

UNITED STATES PUBLIC HEALTH SERVICE
CENTER FOR BIOLOGICS EVALUATION AND RESEARCH

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INTERNAL MEMORANDUM

DATE: Feb 19, 20113

FROM: Jan Simak, Ph.D.
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THROUGH: Jaroslav G. Vostal, M.D., Ph.D.
Chief, Laboratory of Cellular Hematology

TO: Sondag L. Kelly, M.S.
Regulatory Project Manager

SUBJECT: Final Memorandum

Submission type: NDA
BN 090067

Product Name: Isoplate Solution in the 500 mL EXCEL Container

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

CBER Rec. Date: Class 1 resubmission Jan 7, 2013

ADD: March 5, 2013

Conclusion and Recommendation: Approval of the NDA with a post marketing requirement for the sponsor to conduct a controlled study to track the adverse event rate in the recipients.

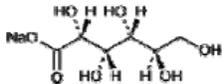
Background & Introduction

Platelet transfusion products are procured from donors either by preparation from a whole blood donation or through an automated apheresis procedure. Currently in the U.S. platelets for transfusion, after their collection, are stored in the plasma of donors or in a newly approved platelet additive solutions (PAS) InterSol[®] (Fenwal; BN080041). In the last 25 years, alternate storage solutions with a range of plasma concentrations have been proposed. In 1995 Plasma Additive Solution (PAS) II was the first solution used in

European blood centers to store pooled buffy coat platelet products. PAS II contains acetate as a nutrient for the platelets, citrate to prevent clumping and activation, and sodium chloride for osmolarity. InterSol[®] is similar to PAS II with the addition of phosphate. The InterSol[®] formulation is currently used in Europe as a processing solution in the pathogen inactivation process INTERCEPT Blood system for platelets. The InterSol[®] has also been approved in a number of European countries as a stand alone configuration (i.e. independent of pathogen reduction) for the storage of platelets in a fixed mixture ratio with plasma. Composition of the new PAS Isoplate submitted in this NDA is different from Intersol, containing additional components including potassium, magnesium and gluconate. Both Intersol and Isoplate do not contain D-glucose and therefore there are used to replace just 65% of plasma. The residual 35% of plasma are essential source of energy for the stored platelets. This submission pertains only to leukoreduced apheresis platelets collected by Trima Accel system (Terumo BCT). The NDA approval is linked to the recent 510(k) clearance of BK120049 Trima Accel System (Version 6.2) for the collection of hyperconcentrated platelets.

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

Since the identical solution Isolyte was previously independently approved by CDER, this NDA was not presented to the Blood Products Advisory Committee and this was based on the criteria of Section 918 of FDAAA.

Isoplate Solution Indication for Use

Isoplate™ Solution Platelet Additive Solution [PAS-F] 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 Terumo BCT's Trima Accel® System. The solution should never be infused directly to the patient. Platelet Pheresis, Leukocytes Reduced Platelet Additive Solution [PAS] products are stored in a mix of 65% Isoplate™ and 35% plasma. Platelets in Isoplate™ Solution can be stored at a concentration range of 700-2100 x 10⁶/mL for up to 5 days at 20-24°C with continuous agitation in the EXCEL® container.

NDA review team

Reviewed Discipline	Reviewer Name – Final review Document(s) Date
Clinical Review	Jan Simak, CBER/OBRR/DH/LCH – Feb 19, 2013
Clinical Pharmacology Review	N/A
Labeling Review	Lore Fields, CBER/OBRR/DBA – Feb 13, 2013
Statistical Review	Chinying Wang, CBER/OBE – May 4, 2012
CMC Review	Minerva Hughes (CDER) – Feb 24, 2012
Pharmacology/ Toxicology Review	Jolanda Branch, CBER/OBRR/DH – Feb 8, 2012
Biomonitoring Review	Anthony Hopkins, CBER/OCBQ – March 12, 2012
Establishment Review	Nawab Siddiqui, CBER/OCBQ – March 8, 2012
Advisory Committee Transcript	N/A
Proprietary Name Review	Dana Martin, OCBQ/DCM/APLB - Jan 29, 2013
Epidemiology Review	Faith Barash, CBER/OBE – Apr 9, 2012

Review Summary

Product Quality

The Chemistry, manufacturing and control (CMC) section of this application was reviewed by both CDER Office of New Drugs Quality Assessment as a consult review for all CMC sections.

CMC

The Isoplate Solution is identical to the Isolyte® S, pH 7.4 (Multi-Electrolyte Injection) an FDA approved sterile, nonpyrogenic intravenous injection packaged in B. Braun's EXCEL® Container. The Isolyte® S, pH 7.4 is 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 alkalizing agent.

Each drug substance manufacturer included appropriate statements of compliance with applicable guidelines and regulations for safety.

Considering previously approved ANDA 19-696 for identical product, new NDA 090067 provided sufficient information to assure the identity, strength, purity, and quality of the drug product. Therefore, the NDA is recommended for approval from the chemistry, manufacturing, and controls perspective.

CBER Lot Release

CBER lot release does not apply since each collected blood product is traditionally considered to be manufactured from a single product lot.

Facilities review/inspection

The Isoplate Solution is identical in formulation, packaging, sterilization, and manufacturing as B. Braun’s already approved Isolyte S, pH 7.4 (Multi-Electrolyte Injection), ANDA 019696. The only difference between the Isoplate product and the approved Isolyte S, pH 7.4 (Multi-Electrolyte Injection) product is the indication. The manufacturing facility located at Irvine California was inspected last on February 23-March 5, 2009.

B. Braun Medical Inc.
2525 McGaw Avenue
Irvine, CA 92614
FEI: 2021236

Date of Last FDA Inspection: February 23-March5, 2009

OCBQ/DMPQ CBER recommended approval and issued the Categorical Exclusion memo.

Environmental Assessment

No adverse impact is expected on animals, plants, humans, other organisms, or ecosystems.

Nonclinical Pharmacology/Toxicology

Toxicology studies of the Isoplate (Isolyte) solution itself were assessed as a part ANDA 019696 and found acceptable. 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 container closure system used in manufacturing the FDA approved product Isolyte is identical to that used in the Isoplate Solution product. The analysis of the material used to manufacture the Excel® plastic container was performed in –(b)(4)----:

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All information related to the container closure system presented in this NDA has already been approved for use by the Agency and is currently used in approximately 29 approved products. The complete description of the testing and the results are provided in B. Braun's DMF (b)(4), Material Qualification for the Excel® Plastic Container, submitted to the FDA on June 30, 1986.

Review of Clinical Studies

Prior to the submission of this NDA FDA had reviewed and approved the study protocols under IND 13684.

Efficacy studies consisted of in vitro testing and in vivo radiolabeling studies.

In vivo radiolabeling studies for 5-day test platelets (Protocol III, 5.3.5.1.2 of the original submission)

In recovery and survival studies of radiolabeled platelets as compared to “fresh” radiolabeled control platelet samples drawn and prepared on day of reinfusion of test samples the 5-day test product showed successful results for both recovery and survival. Success criteria are Test/Control ratio: > 66% for recovery, and > 58% for survival. These criteria are satisfied if the upper limit of a two-sided 95% confidence interval of the mean percent recovery of $(0.66 \text{ Control} - \text{Test})$ is < 0 and the upper limit of a two-sided 95% confidence of the mean percent survival of $(0.58 \text{ Control} - \text{Test})$ is < 0 . For the test product the mean recovery ratio was 88% and the mean survival ratio was 79%.

In vitro platelet quality study (Protocol II, 5.3.5.1.1. of the original submission)

All parameters, except for pH, were compared to a concurrent control (platelets stored in plasma). A relative difference of less than 20% between test and control for each of these parameters is deemed not clinically relevant. A difference of > 20% in some in vitro parameters may be clinically meaningful. A non-inferiority statistical approach was used to assess the 20% difference.

For in vitro testing the control consisted of an apheresis platelet product collected from the same donor (paired control) and stored in 100% plasma.

- a. pH (primary parameter): success criterion for pH is ≥ 6.2 for 95% of the products with 95% confidence. All 66 test products in the study met the FDA criteria.

- b. Of the remaining in vitro test parameters, the *in vitro* Isoplate stored platelet quality study failed in one secondary endpoint, the surface P-selectin expression, which was more than 20% higher in the test group ($22 \pm 15.4\%$) compared to control ($15.1 \pm 9.1\%$). The high P-selectin expression (> 20% higher compared to control) on 5 day Isoplate stored platelets is a significant finding that may have clinical consequences. Similar finding of elevated P-selectin expression were observed in the Intersol stored platelets and PMR was issued for

the Intersol product. To assure clinical safety of the product, a postmarket study focused on platelet transfusion adverse events will be required in the same extent as required for Intersol.

Review of the available European hemovigilance data for Intersol stored platelets (Transfusion Clinique et Biologique 2007: 100-106; Transfusion Clinique et Biologique 2008: 289-293; French annual hemovigilance report 2008) and randomized studies (Transfusion 2000; 40:398-403; Blood 2006; 108:3210-3215) on the use of either InterSol or other similar platelet additive solutions for storage of platelets revealed no alarming findings that would preclude approval of the product. Nevertheless, post marketing studies were considered necessary to track adverse events in the recipients.

Conclusions:

Efficacy: Demonstrated by successful outcomes in the primary parameters of pH, *in vivo* recovery and *in vivo* survival.

Safety: Platelets stored in similar additive solution Intersol and transfused to patients raised no undue safety concerns.

In order to further track adverse events in the recipients of Trima Accel platelets stored in 65% Isoplate/ 35% plasma, Terumo BCT committed to conducting a controlled postmarketing study (PMR) pursuant to Section 505(o) of the Federal Food, Drug, and Cosmetic Act (FDCA) and consistent with the July 2009 FDA Guidance “Postmarketing Studies and Clinical Trials—Implementation of Section 505 (o) of the FD&C Act.” Adverse events, i.e. transfusion reactions, will be captured through retrospective surveillance of the test and the control products. Transfusion reactions will be classified and compared by type (e.g. TRALI, febrile non-hemolytic transfusion reaction, allergic reaction, etc...). Terumo BCT will conduct the postmarketing requirement at selected institutions that are currently transfusing Trima Accel platelets in plasma and are planning to switch to Trima Accel Isoplate platelets.

The study protocol and statistical plan including hypothesis testing has been submitted as an Amendment 17 of this NDA and will be further modified to achieve harmonization with the recently finalized PMR study protocol for the Intersol stored platelets. B. Braun on behalf of Terumo BCT commits to begin the PMR study within 3 months of FDA approval of the final protocol. The study including 12,000 transfusion is expected to take 6 years to complete and the final report will be submitted within 6 months after completing the study (Am. 22).

Pediatrics

This application 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)

Other Special Populations N/A**Overall Comparability Assessment**

The Isoplate Solution is identical to the Isolyte® S, pH 7.4 (Multi-Electrolyte Injection) an FDA approved sterile, nonpyrogenic intravenous injection packaged in B. Braun's EXCEL® Container. The Isolyte® S, pH 7.4 is approved, as of September 29, 1989 (ANDA 19-696). The preclinical data obtained as a part of ANDA 19-696 reveal no toxicological or biocompatibility concerns. Clinical data demonstrate the efficacy of platelets stored in the Isoplate. Results of an in vitro test indicating increase in platelet activation are similar to that of previously approved Intersol PAS (BN080041). These in vitro findings prompt FDA to require post marketing studies for both Intersol and Isoplate to assess adverse events in the recipients.

Safety

Toxicology studies conducted on the Isoplate/Isolyte solution itself and biocompatibility testing of the leachables/extractables plastic materials from its container bag were assessed and found acceptable. Evaluation of available European hemovigilance data (Transfusion Clinique et Biologique 2007: 100-106; Transfusion Clinique et Biologique 2008: 289-293; French annual hemovigilance report 2008) and randomized studies (Transfusion 2000;40:398-403; Blood 2006;108:3210-3215) on the use of similar platelet additive solutions (Intersol) for the storage of platelets revealed no alarming safety issues.

Advisory Committee Meeting

OBRR reviewed information from this application and determined that referral to the Blood Products Advisory Committee (BPAC) prior to licensure was not needed for the following reasons (FDAAA [HR 3580-138 SEC. 918]: REFERRAL TO ADVISORY COMMITTEE):

- The Isoplate Solution is identical to the Isolyte® S, pH 7.4 (Multi-Electrolyte Injection) an FDA approved sterile, nonpyrogenic intravenous injection packaged in B. Braun's EXCEL® Container. The Isolyte® S, pH 7.4 is approved, as of September 29, 1989 (ANDA 19-696).
- The study design to evaluate efficacy of InterSol was adequate and the results of the study supports the storage of Trima Accel apheresis platelets in a mixture of 65% Isoplate/35% plasma for up to 5 days.
- The use of a similar PAS InterSol as a stand-alone platelet additive solution has been approved in Europe since 2007. As a component of a pathogen reduction

system for platelets InterSol has been in use in Europe since 2003. European hemovigilance data revealed no alarming safety issues.

- BPAC discussion of this application is unlikely to change the outcome of the review of this file from a regulatory standpoint.

Labeling

Sponsor revised the labeling according to the FDA comments. The labeling is acceptable .

A Proprietary Name Review was conducted by Advertising, Promotional, and Labeling Branch (APLB). APLB recommended that the proposed proprietary name, Isoplate Solution in the 500mL EXCEL® container, be found acceptable.

Risk/ Benefit Assessment

The clinical studies described above revealed that one of the secondary endpoint of in vitro study failed to meet the FDA acceptance criteria. The platelet surface expression of P-selectin (CD62) was significantly increased (> 20% higher compared to control) in Isoplate stored platelets compared to the control. This finding indicates increased activation of Isoplate stored platelets that may have clinical consequences. Similar finding of elevated P-selectin expression was observed in the Intersol stored platelets and PMR was issued for the Intersol product. To assure clinical safety of the product, a postmarket study focused on platelet transfusion adverse events will be required in the same extent as required for Intersol. The NDA approval is recommended since available European data on the use of a similar PAS InterSol or other similar platelet additive solutions for the storage of platelets raised no undue safety concerns (Transfusion Clinique et Biologique 2007: 100-106; Transfusion Clinique et Biologique 2008: 289-293; French annual hemovigilance report 2008; Transfusion 2000;40:398-403; Blood 2006;108:3210-3215).

Recommendation for Postmarketing Activities.

The approval letter should include a post marketing requirement for the sponsor to conduct a controlled study to track the adverse event rate in the recipients.

Summary and Conclusion

This is a New Drug Application from B. Braun to gain approval for a new (second in US) platelet additive solution Isoplate® (PAS-F) for the storage of Trima Accell (terumo BCT)-derived apheresis platelets in a mixture of 65% Isoplate® /35% plasma for up to 5 days. The sponsor submitted studies which met FDA criteria demonstrating the efficacy of these platelets at end of 5-day storage. The sponsor agreed to a post marketing requirement to track the transfusion adverse event rate in the recipients. FDA review of the other disciplines in the submission was equally satisfactory. Based on the above I recommend approval of this NDA.