

**Mid-cycle Review Memo for Isoplate
OBE/DE Review for Pharmacovigilance Planning**

NDA BN090067

Sponsor: B. Braun Medical, Inc.

Product: Isoplate Solution

Indication: Platelet additive solution for the storage of leukoreduced hyperconcentrated Apheresis platelets collected on CaridiansBCT Trima Accel® System under standard blood banking conditions.

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I. Introduction

OBE/DE/PVB has completed a review of NDA BN090067, a NDA re-submission for Isoplate Solution. The purpose of this review is to identify potential safety issues that may need to be addressed through post-marketing safety monitoring, studies, or other pharmacovigilance activities, should the product be licensed. Information on the clinical studies and safety data in this review is derived from information presented in the NDA in Clinical Overview, Clinical Summary, Draft Labeling and Reports of Post-marketing Experience. Tables and diagrams and text in italics in this document are copied from the applicant's submission.

II. Product Background

The Isoplate Solution is identical to Isolyte® S, pH 7.4 (Multi-Electrolyte Injection), an 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 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**".

Isoplate

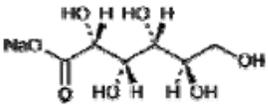
Isoplate Solution is a multi-electrolyte injection composed of the following active drug substances: Sodium Chloride USP, Sodium Acetate Trihydrate USP, Potassium Chloride USP, Magnesium Chloride Hexahydrate USP, Sodium Phosphate Dibasic Heptahydrate USP, Potassium Phosphate Monobasic NF, and Sodium Gluconate USP. *The formulations, manufacturing procedures and sterilization procedures are identical to the approved product, Isolyte S, pH 7.4 (Multi-Electrolyte Injection), ANDA 01969.* According to the sponsor, “*the only difference between the two products is the indication*”. The proposed indication for Isoplate is “*as a platelet additive solution for the storage of leukoreduced hyperconcentrated apheresis platelets collected on CaridiansBCT’s Trima Accel System under standard blood banking conditions*”. “*Isolyte S, pH 7.4 was approved as an intravenous injectable solution in the United States under ANDA 019696 on September 29, 1989, and is commercially distributed in the United States.*” “*Isolyte S is indicated for intravenous injection in adults as a source of electrolytes and water for hydration, and as an alkalinizing agent.*”

The platelet product approved for transfusion in the United States today is standard platelets, collected and stored in plasma for up to five days. Hyperconcentrated platelets are collected in significantly less plasma, diluted, and stored in a platelet additive solution (P.A.S.) for five days. Hyperconcentrated platelets diluted and stored in P.A.S. have been transfused in Europe for over 20 years. Per the sponsor, Advantages to hyperconcentrated platelets in P.A.S. include: reduced adverse transfusion reactions, facilitated ABO incompatible transfusions, and availability of additional plasma for other purposes. The Trima Accel system is routinely used in Europe to collect hyperconcentrated platelets that are diluted and stored in P.A.S. for transfusion.(NDA Section 2.5.1, p. 1)

The composition of Isoplate Solution has a history of successful use as a P.A.S. in Europe. In a study by Rock et al (1991), PlasmaLyte-A (similar in formulation to Isoplate Solution) was used to store hyperconcentrated platelets prepared from whole blood for five days with 10% – 15% plasma carryover. The primary conclusions from this study were:

- *In vitro platelet quality for hyperconcentrated platelets in PlasmaLyte-A was at least as good as platelet quality for standard platelets in plasma.*
- *In vivo radiolabel recovery for platelets stored in PlasmaLyte-A was at least as good as recovery for standard platelets stored in plasma. (NDA Section 2.5.1, p. 1).*

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.

III. Clinical Studies

The clinical development for this drug was to add a new indication to the existing, approved drug product, Isolyte S, pH 7.4 (Multi-Electrolyte Injection), since the safety” of Isolyte S “was proven for intravenous use”(NDA 2.5.1, p.1). CBER accepted studies verifying that platelets stored in Isoplate had similar quality assays to platelets stored in conventional plasma as the clinical studies for this BLA.

Clinical efficacy of Isoplate solution as a platelet additive solution was demonstrated in two clinical trials: *In Vitro Platelet Quality Study* and *In Vivo Platelet Study*. *The In Vitro Platelet Quality Study evaluated the quality of hyperconcentrated platelets collected on the Trima Accel system, Version 6.0, diluted in Isolyte S, and stored for five days (Test) compared to standard apheresis platelets stored in plasma (Control).*

The other study evaluated the in vivo quality of hyperconcentrated platelets collected on the Trima Accel system, Version 6.0, diluted in Isolyte S and stored for five days (Test) compared to fresh platelets prepared from whole blood (Control).

The overall objective of these studies was to demonstrate non-inferiority of the Test product to the currently approved product, standard platelets stored in plasma.

In the *In Vivo* Platelet Quality Study, hyperconcentrated platelet products stored in Isoplate Solution for five days met primary outcomes of platelet recovery and survival compared to fresh autologous platelet controls (NDA 2.5.4, p. 5). However, at one study site (Yale), 17 of the 28 enrolled subjects were excluded from analysis for a variety of reasons (e.g., isotope not received, incomplete apheresis due to infiltration, and radiolabel anomalies). In comparison, only 3 of the 15 subjects enrolled at the second site (Dartmouth) were excluded.

In the *In Vitro* Platelet Quality Study, Hyperconcentrated platelets stored in Isoplate Solution for five days met the acceptance criteria for the primary outcome (pH), and three additional secondary outcomes (ESC, HSR and morphology). P-selectin, a secondary outcome, was higher in the Isoplate stored product and did not meet the statistical acceptance criterion; however, the sponsor notes that P-selectin values for the Test platelets were well within the range of commonly transfused platelet products in the United States (NDA 2.5.4, p. 4).

No patients were directly transfused with Isoplate Solution or platelets stored in Isoplate Solution for either study. The 43 subjects participating in the in vivo study were infused with a small volume of radiolabeled Test and Control platelets to evaluate in vivo radiolabeled recovery and survival. *Platelets were washed during the radiolabeling process, leaving an insignificant carry over of Isoplate solution (NDA 2.7.4.1, p.1).* No adverse reactions were reported in subjects infused with these radiolabeled platelets (BLA Section 1.14, Proposed Label).

In the face to face meeting with the sponsor on September 9, 2009, Office of Blood Research and Review raised a concern that the *high P-Selectin expression noted in the in vitro study is a significant finding that may have clinical consequences. FDA considers P-selectin as a marker of activation indicating that the test platelets were more activated compared to controls. Elevated platelet surface P-selectin may indicate other activation changes which may lead to unexpected clinical adverse events* (NDA, 1.6, CRMTS #7174). It is not known whether this finding might have clinical significance. For this reason, a post-marketing study was requested and agreed to by B. Braun.

Protocol II – In Vitro Platelet Quality Study

Objectives: Verify that *in vitro* platelet quality (functional assays) of hyperconcentrated platelets collected on the Trima Accel system, Version 6.0, diluted in Isolyte S pH 7.4 and stored for 5 days meet FDA requirements in comparison to plasma stored platelets.

Methodology: This was a paired study. Each subject underwent a control, single unit collection and a test single unit collection on the same day, separated by at least 90 minutes. The order was randomized. The products were stored and analyzed after 5 days of storage using a variety of in vitro functional assays.

100 subjects were enrolled in this study resulting in 66 paired evaluable data points.

There were no patients treated in this study.

Safety Results: There were no deaths, serious adverse events, unexpected adverse events, serious device incidents reported in the study. There were 24 adverse expected events typical for apheresis procedures.

Conclusion: Hyperconcentrated platelets collected on the Trima Accel system and stored in Isolyte S for 5 days met the acceptance criteria for pH, ESC, HSR and morphology. While P-selectin expression values did not meet the statistical acceptance criterion, the P-selectin expression on these platelets was within the range of those for commonly transfused platelet products. Isolyte S is an effective platelet additive solution for platelet storage for up to 5 days.

Protocol III – *In Vivo* Platelet Study

Objectives: Verify that autologous, *in vivo* radiolabeled recovery and survival of hyperconcentrated platelets collected on the Trima Accel system, Version 6.0, diluted in Isolyte S pH 7.4, and stored for five days meet FDA requirements in comparison with paired fresh autologous platelets.

Methodology: This was a paired study. Each subject donated a platelet product in the test arm which consisted of a single hyperconcentrated platelet unit collected on Trima Accel Version 6.0, diluted with Isolyte S and stored for 5 days. On day 5, the subject returned to donate platelets in the Control arm, which consisted of fresh platelets prepared from whole blood. On day 5, an aliquot of test platelets was labeled with either Cr 51 or In 111 randomly determined. On day 5, subjects were simultaneously infused with aliquots of radiolabeled, autologous platelets from both the test and control arms. After infusion, multiple samples of blood were drawn from the subject on the same day and up to ten days after infusion to determine radiolabeled recovery and survival of test platelets.

64 subjects were approved in this study to achieve 24 paired evaluable data points. 60 subjects were enrolled in this study to achieve 25 paired evaluable data points for recovery and survival. No patients were treated in this study. The subjects enrolled were representative of the regular donor population.

Safety Results:

There were no deaths, serious adverse events, unexpected adverse events, device incidents reported in this study. There were 15 expected adverse events reported to the study sponsor, which were typical for apheresis procedures as described in the protocol. There were no adverse events reported for the investigational drug, because Isolyte S was not transfused. No adverse events were reported in relation to the infusion of radiolabeled test and control platelets.

Conclusions:

Leukoreduced hyperconcentrated apheresis platelets collected on Trima Accel system, Version 6.0 and stored in Isolyte S for 5 days met the acceptance criteria for radiolabeled recovery and survival. In summary, Isolyte S is an effective platelet additive solution for platelet storage up to 5 days.

IV. Safety Database

Clinical Study Adverse Events

There were no adverse events reported in the *in vivo* or *in vitro* studies, as no subjects were directly transfused with the solution or platelets stored in the solution. The indication is not for direct intravenous infusion.

There were a total of 39 anticipated adverse events reported to the study sponsor for Test and Control apheresis procedures. All adverse events were in association with the apheresis

procedure itself and were anticipated (e.g. citrate reactions, infiltrations, hematomas). There were no deaths, serious adverse events, or unexpected adverse events reported. All adverse events reported were either mild or moderate. The sponsor does not expect platelets stored in Isoplate Solution to cause adverse events other than those normally associated with platelet transfusion.

The following list shows the 15 reported adverse events by subject ID for Dartmouth and Hoxworth.

There were no serious or unanticipated adverse events reported in this study.

Adverse Event Listing – Protocol III: *In Vivo* Platelet Study

Adverse Event Listing – Protocol III: *In Vivo* Platelet Study

The following list shows the 15 reported adverse events by subject ID for Dartmouth and Hoxworth.

There were no serious or unanticipated adverse events reported in this study.

Site Subject ID Event Severity Seriousness

Dartmouth

(8)

- (b)(4)- Citrate Reaction Mild Not Serious

Hoxworth

(7)

- (b)(4)----- Headache -Unrelated Mild Not Serious
- (b)(4)----- Citrate Reaction Mild Not Serious
- (b)(4)----- Citrate Reaction Mild Not Serious
- Menstrual cramps -Unrelated Mild Not Serious
- (b)(4)----- Headache -Unrelated Mild Not Serious
- (b)(4)----- Hurt Hand -Unrelated Mild Not Serious
- (b)(4)----- Citrate Reaction Mild Not Serious

Post-Marketing Experience

Isolyte S’s currently approved indication is for use in adults as an alkalinizing agent and a source of electrolytes and water for hydration. In the past 19 years, there were seven adverse events reported to the sponsor from the United States. Six were non-serious unexpected events (i.e., hyponatremia) and one was a serious unexpected event (anaphylaxis).

According to the sponsor, from 2002 to Feb 2009, there were ---(b)(4)----- units distributed in the US.

Isoplate Solution is identical in formulation to Isolyte S but has not been approved as a platelet additive solution; therefore, there is no post-marketing information. According to the sponsor, *hyperconcentrated platelets stored in platelet additive solution have been collected and transfused in Europe for over 20 years*. However, Isoplate Solution has not been commercialized for routine use in Europe.

V. Pharmacovigilance Planning

Proposed Pharmacovigilance Plan (PVP)

When a new product is marketed, the exposed population may differ from the population studied in the pre-approval studies.

For most products, routine pharmacovigilance (i.e., compliance with applicable postmarketing reporting requirements under FDA regulations) is sufficient for post-marketing risk assessment. As outlined in Guidance for Industry: Good Pharmacovigilance Practices and Pharmacoepidemiologic Assessment (<http://www.fda.gov/CDER/guidance/63590CC.htm>), FDA believes pharmacovigilance plans may be appropriate when: 1) Serious safety risks have been identified pre- or post-approval, or 2) at risk populations have not been adequately studied. The ICH E2E Pharmacovigilance Planning guidance (<http://www.fda.gov/cber/gdlns/ichpvp.htm>) indicates that for products with important identified risks, important potential risks, or missing information, additional actions designed to address these concerns should be considered as part of the pharmacovigilance plan. The pharmacovigilance plan is developed by a product's sponsor and is specifically focused on detecting new safety risks and/or evaluating already identified safety risks.

This information is provided from the sponsor's assessment of the data accumulated in post-market surveillance in the U.S. and other countries/ regions where Isolyte is currently licensed and marketed, as well as safety data accumulated in the clinical studies presented.

The sponsor anticipates that Isoplate Solution will pose no additional risk than the approved Isolyte S, pH 7.4 solution (Multi-Electrolyte Injection), ANDA 019696. The Benefit/Risk Relationship is discussed in section 1.16 Risk Management Plans, in the NDA BN090067. It states that *a post marketing study was requested and agreed to by B. Braun and Caridian BCT*, however, details of the study protocol, or other pharmacovigilance plans, are not supplied.

Benefit/Risk Relationship

Per the Sponsor, this Isoplate Solution presents no additional risk than the already approved Isolyte S, pH 7.4 (Multi-Electrolyte Injection). Isolyte S, pH 7.4 is an IV injection and Isoplate solution, a platelet additive solution, is administered as an IV injection as well. In accordance with the pre-NDA meeting minutes (CRMTS #7147), a post-marketing study was requested and agreed to by B. Braun and CaridianBCT.

Safety Concerns

In the *in vitro* study, the new PAS Isoplate was shown to have theoretical adverse effects on stored platelets in vitro (increased platelet activation marker p-selectin). It is not known whether

this finding has clinical significance. It is the consistent position of OBRR that high P-selectin expression (>20% higher as compared to control) is a significant finding that may have clinical consequences. For this reason, OBRR request that the sponsor conduct a large scale postmarketing study focused on platelet transfusion adverse events.

VI. Assessment and Recommendations

1. The NDA does not contain a complete Pharmacovigilance Plan. Please submit a detailed pharmacovigilance plan in accordance with the ICH E2E Pharmacovigilance Planning (PVP) Guidance which can be found at: <http://www.fda.gov/RegulatoryInformation/Guidances/ucm129411.htm>. The E2E PVP guidance indicates that for products with important identified risks, important potential risks, or important missing information, additional pharmacovigilance actions designed to address these concerns should be considered as part of a PVP.
2. A potential safety concern over the high level of P-selectin compared to controls was identified from the results of the *in vitro* study. We note OBRR's comments that this could represent platelet activation and potential clinical adverse events.
3. No clinical studies assessing safety outcomes in patients receiving Isoplate stored platelets have been conducted.
4. Isolyte has a long history of use and no known safety concerns have been identified with this product. However, this does not necessarily ensure safety of platelets stored in this solution. We also note that P.A.S. solutions have been used extensively in Europe with an apparently good safety record, but that does not include this specific product.
5. Given the absence of available safety data in patients transfused with Isoplate stored platelets and the potential safety risk associated with the increased marker of platelet activation noted during the clinical studies, we concur with OBRR's recommendation that a post-market study will be useful to evaluate potential clinical outcomes in patients receiving Isoplate stored platelets, and should be instituted as a post-market requirement if Isoplate is approved. Because this potential risk is based on an elevated chemical marker as opposed to observed clinical adverse events, our recommendations are based on OBRR's concerns about platelet activation. Intersol by Fenwal, Inc. is a recently approved platelet storage product similar to Isoplate; the Intersol approval also included a post-market requirement to study platelet transfusion adverse events that was based on an elevated P-selectin level. Due the large size of this study (over 5000 transfusions anticipated), we recommend initiating discussion with the Isoplate sponsor regarding the post-market requirement as soon as possible during the BLA review. Optimally, key elements of the proposed study, including study design, size, and assessment of clinical outcomes should be agreed upon at the time of approval, if Isoplate is approved. The sponsor should be requested to submit a draft protocol that includes information about the study size and ability to detect a difference between test and control platelets for potential adverse events (e.g., adverse events related to clotting, thrombosis, coagulopathies, and transfusion related acute lung injury).

VII. Letter Ready Comments

- 1.** Please submit a Pharmacovigilance Plan in accordance with Guidance for Industry: Good Pharmacovigilance Practices and Pharmacoepidemiologic Assessment (<http://www.fda.gov/CDER/guidance/63590CC.htm>). FDA believes pharmacovigilance plans may be appropriate when: 1) Serious safety risks have been identified pre- or post-approval, or 2) at risk populations have not been adequately studied. The ICH E2E Pharmacovigilance Planning guidance (<http://www.fda.gov/cber/gdlns/ichpvp.htm>) indicates that for products with important identified risks, important potential risks, or missing information, additional actions designed to address these concerns should be considered as part of the pharmacovigilance plan. The pharmacovigilance plan is developed by a product's sponsor and is specifically focused on detecting new safety risks and/or evaluating already identified safety risks.

- 2.** In the IND study, the new PAS Isoplate has shown some theoretical adverse effects on stored platelets in vitro (increased platelet activation marker p-selectin). It is not known whether this finding has clinical significance. The potential safety risk associated with elevated marker of platelet activation is the basis for a post-marketing requirement. As noted in your NDA (1.16 Risk Management Plan), if Isoplate is approved, you will be required to conduct a post-marketing study to assess the safety of transfused Isoplate stored platelets compared to appropriate controls. Timing for submission of the final protocol will be negotiated during review of the BLA.