approval is dependent on CaridianBCT's Trima Accel system 510(k) for the collection of hyperconcentrated platelets.

CaridianBCT is waiting for the FDA to contact B. Braun requesting the 510(k) be submitted.

Reviewer's comment: Response is satisfactory. Sponsor should be advised to submit the Trima Accel system 510(k) for the collection of hyperconcentrated platelets.