

Complete Response Letter, Isoplate Solution

• DEPARTMENT OF HEALTH & HUMAN SERVICES
Service

Public Health

Food and
Drug Administration

1401 Rockville Pike

Rockville, MD 20852-1448

Our STN: BN090067
B. Braun Medical, Inc.
Attention: Mrs. Susan K. Olinger
901 Marcon Boulevard
Allentown, PA 18109

Dear Mrs. Olinger:

Please refer to your New Drug Application (NDA) dated June 14, 2010, that we received June 14, 2010, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Isoplate Solution, Multi-Electrolyte Injection, magnesium chloride USP 30mg/100mL.

We acknowledge receipt of your amendments dated June 18, 2010, November 11, 2010, and November 16, 2010.

We have completed our review of your application, as amended, and have determined that we cannot approve this application in its present form. We have described our reasons for this action below and, where possible, our recommendations to address these issues.

CLINICAL:

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 ($22 \pm 15.4\%$) compared to the control group ($15.1 \pm 9.1\%$). 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.

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.

Protocol III: In Vivo Platelet Study:

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 11 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)(4) should be regarded as a product failure. The frequency of exclusion such as "radiolabel anomalies" ----(b)(4)-----, or "isotope not received" (b)(4)-, 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.

Trima device modification:

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 hyperconcentrated platelets.

STATISTICAL:

6. For both studies conducted under Protocols II and III, please provide the computed confidence intervals to determine whether the acceptance criteria are met. In addition, please include the computer programs and datasets used in your analyses.

CLINICAL PHARMACOLOGY:

7. 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 combination product (Isoplate and plasma); this is of concern because there can be an accumulation of extractables/leachables 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 that these are within an acceptable range. Please see the comments below:

- a. Please note the toxicological evaluation of extractables/leachables 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.
- c. Please keep labeling (overdose, warnings, precautions, and contraindications) consistent with the FDA approved product Isolyte.

CMC:

8. Provide complete 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. A statement of compliance with the appropriate indirect food contact regulations may be sufficient to establish the safety of the materials used.

9. The draft labels and labeling do not comply with the established name requirements as per 21 CFR 201.10. Submit revised labels and labeling that include the drug's established name, multiple electrolytes injection type I, as defined by the USP monograph.

LABELING:

Package Insert:

10. The labeling should include the ISBT name for product labeling. Please revise the labeling to include the ISBT approved name. Example: Isoplate Solution (next line) Platelet Additive Solution [Insert designation].

11. You have used the following indications for use statement: INDICATIONS AND USAGE: Isoplate Solution is indicated as a platelet additive solution for the storage of leukoreduced hyperconcentrated apheresis platelets collected on CaridianBCT's Trima Accel® System under standard blood banking conditions. Please revise the Indications and Usage statement to the following:

INDICATIONS AND USAGE:

Isoplate Solution is an isotonic solution to replace a portion of the plasma to store Platelet Pheresis, Leukocytes Reduced PAS products collected using a hyperconcentrated collection on CaridianBCT's Trima Accel® System. The solution should never be infused directly to the patient.

Platelet Pheresis, Leukocytes Reduced Platelet Additive Solution [Insert designation] products are stored in a mix of 65% Isoplate and 35% plasma. Platelets in Isoplate Solution can be stored at a concentration range of (b)(4)-2100 x 10⁶/mL for up to 5 days at 20-24 °C with continuous agitation in the [Insert storage bag] container.

12. You have the following under dosage and administration: DOSAGE AND ADMINISTRATION Leukoreduced apheresis platelets are stored in a mix of 65% Isoplate Solution and 35% plasma. Platelets in Isoplate Solution can be stored at a concentration range of (b)(4)-2100 x 10⁶/mL for up to 5 days at 20-24 °C with agitation. Please revise the statement to read:

Dosage and Administration:

Isoplate Solution may only be used with the Trima Accel automated blood cell separator device. For full instructions on the use of Isoplate Solution with the Trima Accel see the Trima Accel Operator's Manual.

[Insert directions on how to connect the solution to the Trima kit]

13. Contraindications: The labeling for the drug approved in CDER under the ANDA has several warnings on usage with certain patient populations. Please clarify why those warnings have not been included in this package insert or supply studies that have changed the warnings.

14. You have the following statement in the Adverse Reactions section: Isoplate Solution is added to leukoreduced hyperconcentrated platelets after the Trima Accel apheresis procedure is complete. It is not for direct intravenous infusion. Isoplate Solution is not expected to cause adverse events other than those normally associated with platelet transfusion.

Please revise the statement to: Isoplate Solution is added to Platelet Pheresis, Leukocytes Reduced PAS products collected using a hyperconcentrated Trima Accel apheresis procedure after completion. It is not for direct intravenous infusion. Isoplate Solution is not expected to cause adverse events other than those normally associated with platelet transfusion.

- You have the following language in the description: Isoplate Solution is indicated as a platelet additive solution for the storage of hyperconcentrated leukoreduced apheresis platelets collected on CaridianBCT's Trima Accel® System under standard blood banking conditions.

Please revise to: Isoplate Solution is indicated as a platelet additive solution for the 5 day storage of Platelet Pheresis, Leukocytes Reduced PAS products collected using a hyperconcentrated collection on CaridianBCT's Trima Accel® System. Platelets in Isoplate Solution can be stored at a concentration range of (b)(4)-2100 x 10⁶/mL for up to 5 days at 20-24 °C with agitation.

16. Clinical Studies, *In Vivo* Study: You state: A paired study was completed to verify that *in vivo* radiolabeled recovery and survival of hyperconcentrated platelets collected on the Trima Accel System, diluted in Isoplate Solution, and stored for five days (Test) meet FDA acceptance criteria in comparison with fresh autologous platelets (Control). Please revise the statement to include that the products are leukocyte reduced.

17. Clinical Studies, *In Vitro* Study: You state: A paired study was completed to verify that *in vitro* platelet quality (functional assays) of hyperconcentrated platelets collected on the Trima Accel System, diluted in Isoplate Solution, and stored for five days (Test) meet FDA acceptance criteria in comparison to plasma-stored platelets (Control). Please revise the statement to include that the products are leukocyte reduced.

Container Label:

18. The labeling should include the ISBT name for product labeling. Please revise the labeling to include the ISBT approved name

SAFETY UPDATE:

When you respond to the above deficiencies, include a safety update as described at 21 CFR 314.50(d)(5)(vi)(b). The safety update should include data from all nonclinical

and clinical studies/trials of the drug under consideration regardless of indication, dosage form, or dose level.

19. Describe in detail any significant changes or findings in the safety profile.

20. When assembling the sections describing discontinuations due to adverse events, serious adverse events, and common adverse events, incorporate new safety data as follows:

- Present new safety data from the studies/clinical trials for the proposed indication using the same format as the original NDA submission.
- Present tabulations of the new safety data combined with the original NDA data.
- Include tables that compare frequencies of adverse events in the original NDA with the retabulated frequencies described in the bullet above.
- For indications other than the proposed indication, provide separate tables for the frequencies of adverse events occurring in clinical trials.

21. Present a retabulation of the reasons for premature trial discontinuation by incorporating the drop-outs from the newly completed trials. Describe any new trends or patterns identified.

22. Provide case report forms and narrative summaries for each patient who died during a clinical trial or who did not complete a trial because of an adverse event. In addition, provide narrative summaries for serious adverse events.

23. Describe any information that suggests a substantial change in the incidence of common, but less serious, adverse events between the new data and the original NDA data.

24. Provide updated exposure information for the clinical studies/trials (e.g., number of subjects, person time).

25. Provide a summary of worldwide experience on the safety of this drug. Include an updated estimate of use for drug marketed in other countries.

26. Provide English translations of current approved foreign labeling not previously submitted.

Within one year after the date of this letter, you are required to resubmit or take other actions available under 21 CFR 314.110. If you do not take one of these actions, we may consider your lack of response a request to withdraw the application under 21 CFR 314.65. You may also request an extension of time in which to resubmit the application. A resubmission must fully address all the deficiencies listed. A partial response to this letter will not be processed as a resubmission and will not start a new review cycle.

Under 21 CFR 314.102(d), you may request a meeting or telephone conference with us to discuss what steps you need to take before the application may be approved. If you wish to have such a meeting, submit your meeting request as described in the FDA's "Guidance for Industry - Formal Meetings Between the FDA and Sponsors or Applicants," May 2009 at:

<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM153222.pdf>.

The drug product may not be legally marketed until you have been notified in writing that this application is approved.

If you have any questions, please contact the Regulatory Project Manager, Iliana Valencia, at
(301) 827-6161.

Sincerely yours,

/s/

Basil Golding, M.D.

Director

Division of Hematology

Office of Blood Research and Review

Center for Biologics

Evaluation and Research