

UNITED STATES PUBLIC HEALTH SERVICE
CENTER FOR BIOLOGICS EVALUATION AND RESEARCH

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INTERNAL MEMORANDUM

DATE: May 8, 2012

FROM: Jan Simak, Ph.D.
Senior Investigator, Laboratory of Cellular Hematology

THROUGH: Jaroslav Vostal, M.D., Ph.D.
Chief, Laboratory of Cellular Hematology

TO: Iliana Valencia, M.S.
Chief, RPM Branch, DBA

SUBJECT: Midcycle Memorandum

Submission type: NDA
BN 090067 Complete Response Letter Memo

Product Name: Isoplate Solution in the 500 mL EXCEL Container

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

CBER Rec. Date: 11/10/2011

Conclusion and Recommendation:

We have determined that we cannot approve this application in its present form. The CR letter should be issued with the following reason for this action:

Clearance of the 510(K) submission for modification of the Trima device (Terumo BCT) for the collection of hyperconcentrated platelets is required before this application may be approved as this will constitute the only approved use of this product. Please notify us in writing when the 510(K) is cleared.

Background Summary:

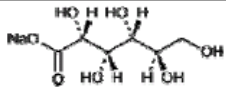
CBER issued a Non-Approval Letter of BN 090067 on Feb. 4, 2011.

CBER received on November 10, 2011, resubmission of the NDA and considers this a complete, class 2 response to February 4, 2011, Action Letter. Therefore, the goal date is May 11, 2012. FDA will send the CR letter because the sponsor did not submit a 510k submission for modification of the Trima device (Terumo BCT) for the collection of hyperconcentrated platelets. CBER management (Dr. Yetter) decided that the clearance of the 510(K) submission for modification of the Trima device (Terumo BCT) for the collection of hyperconcentrated platelets is required before this application may be approved as this will constitute the only approved use of this product.

Drug description

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

Isoplate Solution Indication for Use

Indicated as a platelet additive solution for the storage of leukoreduced hyperconcentrated apheresis platelets.

NDA review team

Review Discipline	Reviewer Name
Regulatory	Iliana Valencia (OBRR/DBA/RPMB)
Clinical	Jan Simak (OBRR/DH/LCH)
Pharmacology	Yolanda Branch (OBRR/DH/
Statistical	Chinying Wang (OBE/DB/TEB)
CMC/CDER	Minerva Hughes (OPS/ONDQA/NDQAII/Branch IV)
DMPQ	Nawab Siddiqui (OCBQ/DMPQ/BII)
Labeling	Lore Fields (OBRR/DBA/BPB)
BIMO	Anthony Hawkins (OCBQ/DIS/BMB)
Epidemiology	Faith Barash (OBE/DE/TBSB)
PNR Review	Dana Martin (OCBQ/DCM/APLB)

Review Conclusions

Fileability: Yes, the application was found sufficiently complete to permit a substantive review. The review classification for this application is Standard. Therefore, the user fee goal date is May 11, 2012. NO OUTSTANDING ISSUES

PREA: No, as assessed for the original submission, this application similarly to BN080041 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)
NO OUTSTANDING ISSUES

BIMO: Documentation discrepancies noted at the New Haven, CT, study site. Clinical Investigator Inspection of the additional clinical site Dr. Cancelas-Perez, Hoxworth Blood Center was performed and showed one minor problem with randomization schedule. Information letters issued. Final memo from Anthony Hawkins received 3/12/2012. NO OUTSTANDING ISSUES

DMPQ: Company was asked to submit the Categorical exclusion under 21 CFR 25.31(a). They have submitted Categorical exclusion under 21 CFR 25.31(J). This does not apply to this NDA. No other issues for the response to CR letter. (email from Nawab Siddiqui 11/18/2011). NO OUTSTANDING ISSUES

Epidemiology: Pharmacovigilance Plan was requested (memo with letter ready comments from Faith Barash 1/30/12), Sponsor provided time line for the PMR study. PMR recommended by CBER safety WG on 4/12/2012. Design of PMR study including SAP will be further negotiated with the sponsor when the NDA is approved.

CDER consult CMC review: The Applicant's response is complete for filing from the CMC (i.e., CDER consulted CMC) perspective. Of note, all review comments regarding labeling from the CDER consult final discipline review were not conveyed to the applicant in the CR letter (email from Minerva Hughes of 2/1/2012). Outstanding labeling issues were resolved by DBA labeling reviewer. Consult review memo from Minerva Hughes, Ph.D. of 2/24/2012. NO OUTSTANDING ISSUES

Pharm./tox review: The nonclinical responses to CR letter were sufficient. Midcycle memo received from Yolanda Branch 2/15/2012. NO OUTSTANDING ISSUES

Labeling: Midcycle memo from Lore Fields (DBA) of 2/23/2012 minor outstanding issues in the package insert and container label. NO OUTSTANDING ISSUES

Satistics: Response to stat comment (item 6) is satisfactory. Midcycle memo from Chinying Wang received on 2/15/2012. NO OUTSTANDING ISSUES

PNR: PNR reevaluation will be performed prior to the NDA approval.