

Midcycle Review Memo, November 17, 2010

- Isoplate Solution

- **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/TBSB has completed a review of NDA BN090067, a NDA application 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 Section 2.5 Clinical Overview, Section 2.7 Clinical Summary, Section 1.14.1 Draft Labeling, and Section 5.3.6 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

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 019696 (NDA2.5.1, p.1).* According to the sponsor, *"the only difference between the two products is the indication" (NDA 2.5.1, p. 1).* 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"(NDA 2.5.1, p. 1).* *"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 (NDA 5.3.6, p. 1)."*

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).*

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 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).

In the In Vivo Platelet Quality Study, hyperconcentrated platelet products stored in Isoplate Solution for five days met both 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.

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.

IV. Safety Database

Clinical Study Adverse Events

There were no adverse events reported in the in vivo or in vitro studies, as no patients 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 43 anticipated adverse events reported to the study sponsor for over 165 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.

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.

Safety Concerns

There are no obvious safety concerns identified. However, 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. For this reason, OBRR requested that the sponsor conduct a postmarketing study focused on platelet transfusion adverse events.

VI. Assessment and Recommendations

There are no concerns regarding approval and marketing for Isoplate Solution.

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.