

Final Pharmacovigilance Plan Review Memo, February 13, 2013 - Isoplate Solution

Pharmacovigilance Plan Final Review Isoplate Solution in the 500 mL EXCEL Container

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Subject: Final Pharmacovigilance Plan Review
Memorandum
Isoplate BN 090067

Applicant: B. Braun Medical Inc.
Product: Isoplate Solution in the 500 mL EXCEL
Container

Proposed Indication: Platelet Additive Solution
Current Indication: Platelet Additive Solution
**Submission type (original BLA,
supplement,
labeling supplement, etc.)** NDA BN 090067

Submission Date: 5/14/2010
PVP Submission Date (if applicable): 8/15/2012
Action Due Date: March 5, 2013

1. Introduction

Product description

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 proposed indication is for use as a platelet additive solution (PAS). It is manufactured by B. Braun and used in conjunction with Trima Accel Instrument. Isoplate Solution is identical to Isolyte S, pH 7.4 (Multi-Electrolyte Injection), an FDA approved sterile, non-pyrogenic intravenous injection packaged in B. Braun's EXCEL® Container and approved by CDER on September 29, 1989 for the following indication: For use in adults as a source of electrolytes and water for hydration, and as an alkalinizing agent. The only difference between the two products is the indication. Hyperconcentrated platelets stored in platelet additive solutions (PAS) have been collected and transfused in Europe for over twenty years.

Advantages to hyperconcentrated platelets include:

- Reduced allergic or febrile reactions during transfusion
- Facilitated ABO-incompatible transfusions
- Availability of additional plasma for other purposes

Pertinent regulatory history

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.

FDA approved a sterile, non-pyrogenic intravenous injection, Isolyte-S, packaged in B. Braun's EXCEL® Container and approved as of September 29, 1989 for the following indication: For use in adults as a source of electrolytes and water for hydration, and as an alkalinizing agent.

B. Braun Medical Inc. (B. Braun) submitted an amendment in response to communication and guidance received from the Agency during a teleconference held on March 28, 2012, wherein Terumo BCT committed to providing a Pharmacovigilance Plan including a Post Market Study Protocol and a statistical plan to the Agency. A request for an ICH compatible pharmacovigilance plan was made on April 9, 2012. CBER sent a Complete Response for Isoplate Solution on May 9, 2012, with a number of concerns.

Objectives/Scope of the review

The purpose of this review is to identify potential safety issues that may need to be addressed through post marketing safety surveillance or studies should the product be licensed.

2. Materials reviewed

Pharmacovigilance Plan

The submitted pharmacovigilance plan has been designed by Terumo BTC to be in compliance with the Guidance for Industry: Good Pharmacovigilance Practices and Pharmacoepidemiologic Assessment and ICH E2E Pharmacovigilance Planning. B. Braun is providing the pharmacovigilance plan in the Risk Management Plan, Module 1.16.

The data presented were reviewed to determine if there is a safety signal associated with apheresis platelets stored in PAS.

Post licensure Safety Data

Information on the clinical studies and safety data is derived from information presented in the NDA Section 2.5.1 Clinical Overview, Section 2.7 Clinical Summary, Section 1.14.1 Draft Labeling, and Section 5.3.6 Reports of Post-Marketing Experience.

Query of the FAERS database for adverse event reports for Isoplate or Intersol returned no data.

A total of 17 adverse event cases associated with equivalent products were found in AERS (Risk Management Plan 1.16 p.5) per sponsor. 13 were associated with Plasmalyte and four were associated with Isolyte S. Only one of the Plasmalyte cases was specifically associated with platelet transfusion. The four Isolyte S cases appear to be duplicate reports of two AE's. Isolyte S is classified as the primary suspect for one of the AE's and concomitant for the other.

An internal query of the Terumo BCT complaint system was conducted, and returned no complaints.

Literature Search

Isoplate is not yet approved, and as such, no publications exist for this PAS solution.

An equivalent solution, InterSol (Fenwal, Inc.) was approved for use in the United States on December 9, 2009. 8 articles were published for InterSol, 7 of which were reviews of in vitro studies and did not include in vivo or transfusion related data. One article included in vivo data, and this provided data on platelet product efficacy but not safety.

There are no 921 or 915 postings, and there are no PSUR's to review.

3. Pharmacovigilance Plan Review

Clinical Safety Database

Isoplate platelet additive solution has not been marketed, and as such there is no previous clinical data.

Isolyte S, an identical solution, is currently approved with an indication 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.

Hyperconcentrated platelets stored in platelet additive solution have been transfused in Europe for over 20 years. Isoplate has a similar composition to other formulations shown to be safe and effective.

Safety concerns

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).

There are no other important identified safety issues, important potential safety issues or important missing information to report. (BLA 1.16)

4. Review of other information from the Managed Review process

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.

Of additional note, a microbial laboratory study was conducted to characterize bacterial growth in apheresis. Results indicate that Isoplate does not increase the overall risk of bacterial growth or bacterial reactions to contaminated platelet products in comparison to current plasma-stored platelet products.

5. Post licensure Safety Review

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 specifically for Isoplate Solution. (BLA 5.3.6)

Post-marketing experience of Isolyte S

Isolyte S is currently approved for use in adults as a source of electrolytes and water for hydration, and as an alkalinizing agent. B. Braun researched the distribution of the approved product in other countries over the past six years. According to the sponsor, from 2002 to Feb 2009, there were ----(b)(4)----- units distributed in the United States. Please find this distribution listed in **Table 1** below.

Table 1- Distribution of Isolyte S, pH 7.4, from 2002- Feb 2009

Material	Size	Sold to Country	Units
L7070	Isolyte S 1L	Hong Kong	--(b)(4)--
L7070	Isolyte S 1L	USA	----(b)(4)--
		Result	----(b)(4)--
L7071	Isolyte S 500	USA	--(b)(4)--
		Result	--(b)(4)-
		Overall Result	----(b)(4)---

In the past 19 years, there were only seven adverse events reported to B. Braun from the United States. Six were non-serious unexpected events (i.e., hyponatremia) and one was a serious unexpected event (anaphylaxis).

- There have been no Prior safety changes to the label
- There have been no 921 postings
- There have been no 915 reviews
- There have been no Pediatric Advisory Committee presentations
- U.S. post marketing studies and surveillance – see above
- Conclusions from periodic internal surveillance reports not applicable.

6. Integrated Risk Assessment

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.

No clinical studies assessing safety outcomes in patients receiving Isoplate stored platelets have been conducted.

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 platelet additive solutions have been used extensively in Europe with an apparently satisfactory safety record, but that does not include this specific product.

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 the sponsor's recommendation that a post-market study will be useful to evaluate potential clinical outcomes in patients receiving Isoplate stored platelets. We also concur with OBRR

that this study 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 previously 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, and performance of a similar post-market study for Isoplate Solution is reasonable.

Review of Post marketing Study proposal

Title: PAS Post-Market Surveillance of Adverse Reactions to Transfusion of Hyperconcentrated Platelets Collected on Trima Accel and Stored in Isoplate for up to 5 Days

Objective: The objective of this study is to collect data on the rate of adverse transfusion reactions to Isoplate-stored platelets compared to plasma stored platelets

Study Type: Open-label, Non-randomized, Retrospective Post-Market Surveillance Study

Test Product: Leukoreduced Hyperconcentrated Apheresis Platelets Collected on Trima Accel and Stored in Isoplate for up to 5 days

Control Product: Leukoreduced Apheresis Platelets Stored in Plasma for up to 5 days

Sponsor: Teruma BCT

Protocol number: BCT 12-02

The Trima Accel System is an apheresis device intended for use in automated blood component collection procedures. Hyperconcentrated apheresis platelets consist of the same number of platelets as that collected in standard apheresis, but in 65% less plasma, which are then diluted and stored with platelet additive solution (PAS).

The solution itself has no pharmacologic effect.

The study is designed to determine the rate of adverse reactions (ARs) in patients who receive platelet transfusions.

AR rate: **Total number of AR's**

Total number of platelet units transfused

The primary objective of this retrospective post marketing study is to demonstrate that the overall rate of transfusion related adverse events is similar between patients receiving Isoplate stored platelets and plasma stored platelets.

Non-inferiority will be assessed using one sided 97.5% confidence limit.

For an overall adverse event rate in the control arm that is $\leq 5\%$, the non-inferiority margin will be calculated as a function of the rate observed in the control arm.

The duration of the study is anticipated to be 3 years. The study will be open to at least 3 institutions.

The sample size estimate has a large range. The aggregate event rate will be calculated after the results of the initial 700 transfusions have been entered into the database.

7. Recommendations

Based on section 901 of FDAAA and July 2009 FDA Guidance “Post marketing Studies and Clinical Trials-Implementation of Section 505 (o) of the FD&C Act”, the identified concerns meet one of the criteria of a PMR: “To identify an unexpected serious risk when available data indicates the potential for a serious risk”

In addition to routine pharmacovigilance activities, the sponsor will study adverse events in recipients of Isoplate platelets and compare them to a control as a post-marketing requirement. The study will have the same design as the PMR study for the approved platelet additive solution “Intersol” (Fenwal, Inc.).

- The proposed Post-Market Surveillance Study will start within 3 months after FDA approval of the final PMR protocol and statistical analysis plan.
- Submit the PMR timeline.
- Estimate the length of the study and the estimated date of submission of the final report.
- Submit serious unexpected adverse event reports if there is a reasonable possibility that the product caused the adverse event in an expedited manner to FAERS (MedWatch). (21 CFR 314.80).
- Provide quarterly submissions of adverse event summaries (21 CFR 601.70).
- In addition to the interim data analysis at 50% completion of the aforementioned PMS Study, an interim data analysis will be conducted after every 700 data points collected for platelet transfusions utilizing Isoplate. (BLA 1.16 p.2)
- Provide Surveillance and Lot Distribution Reports