INTERSOL - platelet additive 3 solution
Fenwal, Inc.

Direction Insert

Rx only

Store at Controlled Room Temperature. Protect from freezing. Avoid excessive heat. Definition of "Controlled Room Temperature":

"A temperature maintained thermostatically that encompasses the usual and customary working environment of 20° to 25°C (68° to 77°F); that results in a mean kinetic temperature calculated to be not more than 25°C; and that allows for excursions between 15°C and 30°C (59° and 86°F) that are experienced in pharmacies, hospitals, and warehouses. Provided the mean kinetic temperature remains in the allowed range, transient spikes up to 40°C are permitted as long as they do not exceed 24 hours ... The mean kinetic temperature is a calculated value that may be used as an isothermal storage temperature that simulates the non isothermal effects of storage temperature variations."

Reference: United States Pharmacopeia, General Notices. United States Pharmacopeial Convention, Inc. 12601 Twinbrook Parkway, Rockville, MD.

Dispose of waste in appropriate biohazard container or according to local regulatory requirements.

Indications and Usage:
InterSol solution is an isotonic solution designed to replace a proportion of the plasma used in the storage of leukoreduced apheresis platelets under standard blood banking conditions. There is no direct therapeutic effect to be expected from the formulation. The solution should never be infused directly into a patient.

InterSol platelets are leukocyte-reduced apheresis platelet concentrates that are stored in a mix of 65% InterSol and 35% plasma, nominal. InterSol platelets prepared within the ranges described in the apheresis system Operator's Manuals may be stored for up to 5 days at 20-24°C, with continuous agitation.

Dosage and Administration:
InterSol solution is to be used with the AMICUS Separator System or the TRIMA ACCEL system. For full instructions on the use of InterSol solution, see the Operator's Manual for the respective platelet collection system.

Dosage Forms and Strengths:
InterSol solution is provided as a 500 mL sterile and non-pyrogenic solution in a non-PVC plastic container with a sterile and non-pyrogenic fluid path. Each 100 mL contains 305 mg Dibasic Sodium Phosphate, Anhydrous, USP; 93 mg Monobasic Sodium Phosphate, Monohydrate, USP; 318 mg Sodium Citrate, Dihydrate, USP; 442 mg Sodium Acetate, Trihydrate, USP; 452 mg Sodium Chloride, USP; Water for Injection, USP quantity sufficient.

Contraindications:
InterSol solution is added to apheresis-derived leukoreduced platelet concentrates after the apheresis procedure is complete. It is not for direct intravenous infusion. There are no known contraindications associated with the use of InterSol solution for the preparation of InterSol platelets.

Warnings and Precautions:

- InterSol solution is NOT FOR DIRECT INTRAVENOUS INFUSION.
- Do not use if particulate matter is present or if the solution is cloudy.

- Do not use if the container is damaged, leaking or if there is any visible sign of deterioration.
- Do not vent.
- Do not reuse. Discard unused or partially used InterSol solution.
- Protect from sharp objects.
- Verify that the InterSol solution has been securely attached to the PAS Connector line to avoid disconnection and leaks.

Adverse Reactions:
InterSol solution is added to leukoreduced platelet concentrates after the apheresis procedure is complete. It is not for direct intravenous infusion. InterSol solution is not expected to cause adverse events other than those normally associated with platelet transfusion.

Drug Abuse / Dependence:
InterSol solution is used as a storage solution for platelet concentrates and has no pharmacological effect.

Overdosage:
InterSol solution is used as a storage solution for platelet concentrates and it is not for direct intravenous infusion.

Description:
InterSol solution is an isotonic solution designed to replace a proportion of the plasma used in the storage of platelets. The solution contains constituents that are naturally occurring components present in many cellular systems: sodium acetate as a nutrient, sodium citrate to prevent platelet clumping and activation, sodium phosphate for buffering and sodium chloride for osmolarity. InterSol solution does not have a pharmacological effect in vivo, but rather acts to provide the appropriate environment and nutrients in lieu of a portion of the plasma normally used for the storage of platelets.

Clinical Pharmacology:
InterSol solution is used as a storage solution for platelet concentrates and it is not for direct intravenous infusion. This solution has no pharmacological effect.

Clinical Studies:

<u>In Vitro Biochemical and Functional Evaluations AMICUS-derived, leukoreduced platelets</u>
InterSol platelet concentrates (n=70) prepared using the AMICUS separator and stored for 5 days showed a median and mean pH value on Day 5 of 7.2 and 7.2 ± 0.1 (range: 6.9-7.5), respectively, with a lower non-parametric 95%/95% tolerance limit of 6.9.

Supplemental in vitro assessments of InterSol platelets and AMICUS-derived leukoreduced platelets stored in 100% plasma are presented in Table 2.

InterSol platelets irradiated (n=18) at either 2500 or 2800 cGray (dependent on site procedures) were compared to non-irradiated InterSol platelets. At the end of storage on Day 5 the platelet yields of the irradiated products were concentrated between 2.5×10^{11} to 3.5×10^{11} and included one product with a yield less than2.5×10^{11} and two products with yields greater than 3.5×10^{11}. In vitro testing is not predictive of in vivo performance, which was not evaluated. Summary statistics are presented in Table 3.

<u>In Vivo Recovery and Survival in Healthy Subjects AMICUS-derived, leukoreduced platelets</u>

In vivo evaluation of InterSol platelets at Day 5 (n=33) compared to a fresh platelet control resulted in a mean percent recovery of 46.4 ± 11.9 percent and 58.0 ± 10.7 percent and mean survival of 5.7 ± 1.4 days and 8.0 ± 1.4 days, respectively. The in vivo data collected were used to calculate the upper limit of a two-sided 95% confidence interval of the mean percent recovery of the algebraic expression (0.66 x Fresh – 5 Day), and of the mean percent survival (days) of the algebraic expression (0.58 x Fresh – 5 Day). The upper bound of the two-sided 95% confidence intervals for recovery and survival on Day 5 was –4.6 and –0.6 respectively and met the requirement of less than 0.

Post-Market Transfusion-Related Adverse Events (AE) Study AMICUS-derived, leukoreduced platelets

An open label, non-randomized, retrospective medical record review study was performed in 6 centers to demonstrate that the overall rate of transfusion-related AEs in patients receiving InterSol Platelet transfusions was not more than double the rate in patients receiving apheresis platelets stored in 100% plasma (Plasma Platelets). The study categorized adverse transfusion reactions according to the definitions outlined by the Biovigilance Component of the National Healthcare Safety Network (NHSN) System. All sites that participated were required to have systems in place to observe transfusion-related AEs and to record when no transfusion-related AE was observed. An independent Clinical Events Committee (CEC) blinded to platelet type and study site adjudicated the reported events.

Patients were prescribed platelet transfusions per each site's standard practice. The type of platelet unit the patient received was based on the site's inventory at the time the transfusion was ordered. Site personnel observed the platelet transfusion recipient following their standard procedures. Signs and symptoms of a potential transfusion-related reaction were noted using existing reporting systems. A total of 14,005 transfusions from 6 study sites were included in the final analysis. A total of 4,160 InterSol Platelet transfusions were given to a total of 1,444 patients, and 9,845 Plasma Platelet transfusions were given to 2,202 patients. There were 165 CEC-adjudicated adverse reactions reported. Of those, 23 events were associated with InterSol Platelets and 142 events were associated with Plasma Platelets.

Overall, 1.13% of all transfusions resulted in an AE. The percentage of InterSol Platelet transfusions which led to AEs was 0.55%, while 1.37% of Plasma Platelet transfusions resulted in AEs. The 97.5% upper confidence limit for the relative risk of transfusion-related AE associated with InterSol Platelets relative to Plasma Platelets was 0.66, indicating that the study objective of ruling out a doubling of transfusion-related AEs for InterSol vs. Plasma Platelets was met.

The majority of the 165 CEC-adjudicated reactions were Allergic (n=93) or Febrile Non-Hemolytic Transfusions Reactions (FNHTR, n=56), at 0.66% and 0.40% of total transfusions, respectively. There were allergic reactions associated with 0.29% of InterSol Platelet transfusions and 0.82% of Plasma Platelet transfusions. FNHTR events were associated with 0.17% of InterSol Platelet transfusions and 0.50% of Plasma Platelet transfusions.

No InterSol Platelet transfusion was associated with more than one reaction. Seven (7) Plasma Platelet transfusions (0.07% of total transfusions) were associated with two (2) separate adverse reactions each. Two (2) InterSol Platelet and five (5) Plasma Platelet adverse reactions were classified as severe. All other reactions were classified as non-severe. All adverse reactions were reported with an outcome of "Minor or No Sequelae".

No adverse safety trends were identified after review of all the AEs by the independent Clinical Events Committee.

Table 1: *In Vitro* Assessments, AMICUS Separator-derived, leukoreduced platelets

Parameter	Day	InterSol n, mean (sd)	Plasma n, mean (sd)
Glucose (mg/dL)	5	67, 45 (17)	67, 230 (36)
Lactate (mM/L)	5	67, 10.4 (2.0)	67, 9.9 (2.3)
pO_2 (mmHg)	5	70, 145 (34)	70, 147 (32)
pCO_2 (mmHg)	5	70, 22 (5)	70, 31 (6)
Bicarbonate (mM/L)	5	70, 5.3 (1.5)	70, 11.1 (2.7)
Lactate Dehydrogenase (U/L)	1	70, 68 (30)	70, 126 (50)
Lactate Dehydrogenase (U/L)	5	70, 147 (84)	70, 154 (57)
CD62 Expression (%)	5	63, 11.3 (5.8)	65, 8.1 (5.0)
Morphology Score (Max Score 400)	5	70, 295 (71)	70, 303 (69)
Hypotonic Shock Response (%)	5	70, 52.8 (9.1)	70, 67.3 (9.5)
Extent of Shape Change (%)	5	70, 13.3 (6.8)	70, 23.3 (4.7)

Table 2: *In Vitro* Assessments—Irradiated and Non-Irradiated Platelets, AMICUS Separator-derived, leukoreduced platelets

Parameter	Day	InterSol Irradiated n, mean (sd)	InterSol Non-Irradiated n, mean (sd)
Glucose (mg/dL)	5	18, 28 (12)	18, 27 (12)
Lactate (mM/L)	5	18, 11.9 (1.5)	18, 12.0 (1.4)
pO_2 (mmHg)	5	18, 152 (16)	18, 147 (21)
pCO_2 (mmHg)	5	18, 20 (4)	18, 21 (4)
Bicarbonate (mM/L)	5	18, 4.3 (1.2)	18, 4.3 (1.2)
Lactate Dehydrogenase (U/L)	5	18, 233 (117)	18, 223 (120)
CD62 Expression (%)	5	18, 16.4 (4.3)	18, 16.2 (3.9)
Morphology Score (Max Score 400)	5	18, 291 (73)	18, 297 (79)
Hypotonic Shock Response (%)	5	18, 51.4 (8.2)	18, 52.7 (8.1)
Extent of Shape Change (%)	5	18, 8.3 (3.9)	18, 10.7 (4.1)

In Vitro Biochemical and Functional Evaluations, TRIMA ACCEL-derived, leukoreduced platelets

InterSol platelet concentrates (n = 60) prepared using the Trima Apheresis system and stored for 5 days showed a mean pH value on Day 5 of 7.2 ± 0.1 (range 7.0 – 7.3), with a lower one-sided 95% confidence interval of 0.951.

Supplemental in vitro assessments of TRIMA ACCEL-derived leukoreduced platelets stored in InterSol platelet and 100% plasma are presented in Table 3.

In Vivo Recovery and Survival in Healthy Subjects, TRIMA ACCEL-derived, leukoreduced platelets

In vivo evaluations of TRIMA ACCEL-derived platelets stored in InterSol at Day 5 (n = 24) compared

to fresh platelet control resulted in a mean percent recovery of 45.2 ± 12.3 percent and 56.0 ± 13.2 percent and a mean survival of 5.4 ± 1.0 days and 7.9 ± 1.5 days, respectively. The in vivo data collected were used to calculate the upper limit of a one-sided 97.5% confidence interval of the mean percent recovery of the algebraic expression of (0.66 x Fresh – 5 Day) and the mean percent survival (days) of the algebraic expression (0.58 x Fresh – 5 Day). The lower limit of the one-sided 97.5% confidence intervals for recovery and survival on Day 5 was 4.0 and 0.4 respectively and met the requirement of greater than 0.

Table 3: *In Vitro* Assessments, TRIMA ACCEL-derived, Leukoreduced Platelets

Parameter	Day	InterSol n, mean (sd)	Plasma n, mean (sd)
Glucose (mg/dL)	5	60, 2.6 (1.0)	60, 15.9 (2.2)
Lactate (mM/L)	5	60, 8.1 (2.2)	60, 7.3 (2.3)
pO_2 (mmHg)	5	60, 67.1 (18.9)	60, 62.0 (19.1)
pCO_2 (mmHg)	5	60, 9.9 (1.8)	60, 15 (1.7)
Bicarbonate (HCO_3) (mM)	5	60, 4.65 (0.9)	60, 11.6 (1.9)
Lactate Dehydrogenase (U/L)	1	60, 69 (17.6)	60, 136.7 (26.1)
Lactate Dehydrogenase (U/L)	5	60, 134.2 (61.5)	60, 151.5 (30.7)
P-selectin (%)	5	60, 26.3 (7.6)	60, 9.4 (4.4)
Morphology	5	60, 293.1 (31.8)	60, 308.7 (33.3)
Hypotonic Shock Response (HSR) (%)	5	60, 44.5 (8.4)	60, 56.5 (9.7)
Extent of Shape Change (%)	5	60, 24.1 (6.0)	60, 30.7 (5.1)

How Supplied/Storage and Handling:
500 mL sterile solution in a non-PVC plastic container with a sterile, non-pyrogenic fluid path. The InterSol solution container is supplied in a vented plastic overwrap covering that serves as a dust cover for the container. The dust cover is not a sterility barrier and is not an element that defines the expiration date of the InterSol product.

Symbols with Definitions:

	Caution, consult instructions for use
	Sterilized by a combination of steam and radiation. Sterile fluid path.
	Non-pyrogenic fluid path
	Do not reuse
	Do not use if the product sterile barrier system is compromised
	Code
	Lot
	Expiration Date
	Manufacturer
	Manufacturing facility / Manufactured by
	Fragile
	This way up
	Do not open packaging with sharp objects
	Recyclable
	Do not vent
	Platelet Additive Solution
Rx only	For US Only. United States federal law restricts this device to sale by or on the order of a licensed health care practitioner.

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PACKAGE/LABEL PRINCIPAL DISPLAY PANEL

Code
REF **6B7880**

NDC No.
0942-9602-12

(01) 0 0309429 60212 4

Rx only
500 mL

InterSol Solution Platelet Additive Solution 3

Store at Controlled Room Temperature. Protect from freezing. Avoid excessive heat. Discard unused portion. Each 100 mL contains 305 mg Dibasic Sodium Phosphate, Anhydrous, USP; 93 mg Monobasic Sodium Phosphate, Monohydrate, USP; 318 mg Sodium Citrate, Dihydrate, USP; 442 mg Sodium Acetate, Trihydrate, USP; 452 mg Sodium Chloride, USP; Water for Injection, USP quantity sufficient.

NOT FOR DIRECT INTRAVENOUS INFUSION.

Manufacturer
Fresenius Kabi AG
61346 Bad Homburg / Germany
Tel.: +49 (0) 61 72 / 686-0

Manufacturing facility / Manufactured by
Fenwal International Inc.
Road 357 K.M. 0.8
Maricao, Puerto Rico 00606
Made in US

Caution, consult instructions for use

STERILE IR Sterilized by a combination of steam and radiation. Sterile fluid path.

Nonpyrogenic fluid path

Do not use if the product sterile barrier system is compromised.

Do not reuse

Do not vent

Platelet Additive Solution

LOT [Lot Number]

Exp [Exp. Date: YYYY-MM-DD]

[Code-128 Barcode: Lot]

[Code-128 Barcode: Exp. date]

FRESENIUS KABI

47-17-13-814 REV: A

INTERSOL

platelet additive 3 solution

Product Information			
Product Type	HUMAN PRESCRIPTION DRUG	**Item Code (Source)**	NDC:0942-9602
Route of Administration	INTRAVENOUS		

Active Ingredient/Active Moiety		
Ingredient Name	**Basis of Strength**	**Strength**
Sodium Chloride (UNII: 451W47IQ8X) (CHLORIDE ION - UNII:Q32ZN48698)	Sodium Chloride	452 mg in 100 mL
SODIUM ACETATE (UNII: 4550K0SC9B) (ACETATE ION - UNII:569DQM74SC)	SODIUM ACETATE	442 mg in 100 mL
Trisodium Citrate Dihydrate (UNII: B22547B95K) (Anhydrous Citric Acid - UNII:XF417D3PSL)	Anhydrous Citric Acid	318 mg in 100 mL
SODIUM PHOSPHATE, DIBASIC (UNII: GR686LBA74) (PHOSPHATE ION - UNII:NK08V8K8HR)	SODIUM PHOSPHATE, DIBASIC	305 mg in 100 mL

Sodium Phosphate, Monobasic, Monohydrate (UNII: 593YOG76RN) (PHOSPHATE ION - UNII:NK08V8K8HR)	Sodium Phosphate, Monobasic, Monohydrate	93 mg in 100 mL

Inactive Ingredients

Ingredient Name	Strength
Water (UNII: 059QF0KO0R)	

Packaging

#	Item Code	Package Description	Marketing Start Date	Marketing End Date
1	NDC:0942-9602-12	500 mL in 1 BAG; Type 0: Not a Combination Product		

Marketing Information

Marketing Category	Application Number or Monograph Citation	Marketing Start Date	Marketing End Date
NDA	BN080041	06/05/2019	

Labeler - Fenwal, Inc. (794519020)

Establishment

Name	Address	ID/FEI	Business Operations
Fenwal International, Inc.		091164590	MANUFACTURE(0942-9602)

Revised: 10/2020 Fenwal, Inc.