Canadian Blood Services BLOOD PLASMA STEM CELLS ORGANS & TISSUES

Pathogen Reduced Platelet Concentrates*

This circular of information addresses:

- **Apheresis Platelets Psoralen Treated**

Composition and properties

Apheresis Platelets Psoralen Treated is a platelet concentrate collected into approximately 19 mL of acid citrate dextrose (ACD-A) anticoagulant using automated apheresis techniques, which includes leukoreduction and addition of platelet additive solution E (PAS-E). The component is collected from a male or female donor. Pathogen reduction is achieved with the Cerus INTERCEPT SV Blood System for Platelets, which includes the addition of 15 mL of 3 mM amotosalen solution (a synthetic psoralen), illumination with 3 Joules/cm^2 of UVA light (wavelength 320 to 400 nm), exposure to a compound adsorption device for the removal of residual amotosalen and free photoproducts, and transfer of the pathogen reduced component into a transfusion unit. An apheresis platelet component is labelled as RhD negative if the donor is RhD negative.

Notes:
Acid Citrate Dextrose – Formula A Anticoagulant contains sodium citrate 22.0 g/L, citric acid 7.3 g/L, dextrose 24.5 g/L.
Platelet Additive Solution E contains sodium citrate dihydrate 3.18 g, sodium acetate trihydrate 4.42 g, sodium dihydrogen phosphate dihydrate 1.05 g, disodium phosphate anhydrous 3.05 g, potassium chloride 0.37 g, magnesium chloride hexahydrate 0.30 g, sodium chloride 4.05 g, water for injection 1000 ml.
Amotosalen Solution contains amotosalen HCl 101 mg, sodium chloride 924 mg, water for injection 100 mL

TABLE 1: Typical unit content is based on the number of units (n) tested during development from February 2022 to April 2022, inclusive.

Platelet Component	Unit Volume (mL) Mean ±1 SD	Residual Plasma (mL) Mean ±1 SD	Platelet Count ($x10^9$ platelets per L) Mean ±1 SD	Platelet Yield ($x10^9$ platelets per unit) Mean ±1 SD
Apheresis Platelets Psoralen Treated	277 ± 4 n = 32	116 ± 2 n = 32	909 ± 81 n = 32	252 ± 22 n = 32

Quality criteria that must be met:
Apheresis Platelet Pool input to INTERCEPT SV Blood System for Platelets: Residual Plasma: 32 – 47% in all units; Residual Red Blood Cells: <4x10^6/mL in all units; Residual Leukocytes: <5x10^6 in all units tested.
Apheresis Platelets Psoralen Treated: At component expiry, Volume: ±10% labelled volume in all units tested; Platelet Unit Yield: ≥200x10^9/unit in ≥75% of units tested, pH 6.4 to 7.8 in ≥95% of units tested.

Other component characteristics:
Apheresis Platelets Psoralen Treated: Specific Gravity: 1.01 g/mL.

The donor sample is tested for ABO group, RhD type, anti-A and anti-B titres and clinically significant antibodies against red blood cell antigens. ABO and RhD is indicated on the component label. Units determined to be Low Anti-A/B will be labeled as such.

Prior to making blood components available for transfusion, a sample of each donor's blood must test non-reactive for:

- antibodies to human immunodeficiency virus (HIV-1 and HIV-2), hepatitis C virus (HCV), human T-cell lymphotropic virus, type I and II (HTLV-I/II), hepatitis B core antigen (HBcore)
- hepatitis B surface antigen (HBsAg)
- presence of viral RNA [HIV-1 and HCV]
- presence of viral DNA [hepatitis B virus (HBV)]
- syphilis

A donor sample is only tested for antibodies to *Trypanosoma cruzi* (*T. cruzi* or Chagas Disease) and the presence of viral RNA [West Nile Virus (WNV)] when increased risk is present.

In addition to viral testing, pathogen inactivation treatment is used to inactivate a broad range of pathogens, including viruses, bacteria, and protozoan parasites, thus reducing the risk of transfusion-transmitted infections. Residual donor leukocytes are also inactivated, reducing the risk of transfusion-associated graft versus host disease (TA-GVHD). (1)

In some emergency situations, with the approval of both Canadian Blood Services and recipient's physician, partially tested or untested blood may be released for transfusion.

Packaging

Apheresis Platelets Psoralen Treated are stored in gas-permeable ethylene vinyl acetate (EVA) bags. These platelet component storage bags do not contain di-ethyl hexyl phthalate (DEHP) plasticizer; however, transfusion ports and tubing attached to these bags may be manufactured from polyvinyl chloride (PVC) plastics containing DEHP. In addition, platelets have been in contact with DEHP plasticizer during their collection and manufacturing. (2)

Storage and handling

Apheresis Platelets Psoralen Treated must be stored at 20 - 24°C with continuous gentle agitation. During transport cessation of agitation for 24 hours is acceptable. (3) The shelf life is 7 days.

Visual inspection should be performed. A platelet unit should be mixed thoroughly prior to transfusion. Platelet aggregates may be present.

Apheresis Platelets Psoralen Treated should not be irradiated. INTERCEPT amotosalen processing with UVA light reduces viable T-cells comparable to a 2,500 cGy treatment of gamma irradiation (5-6 log10 inactivation). (1)

Apheresis Platelets Psoralen Treated should not be volume reduced (centrifuged and supernatant removed) unless transferred to a bag suitable for centrifugation. If aliquoting from **Apheresis Platelets Psoralen Treated**, the remaining volume in the parent unit should not be reduced to less than 135 mL due to poor platelet storage characteristics.

Action

The primary role of transfused platelets is to participate in primary hemostasis through the provision of functionally normal platelets.

Indications

The aim of transfusion is to prevent or treat bleeding due to platelet deficiency or dysfunction.

Platelet transfusion is indicated for the treatment of recipients with clinically significant bleeding and low platelet counts secondary to decreased production or dilutional thrombocytopenia.

*for non-pathogen reduced platelet concentrates, please see the Canadian Blood Services Circulars of Information: Platelets (Pooled Platelets LR CPD and Apheresis Platelets) and Apheresis Platelets, PAS Added.

On occasion, platelet transfusion may be indicated for the treatment of recipients with platelet destructive conditions or functionally abnormal platelets in the setting of clinically significant bleeding, medications, prior to an invasive procedure associated with high risk of bleeding.

Prophylactic platelet transfusions may be indicated for very low platelet counts (≤$10x10^9$/L) secondary to decreased production. Prophylactic transfusions at higher platelet count thresholds may be indicated for invasive procedures and/or in the presence of additional risk factors for bleeding.

For further information, refer to the *Clinical Guide to Transfusion,* chapter. 2: Blood Components, and chapter 18: Platelet Transfusion, Alloimmunization and Management of Platelet Refractoriness. (4)

Contraindications

Do not use **Apheresis Platelets Psoralen Treated** for patients with a history of hypersensitivity reaction to amotosalen or other psoralens.

Do not use **Apheresis Platelets Psoralen Treated** for neonatal patients treated with phototherapy devices that emit a peak energy wavelength less than 425 nm, or have a lower bound of the emission bandwidth <375 nm, due to the potential for erythema resulting from interaction between ultraviolet light and amotosalen.

Warnings and precautions

CAN/CSA-Z902 Blood and Blood Components requires that a policy be in place concerning group substitution when platelets with compatible plasma are not available. (5) Hemolysis has been reported as an uncommon complication of plasma ABO incompatibility with platelet transfusions.

The intended recipient must be properly identified before the transfusion is started.

RhD positive platelets given to an RhD negative recipient may cause sensitization. If RhD positive platelets are transfused to an RhD negative recipient, RhIG should be considered.

Apheresis Platelets Psoralen Treated are suspended in approximately 40% donor plasma (or approximately 115 mL per unit) and 60% platelet additive solution E. The plasma in the platelet concentrate may be from a female donor. Multiple transfusions of platelets in PAS E may lead to overdosage of potassium and magnesium. Monitor changes in electrolyte concentration and acid-base balance when multiple transfusions of platelets in PAS-E are administered. (6)

Careful donor selection, laboratory tests, and the use of pathogen inactivation technology do not eliminate the hazard of transmitting infectious disease agents or pathogens (Table 2). While laboratory studies of amotosalen processing with UVA light have shown a reduction in levels of certain viruses, bacteria, and parasites, there is no pathogen inactivation process that has been shown to eliminate all pathogens. (1)

For intrauterine transfusion, clinicians may choose, in addition to the use of leukocyte reduced components, to transfuse non-pathogen reduced platelet concentrates*. There is limited safety data for **Apheresis Platelets Psoralen Treated** when used for intrauterine transfusion. (7)

The benefit and risk of transfusing **Apheresis Platelets Psoralen Treated** components should be carefully assessed and balanced in the case of pediatric transfusions where long-term safety data is limited. Clinicians may choose, in addition to the use of leukocyte reduced components, to transfuse non-pathogen reduced platelet concentrates*.

Apheresis Platelets Psoralen Treated are not recommended for use in patients with destruction of endogenous and exogenous platelets, such as in thrombotic thrombocytopenic purpura, idiopathic thrombocytopenic purpura, or heparin induced thrombocytopenia (HIT) unless the recipient has a life-threatening hemorrhage.

Apheresis Platelets Psoralen Treated contain approximately 115 mL of donor plasma, this component does not contain a significant source of coagulation factors. Recipients with known anaphylaxis to plasma should only receive platelet components under appropriate medical supervision.

The use of **Apheresis Platelets Psoralen Treated** may lead to increased non-immune platelet refractoriness. (8)

Some collection needles are in contact with latex. Canadian Blood Services cannot guarantee that this component is latex free.

Adverse events

Potential adverse events related to a blood transfusion range in severity from minor with no sequelae to life-threatening. Alloimmunization of the recipient may be a consequence of transfusion. All adverse events occurring during a transfusion should be evaluated to determine whether or not the transfusion can be safely continued/restarted. All adverse events suspected to be related to a transfusion (whether during or after a transfusion) should be reported to your local transfusion service and when required (i.e., when the adverse event could be attributed to the quality of a blood component), to Canadian Blood Services and the hospital/regional hemovigilance network. Federal Blood Regulations and Canadian standard *CAN/CSA-Z902 Blood and Blood Components* require reporting of adverse events associated with blood component quality to Canadian Blood Services. (5) (9) (10) For further information, refer to the *CAN/CSA-Z902 Blood and Blood Components* and *Transfusion Transmitted Injuries Surveillance System.* (9) (11) **Apheresis Platelets Psoralen Treated** may cause Acute Respiratory Distress Syndrome (ARDS) with large volume platelet transfusions. An increased incidence of ARDS was reported in a randomized trial for recipients of psoralen treated platelets, 5/318 (1.6%), compared to recipients of conventional platelet components (0/327). Recipients should be monitored for signs and symptoms of ARDS. (1)

* for non-pathogen reduced platelet concentrates, please see the Canadian Blood Services Circulars of Information: Platelets (Pooled Platelets LR CPD and Apheresis Platelets) and Apheresis Platelets, PAS Added.

TABLE 2: The following adverse events have been described with transfusion of fresh blood components (4) (9) (12) (13) (14) (15) (16) (17) (18) (19)			
Event	**Approximate Frequency**	**Symptoms and Signs**	**Notes**
Febrile non-hemolytic transfusion reactions (FNHTR)	0.5-2:100†	Fever, chills and/or rigor.	Diagnosis of exclusion. Rule out other causes.
Mild allergy	1:100	Urticaria, pruritis and/or erythema.	
Transfusion associated circulatory overload (TACO)	0.1-1:100†	Dyspnea, orthopnea, cyanosis, tachycardia, raised venous pressure and/or hypertension.	
Delayed hemolytic transfusion reactions (HTR)	1:25,000	Hemolysis occurs 4 – 14 days post transfusion.	Direct antiglobulin test may be positive.
Acute hemolytic transfusion reactions (HTR)	1:40,000	Fever, chills, hemoglobinuria, dyspnea, shock, disseminated intravascular coagulation, chest pain and/or back pain.	Often due to undetected serological incompatibility or sample misidentification.
Transfusion related acute lung injury (TRALI)	0.5-1:100,000†	New onset of hypoxemia, new bilateral lung infiltrates on chest X-ray and no evidence of circulatory overload.	Approximate frequency based on Canadian Blood Services hospital reported data: • 1:82,350 classified possible TRALI • 1:411,750 classified as TRALI
Septic reaction	Rare	Fever, chills, rigors, nausea, vomiting, diarrhea, abdominal and muscle pain, hypotension, hemoglobinemia, and/or disseminated intravascular coagulation.	Approximate frequency per red blood cell unit based on Canadian Blood Services data: • bacterial sepsis* 1 in 2,128,468 • death from bacterial sepsis* < 1 in 4,256,936 As reported by other international blood agencies (16): • bacterial sepsis 1:500,000 • death from bacterial sepsis 1:10,000,000 Approximate frequency per platelet concentrate based on Canadian Blood Service data: • bacterial sepsis** 1 in 125,000 • death from bacterial sepsis** 1 in 909,091 As reported by other international blood agencies (16): • estimated risk of bacterial sepsis 1 in 100,000 • estimated risk of death from bacterial sepsis 1 in 1,000,000 For evaluation and treatment of a reaction due to suspected bacterial contamination, refer to reference #9. Components treated with pathogen inactivation technology reduce this risk.
Isolated hypotensive reaction	Rare	Hypotension, occasionally accompanied by dyspnea and nausea.	Diagnosis of exclusion. May occur more frequently in recipients on angiotensin-converting enzyme (ACE) inhibitor.
Anaphylaxis	Rare	Severe multi-systemic reaction involving the skin, and/or respiratory, gastrointestinal, cardiovascular systems.	IgA deficient recipients who have formed anti-IgA antibodies may experience anaphylactic reactions. However, in most cases of anaphylactic reactions, no specific antibodies are found in the recipient.
Post transfusion purpura (PTP)	Very rare	Abrupt onset of severe thrombocytopenia 1 – 24 days post transfusion.	Most cases of PTP occur in recipients who are HPA-1b homozygous receiving HPA-1a positive blood components.
Graft-versus-host disease (GVHD)	Very rare	Pancytopenia, rash, liver dysfunction, diarrhea.	Irradiated cellular non-pathogen reduced blood components or components treated with pathogen inactivation technology reduce this risk.
Infectious disease	Very rare‡	Variable according to infectious disease.	Blood components have been described to transmit viruses other than HIV, HBV, HCV, HTLV I/II and WNV as well as parasites and prions. Components treated with pathogen inactivation technology reduce this risk.
Delayed serological	Varies by patient population	Presence of new or amnestic alloantibody.	
Iron overload	Varies by patient population	Early stages may be asymptomatic. Clinical signs relate to hepatic, pancreatic and/or cardiac organ damage.	Due to repeated red blood cell transfusions in certain patient populations.
Hyperkalemia	Varies by patient population	Cardiac arrhythmia, changes in ECG, and/or cardiac arrest.	Seen in massive, rapid transfusion; neonates and infants receiving red blood cells irradiated prior to storage are at particular risk.
Other complications of massive transfusion	Varies by patient population	Complications may include hypothermia, citrate toxicity, acidosis, dilutional coagulopathy.	Appropriate monitoring may abrogate some complications.

† Range of frequency varies based on blood component type.
‡ Transmissible blood-borne infection surveillance is carried out by Canadian Blood Services on a continuous basis, and reported annually. (17)
* Canadian Blood Services Red Blood Cell units transfused between April 1, 2011 and October 31, 2016 (n=4,256,936); frequencies are likely to have quite wide confidence intervals due to quality of reporting.
** Unpublished Canadian Blood Services Surveillance data 2006-2016.

Reporting of suspected cases of transfusion-related infections such as HIV, HCV, HTLV, HBV, WNV and other transfusion-related infections is described in the *Clinical Guide to Transfusion*, chapter 1: Vein to Vein: A Summary of Blood Collection and Transfusion in Canada. (4)

Dose and administration

The number of units of **Apheresis Platelets Psoralen Treated** to be administered depends on the clinical situation of each recipient. The response to platelet transfusions is best assessed by observing whether bleeding stops and by measuring post transfusion platelet counts. Standard doses are:

a) **adults:** one unit of **Apheresis Platelets Psoralen Treated**.

b) **children and neonates:** up to 10mL/kg of **Apheresis Platelets Psoralen Treated**, and up to one standard adult dose (recipients > 15 kg).

Each dose of platelets should increase the recipient's platelet count by at least $15x10^9$/L. (13) In some instances more than one standard dose may be required.

A standard blood administration set containing a 170 – 260 micron filter or a filter of equivalent efficacy, approved by Health Canada, must be used for infusion. Transfusion may proceed as fast as tolerated but must be completed in less than four hours.

No medications or solutions may be added to or infused through the same tubing simultaneously with blood or blood components, unless the solution has been approved for this use by Health Canada or there is documentation

available to show that addition of the solution to the blood component involved is safe. (5) Co-administration of 0.9% sodium chloride injection, ABO-compatible plasma or 5% albumin can be performed at the discretion of the recipient's physician.

All transfusions should be complete within 4 hours of removal from storage. For more information, refer to the *Clinical Guide to Transfusion*. Recipients should be under clinical observation, in accordance with institutional guidelines, during transfusion with close observation during the first 15 minutes.

Transformed and additional information

TABLE 3: Modified Components

Modification	Description	Indication	Storage	Benefits	Adverse events
None currently available from Canadian Blood Services					

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This *Circular* is an extension of the component label and conforms to the applicable Regulations issued by the Health Products and Food Branch, Health Canada. (10)