Y36-002-738

HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use Isoplate™ Solution Platelet Additive Solution [PAS-F] safely and effectively. See full prescribing information for Isoplate Solution Platelet Additive Solution [PAS-F].

Isoplate Solution
Platelet Additive Solution [PAS-F]

Initial U.S. Approval: 2013

INDICATIONS AND USAGE

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 10^6/mL for up to 5 days at 20-24°C with continuous agitation in the EXCEL® container. (1)

DOSAGE AND ADMINISTRATION

Isoplate Solution Platelet Additive Solution [PAS-F] may only be used with the Trima Accel automated blood cell separator device. For full instructions on the use of Isoplate Solution Platelet Additive Solution [PAS-F] with the Trima Accel see the Trima Accel Operator's Manual. (2)

Directions for Connecting the Isoplate Solution Container to the Trima Accel System

At the prompt to connect the platelet additive solution to the Trima Accel tubing set:

1. Remove the overwrap by pulling down at notch and remove solution container.
2. Before use, perform the following checks:
   - Check for leaks by squeezing the bag firmly. If leaks are found, discard solution.
   - Ensure the solution is the Isoplate Solution Platelet Additive Solution [PAS-F] and is within the expiration date.
   - Inspect the solution for cloudiness, haze, or particulate matter. Suspect container should not be used.
3. Remove the protective cap from the port on the Isoplate™ Solution Platelet Additive Solution [PAS-F] container.
4. Connect the Isoplate container to the Trima Accel® set using aseptic technique and hang the solution.
5. Proceed per the Trima Accel Operator's Manual.

DOSAGE FORMS AND STRENGTHS

- 500 mL bag (3)

CONTRAINDICATIONS

There are no known contraindications. (4)

WARNINGS AND PRECAUTIONS

- Isoplate Solution Platelet Additive Solution [PAS-F] is NOT FOR DIRECT INTRAVENOUS INFUSION. (5)
- Verify that the Isoplate Solution Platelet Additive Solution [PAS-F] has been securely attached to the platelet additive solution line on the Trima Accel disposable tubing set using aseptic technique. (5)
- Multiple transfusions of Isoplate-stored platelets may lead to overdosage of potassium, magnesium and gluconate (5, 10).

ADVERSE REACTIONS

- Isoplate Solution Platelet Additive Solution [PAS-F] is added to leukoreduced hyperconcentrated platelets after the Trima Accel apheresis procedure is complete. Isoplate Solution Platelet Additive Solution [PAS-F] is not expected to cause adverse events other than those normally associated with platelet transfusion. (6)

To report SUSPECTED ADVERSE REACTIONS, contact B. Braun Medical Inc. at 1-800-227-2862 or FDA at 1-800-FDA-1088 or *www.fda.gov/medwatch*.

DRUG INTERACTIONS

- Isoplate Solution Platelet Additive Solution [PAS-F] is used as a storage solution for hyperconcentrated platelets and it is not intended for direct intravenous infusion. There are no known drug interactions in its use as a platelet storage solution. (7)

Issued: January 2013

FULL PRESCRIBING INFORMATION: CONTENTS*

*** Sections or subsections omitted from the full prescribing information are not listed.**

FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

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 10^6/mL for up to 5 days at 20-24°C with continuous agitation in the EXCEL® container.

2 DOSAGE AND ADMINISTRATION

2.1 General Dosing Information

Isoplate Solution Platelet Additive Solution [PAS-F] may only be used with the Trima Accel automated blood cell separator device. For full instructions on the use of Isoplate Solution Platelet Additive Solution [PAS-F] with the Trima Accel see the Trima Accel Operator's Manual.

2.2 Directions for Connecting the Isoplate™ Solution Container to the Trima Accel® System

At the prompt to connect the platelet additive solution to the Trima Accel tubing set:

1. Remove the overwrap by pulling down at notch and remove solution container.
2. Before use, perform the following checks:
   - Check for leaks by squeezing the bag firmly. If leaks are found, discard solution.
   - Ensure the solution is the Isoplate Solution Platelet Additive Solution [PAS-F] and is within the expiration date.
   - Inspect the solution for cloudiness, haze, or particulate matter. Suspect container should not be used.
3. Remove the protective cap from the port on the Isoplate Solution Platelet Additive Solution [PAS-F] container.
4. Connect the Isoplate container to the Trima Accel set using aseptic technique and hang the solution.
5. Proceed per the Trima Accel Operator's Manual.

3 DOSAGE FORMS AND STRENGTHS

Isoplate Solution Platelet Additive Solution [PAS-F] in the EXCEL® Container

NDC	Cat. No.	Volume
0264-7771-10	L7771	500 mL

4 CONTRAINDICATIONS

There are no known contraindications.

5 WARNINGS AND PRECAUTIONS

- Isoplate™ Solution Platelet Additive Solution [PAS-F] is NOT FOR DIRECT INTRAVENOUS INFUSION.
- Multiple transfusions of Isoplate-stored platelets may lead to overdosage of potassium, magnesium and gluconate [See *Overdosage (10)*].
- Inspect each container. Read the label. Ensure solution is the one ordered and is within the expiration date.
- Invert container and carefully inspect the solution in good light for cloudiness, haze, or particulate matter. Any container which is suspect should not be used.
- Use only if solution is clear and container and seals are intact.
- Do not reuse. Discard unused or partially used Isoplate Solution Platelet Additive Solution [PAS-F].
- Protect from sharp objects.
- Verify that the Isoplate Solution Platelet Additive Solution [PAS-F] has been securely attached to the platelet additive solution line on the Trima Accel® disposable tubing set using aseptic technique.

6 ADVERSE REACTIONS

Isoplate Solution Platelet Additive Solution [PAS-F] is added to Platelet Pheresis, Leukocytes Reduced PAS products after completion of a hyperconcentrated Trima Accel apheresis collection procedure. It is not for direct intravenous infusion. Isoplate Solution Platelet Additive Solution [PAS-F] is not expected to cause adverse events other than those normally associated with platelet transfusion.

6.1 Clinical Trials Experience

No adverse reactions were reported in subjects infused with a small volume (< 10 mL) of radiolabeled platelets that had been stored for 5 days in 65% Isoplate Solution Platelet Additive Solution [PAS-F], but rinsed prior to infusion.

7 DRUG INTERACTIONS

Isoplate Solution Platelet Additive Solution [PAS-F] is used as a storage solution for hyperconcentrated platelets and it is not intended for direct intravenous infusion. There are no known drug interactions in its use as a platelet storage solution.

9 DRUG ABUSE AND DEPENDENCE

Isoplate Solution Platelet Additive Solution [PAS-F] is used as a storage solution for leukoreduced hyperconcentrated platelets and has no pharmacological effect.

10 OVERDOSAGE

Multiple transfusions of Isoplate-stored platelets may lead to overdosage of potassium, magnesium and gluconate. Monitor changes in electrolyte concentration and acid-base balance when multiple transfusions of Isoplate-stored platelets are administered. In the event of overdose, discontinue transfusion immediately and institute appropriate corrective treatment.

The signs and symptoms of potassium overdose include paresthesias of the extremities, areflexia, muscular or respiratory paralysis, mental confusion, weakness, hypotension, cardiac arrhythmias, heart block, electrocardiographic abnormalities and cardiac arrest. Treatment of hyperkalemia includes the following;

1. Dextrose Injection, USP 10% or 25%, containing 10 units of crystalline insulin per 20 grams of dextrose administered intravenously, 300 to 500 mL/hour.
2. Absorption and exchange of potassium using sodium or ammonium cycle cation exchange resin, orally and as retention enema.
3. Hemodialysis and peritoneal dialysis. The use of potassium-containing foods or medications must be eliminated. However, in cases of digitalization, too rapid a lowering of plasma potassium concentration can cause digitalis toxicity.

Gluconate overdose may cause metabolic alkalosis. Treatment of metabolic alkalosis may include administration of an acidifying agent such as ammonium chloride.

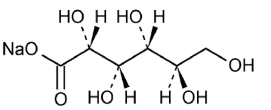
Signs of magnesium overdose include flushing, sweating, hypotension, depressed reflexes, flaccid paralysis, hypothermia, circulatory collapse, cardiac and CNS depression proceeding to respiratory paralysis. Disappearance of the patellar reflex is a useful clinical sign to detect the onset of magnesium overdose. In the event of overdosage artificial ventilation may be required until a calcium salt can be injected intravenously to antagonize the effects of magnesium.

11 DESCRIPTION

Isoplate™ Solution Platelet Additive Solution [PAS-F] is sterile, nonpyrogenic, and contains no bacteriostatic or antimicrobial agents. Isoplate Solution Platelet Additive Solution [PAS-F] is indicated as a platelet additive solution for the 5 day storage of Platelet Pheresis, Leukocytes Reduced PAS products collected using a hyperconcentrated collection on Terumo BCT's Trima Accel® System. Platelets in Isoplate Solution Platelet Additive Solution [PAS-F] can be stored at a concentration range of 700-2100 x 10^6/mL for up to 5 days at 20-24 °C with agitation.

The formulas of the active ingredients are provided in Table 1.

Table 1: Active Ingredients

Ingredients	Molecular Formula	Molecular Weight
Sodium Chloride USP	NaCl	58.44
Sodium Acetate Trihydrate USP	$CH_3COONa•3H_2O$	136.08
Potassium Chloride USP	KCl	74.55
Magnesium Chloride Hexahydrate USP	$MgCl_2•6H_2O$	203.30
Dibasic Sodium Phosphate Heptahydrate USP	$Na_2HPO_4•7H_2O$	268.07
Monobasic Potassium Phosphate NF	KH_2PO_4	136.09
Sodium Gluconate USP		218.14

Each 100 mL of Isoplate Solution Platelet Additive Solution [PAS-F] contains: Sodium Chloride USP 0.53 g; Sodium Gluconate USP 0.5 g; Sodium Acetate Trihydrate USP 0.37 g; Potassium Chloride USP 0.037 g; Magnesium Chloride Hexahydrate USP 0.03 g; Dibasic Sodium Phosphate Heptahydrate USP 0.012 g; Monobasic Potassium Phosphate NF 0.00082 g; Water for Injection USP qs

pH may be adjusted with Glacial Acetic Acid USP or Sodium Hydroxide NF
pH: 7.4 (7.0-7.8)

Calculated Osmolarity: 295 mOsmol/liter

Concentration of Electrolytes (mEq/liter): Sodium 141; Potassium 5; Magnesium 3; Chloride 98; Phosphate ($HPO_4^=$) 1 (0.5 mmole P/liter); Acetate (CH_3COO^-) 27; Gluconate ($HOCH_2(CHOH)_4COO^-$) 23

The EXCEL® Container is Latex-free, PVC-free, and Di(2-ethylhexyl)phthalate (DEHP)-free.

The plastic container is made from a multilayered film. It contains no plasticizers and exhibits virtually no leachables. The solution contact layer is a rubberized copolymer of ethylene and propylene. The container is nontoxic and biologically inert. The container-solution unit is a closed system and is not dependent upon entry of external air during administration. The container is overwrapped to provide protection from the physical environment and to provide an additional moisture barrier when necessary.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Isoplate Solution Platelet Additive Solution [PAS-F] contains the following key components to maintain platelet function:

- Sodium chloride for osmolarity
- Acetate to fuel platelet metabolism
- Gluconate or phosphate for buffering
- Magnesium and potassium to reduce platelet activation[1,2]

Isoplate Solution Platelet Additive Solution [PAS-F] is used as a storage solution for leukoreduced hyperconcentrated platelets and it is not for direct intravenous infusion. This solution has no pharmacological effect; the solution provides the appropriate components for platelet function while allowing for a lower volume of plasma in the platelet product during storage.

14 CLINICAL STUDIES

In Vivo radiolabeled recovery and survival

A paired study was completed to verify that *in vivo* radiolabeled recovery and survival of hyperconcentrated leukocyte reduced platelets collected on the Trima Accel System, diluted in Isoplate Solution Platelet Additive Solution [PAS-F], and stored for five days (Test) meet FDA acceptance criteria in comparison with fresh autologous platelets (Control). Table 2 summarizes the *in vivo* radiolabeled platelet recovery and survival data.

Table 2 – *In Vivo* Radiolabeled Platelet Recovery and Survival Data (N = 23)						
	Recovery			Survival		
	Test	Control	Test/Control	Test	Control	Test/Control
	%	%	%	Days	Days	%
Average	**51.1**	**60.2**	**85**	**6.6**	**8.7**	**76**
St. Dev.	10.9	10.2	10	1.2	0.9	12
Min	32.6	40.4	66	4.5	6.4	52
Max	84.1	82.8	102	8.8	10.0	104

The primary outcomes for this study were:

Recovery: Test minus 66% Control is equal to or greater than zero with one-sided 97.5% confidence limit

Survival: Test minus 58% Control is equal to or greater than zero with one-sided 97.5% confidence limit

Both primary outcomes were met for hyperconcentrated leukocyte reduced platelets collected by apheresis and stored in Isoplate™ Solution Platelet Additive Solution [PAS-F].

In Vitro Platelet Quality Study

A paired study was completed to verify that *in vitro* platelet quality (functional assays) of hyperconcentrated leukocyte reduced platelets collected on the Trima Accel® System, diluted in Isoplate Solution Platelet Additive Solution [PAS-F], and stored for five days (Test) meet FDA acceptance criteria in comparison to plasma-stored platelets (Control).

Table 3 summarizes the *in vitro* platelet quality data.

Table 3 – *In Vitro* Platelet Quality Data (N = 66)		
Functional Assay	Isoplate Stored Apheresis Platelets (Test) Average (Standard Deviation)	Plasma Stored Apheresis Platelets (Control) Average (Standard Deviation)
pH	7.4 (0.2)	7.5 (0.1)
CD62 Expression; P-Selectin (%)	22.8 (15.6)	15.0 (9.8)
Morphology Score (Max Score 400)	289 (49)	292 (47)
Hypotonic Shock Response (%)	53.3 (12.4)	55.9 (10.9)
Extent of Shape Change (%)	23.2 (5.0)	25.0 (6.0)

The primary outcome for this study was:

pH: 95% or more of test units will have a pH (22°C) greater than 6.2 with a one sided confidence interval of 95%

All 66 platelet products collected in this study had pH > 6.2 therefore the primary outcome for pH was met for hyperconcentrated platelets collected by apheresis and stored in Isoplate Solution Platelet Additive Solution [PAS-F].

15 REFERENCES

1. Gulliksson H. Platelet storage media. Transfus Apher Sci 2001;24:241-4.
2. Ringwald J, Zimmermann R, Eckstein R. The new generation of platelet additive solution for storage at 22 degrees C: development and current experience. Transfus Med Rev 2006;20:158-64.

16 HOW SUPPLIED/STORAGE AND HANDLING

Isoplate™ Solution Platelet Additive Solution [PAS-F] is supplied sterile and nonpyrogenic In EXCEL® Containers. The 500 mL containers are packaged 24 per case.

Storage

Store at 20°C to 25°C (68°F to 77°F), excursions permitted between 15°C and 30°C (between 59°F and 86°F). [See USP Controlled Room Temperature.]

Rx only

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