

# CIRCULAR OF INFORMATION

## For the Use of Human Blood Components

### Plasma Components

This component information addresses:

- **Apheresis Frozen Plasma (ACD-A)**
- **Frozen Plasma CPD**
- **Cryosupernatant Plasma CPD**
- **Cryoprecipitate CPD**

### Composition and properties

**Apheresis Frozen Plasma (AFP)** is collected by apheresis. A typical unit contains approximately 38 mL of ACD-A anticoagulant and is stored in a  $\leq -18^{\circ}\text{C}$  freezer within 24 hours of collection.

**Frozen Plasma (FP)** is prepared from whole blood collected in approximately 70 mL of CPD anticoagulant, centrifuged and then separated from the red blood cells and buffy coat. The plasma is stored in a  $\leq -18^{\circ}\text{C}$  freezer within 24 hours of collection. **FP** is not labelled as leukoreduced as some units may contain  $\geq 5 \times 10^6$  leukocytes/unit.

**AFP** and **FP** contain similar levels of all non-labile coagulation factors. The component label clearly indicates the type of anticoagulant in the component.

**Cryosupernatant Plasma** is prepared from slowly thawed **FP** that is centrifuged to separate the plasma from the insoluble cryoprecipitate. The insoluble cryoprecipitate is removed and the remaining plasma is refrozen.

**Cryoprecipitate** is prepared from slowly thawed **FP** that is centrifuged to separate the insoluble cryoprecipitate from the plasma. The insoluble cryoprecipitate is refrozen.

#### Notes:

ACD-A (acid citrate dextrose – Solution A) anticoagulant contains sodium citrate 22.0 g/L, citric acid 7.3 g/L, dextrose 24.5 g/L.

CPD (citrate phosphate dextrose) anticoagulant contains citric acid 3.27 g/L, sodium citrate 26.3 g/L, sodium acid phosphate 2.51 g/L, dextrose 25.5 g/L.

For approximate procoagulant and anticoagulant factor concentrations in some of these components, see <https://professionaleducation.blood.ca>.

Plasma Component	Volume (mL) Mean $\pm$ 1 SD	Factor VIII (IU/mL) Mean $\pm$ 1 SD	Fibrinogen (mg) Mean $\pm$ 1 SD
AFP (ACD-A)	ACD-A: 249 $\pm$ 13 n = 417	1.05 $\pm$ 0.37* n = 30	N/A
FP	289 $\pm$ 16 n = 762	0.88 $\pm$ 0.27 n = 570	N/A
Cryosupernatant Plasma	276 $\pm$ 17 n = 227	N/A	N/A
Cryoprecipitate	10 $\pm$ 1.7 n = 188	N/A	366 $\pm$ 115 n = 188

\*Units (n) tested from March 2019 to May 2019, inclusive.

#### Quality criteria that must be met:

**AFP ACD-A:** Volume:  $\pm 10\%$  labelled volume in all units tested; Factor VIII:  $\geq 0.52$  IU/mL in  $\geq 75\%$  of units tested.

**FP:** Volume:  $\pm 10\%$  labelled volume and  $\geq 100$  mL in all units tested; Factor VIII:  $\geq 0.52$  IU/mL in  $\geq 75\%$  of units tested.

**Cryosupernatant Plasma:** Volume:  $\pm 10\%$  labelled volume and  $\geq 100$  mL in all units tested.

**Cryoprecipitate:** Volume: 5-15 mL in all units tested; Fibrinogen:  $\geq 150$  mg/unit in  $\geq 75\%$  of units tested.

The donor sample is tested for ABO group, RhD type, anti-A and anti-B titres and clinically significant antibodies against red cell antigens. ABO group is indicated on the component label. RhD type may also be indicated on the label. Group A plasma 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

In some cases, a donor sample is also tested for cytomegalovirus (CMV) antibody and/or the presence of IgA; if IgA deficient this is indicated on the label.

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 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

**AFP, FP, Cryosupernatant Plasma** and **Cryoprecipitate** is stored in a di-ethyl hexyl phthalate (DEHP) plasticized bag.<sup>1,2,3,23</sup>

### Storage and handling

Plasma components are stored at  $-18^{\circ}\text{C}$  or colder for a maximum period of 12 months. Once thawed, plasma components should not be refrozen.

Visual inspection should be performed; refer to the *Visual Assessment Guide* for further information.<sup>4</sup>

Thaw component in a watertight protective plastic overwrap using gentle agitation in a waterbath at  $30 - 37^{\circ}\text{C}$  (thawing may take 20 – 30 minutes for **AFP, FP** and **Cryosupernatant Plasma** and up to 10 minutes for **Cryoprecipitate**) or thaw in a microwave specifically manufactured for this use.

- **AFP ACD-A, FP** and **Cryosupernatant Plasma:** store at  $1 - 6^{\circ}\text{C}$  and transfuse within 120 hours.
- **Cryoprecipitate:** store at  $20 - 24^{\circ}\text{C}$  and transfuse within 4 hours. For pooling, mix well with 10 - 15 mL of diluent to ensure complete removal of all material from the container. The preferred diluent is 0.9% sodium chloride injection.

### Action

Transfused **AFP** and **FP** act as plasma protein supplements and plasma volume expanders. These plasma components contain all clotting factors.

Transfused **Cryosupernatant Plasma** provides a source of plasma with reduced levels of von Willebrand factor including high molecular weight multimers.<sup>5</sup>

Transfused **Cryoprecipitate** provides a source of fibrinogen, coagulation factors VIII, XIII, and von Willebrand factor (AHF-VWF). Fibronectin is also present.

## Indications

Alternatives to plasma components should be considered prior to the transfusion.

**AFP** and **FP** may be useful in the management of:

- bleeding patients or patients undergoing invasive procedures who require replacement of multiple plasma coagulation factors,
- patients with massive transfusion with clinically significant coagulation abnormalities,
- patients on warfarin who are bleeding or need to undergo an invasive procedure before vitamin K could reverse the warfarin effect, and where prothrombin complex concentrate is not available or is contraindicated,<sup>6</sup>
- patients with selected coagulation factor or with rare specific plasma protein deficiencies for which a more appropriate alternative therapy is not available,
- preparation of reconstituted whole blood for exchange transfusion in neonates,
- patients with thrombotic thrombocytopenic purpura (TTP) or hemolytic uremic syndrome (HUS) undergoing plasma exchange.

**Cryosupernatant Plasma** may be useful in the management of:

- patients with thrombotic thrombocytopenic purpura (TTP) or hemolytic uremic syndrome (HUS) undergoing plasma exchange,
- patients on warfarin who are bleeding or need to undergo an invasive procedure before vitamin K could reverse the warfarin effect and where prothrombin complex concentrate is not available or is contraindicated.<sup>6,7</sup>

**Cryoprecipitate** may be useful in the management of patients requiring fibrinogen or factor XIII supplementation.

## Contraindications

Recipients with known anti-IgA should receive IgA deficient plasma. Patients with known anaphylaxis to plasma components should only receive plasma components under appropriate medical supervision.

Plasma components should not be used to treat hypovolemia.

**Cryoprecipitate** is not recommended as replacement therapy for patients with Hemophilia A or von Willebrand disease (VWD).

## Warnings and precautions

**AFP**, **FP** and **Cryosupernatant Plasma** must be ABO-compatible; for **Cryoprecipitate**, recipients can be transfused with any ABO group, although neonates and minor children should be given ABO compatible units when possible, or as defined by your facility's policies. RhD need not be considered.

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

Do not use the component if there is evidence of container breakage or of thawing during storage.

DEHP plasticizer is known to leach from DEHP-plasticized bags into blood and blood components. DEHP levels in thawed plasma components may significantly increase over time during storage at 1 – 6°C for 120 hours.<sup>8</sup> Currently, there is no conclusive scientific evidence that DEHP exposure via medical treatments has harmful effects in humans. However, it is recognized that the potentially high risk exposure during medical treatment may raise a concern for harmful effects in humans. Reducing DEHP exposure in neonatal patients has been recommended.<sup>1,9</sup>

Some clotting factor activity in thawed plasma components may be significantly lost during storage for up to 120 hours.<sup>8,10,11,12,13</sup>

Do not use **AFP** or **FP** when coagulopathy can be more appropriately corrected with specific therapy, such as vitamin K or specific factor replacement.

Hemophilia A and B and VWD are more appropriately treated with recombinant or virally inactivated fractionation products or 1-deamino-8-D-arginine vasopressin as initial treatment. For replacement of fibrinogen and factor XIII, commercial virally inactivated concentrates are also available. Some products are only available through the Special Access Programme of Health Canada.

Do not use **Cryosupernatant Plasma** for conditions which require von Willebrand factor supplementation.

Do not use **Cryoprecipitate** to make fibrin glue. Virally inactivated products should be used for this purpose.

Careful donor selection and available laboratory tests do not eliminate the hazard of transmitting infectious disease agents for which testing is performed (see Table 2)<sup>14</sup> or for pathogens that are either not recognized or for which there is no donor screening test.

Virus	Estimated Residual Risk
	Per number of donations
HIV	1 in 21.4 million
HCV	1 in 12.6 million
HBV*	1 in 7.5million
HTLV‡	1 in 619 million

<sup>†</sup> Canadian Blood Services, National Epidemiology and Surveillance data (unpublished).

\*Adjusted for transient nature of HBsAg by the formula of Korelitz with further adjustment to account for the improved sensitivity of newer HBsAg assays.

‡The estimate includes the complimentary benefit of leukoreduction in further reducing the residual risk of transmission via red blood cell and platelet components.

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

## Adverse events

Potential adverse events related to a blood transfusion range in severity from minor with no sequelae to life-threatening. 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. Health Canada, Health Products & Food Branch, Blood Regulations and Canadian Standards Association requires reporting of adverse events associated with blood component quality (e.g., bacterial contamination) to Canadian Blood Services.<sup>15,16,22</sup> For further information, refer to the Canadian Standards Association, *Blood and Blood Components* and *Transfusion Transmitted Injuries Surveillance System*.<sup>15,17</sup>

**TABLE 3:** The following adverse events have been described with transfusion of plasma components. <sup>16,18,19,20,21</sup>

Event	Approximate Frequency	Symptoms and Signs	Notes
Mild allergy	1 in 100	Urticaria, pruritis and/or erythema.	Transfusion can be restarted after assessment and necessary intervention.
Transfusion associated circulatory overload (TACO)	1 in 700	Dyspnea, orthopnea, cyanosis, tachycardia, raised venous pressure and/or hypertension.	Due to excessive volume or excessively rapid transfusion rates. May be difficult to distinguish from TRALI.
Transfusion related acute lung injury (TRALI)	1 in 1,200-5,000	New onset of hypoxemia, new bilateral lung infiltrates on chest X-ray and no evidence of circulatory overload.	Occurs during or within 6 hours of transfusion. May be difficult to distinguish from TACO.
Isolated hypotensive reaction	Unknown	Hypotension, occasionally accompanied by urticaria, dyspnea and nausea.	Diagnosis of exclusion. May occur more frequently in patients on angiotensin-converting enzyme (ACE) inhibitor.
Immediate hemolytic transfusion reactions (HTR)	Rare	Shock, chills, fever, dyspnea, chest pain, back pain, headache and/or abnormal bleeding.	May be associated with ABO plasma incompatibility.
Anaphylaxis	Rare	Hypotension, upper and/or lower respiratory obstruction, anxiety, nausea and vomiting.	Resuscitation according to institutional guidelines. IgA deficient patients who have formed anti- IgA antibodies may experience anaphylactic reactions. However, in most cases of anaphylactic reactions, no specific antibodies are found in the patient.
Transfusion-related alloimmune thrombocytopenia	Rare	Abrupt onset of potentially severe thrombocytopenia within hours of transfusion.	Passive transfer of platelet antibodies leading to thrombocytopenia.
Bacterial contamination	Very rare	Fever, chills, rigors, nausea, vomiting, diarrhea, abdominal and muscle pain, hypotension, hemoglobinemia, and/or disseminated intravascular coagulation.	For evaluation and treatment of a reaction due to suspected bacterial contamination, refer to reference #16.
Infectious disease	See Table 2, Residual risk of tested viruses	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.
Complications of massive transfusion	Dependent on clinical situation	Complications may include hypothermia, citrate toxicity, acidosis.	Appropriate monitoring may abrogate some complications.

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*, section 1: Vein to Vein: A Summary of Blood Collection and Transfusion in Canada.

### Dose and administration

The volume of **AFP**, **FP** and **Cryosupernatant Plasma** transfused depends on the clinical situation and patient size. Common pediatric dosing is 10 - 15 mL per kg body weight.

The volume needed to raise fibrinogen concentration 0.5 - 1.0 g/L can be estimated as one unit of **Cryoprecipitate** per 5 - 10 kg body weight.

Serial laboratory assays of coagulation function may be of assistance in planning dose. 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.

### Modification and additional information

**TABLE 4:** Modified Components

Modification	Description	Indication	Storage	Benefits	Adverse events
CPD FP Divided	One unit of plasma divided into two smaller units.	Neonates and infants.	Once thawed, 1 - 6°C: transfuse within 120 hours.	Reduced donor exposure if both units transfused to the same patient.	As per Table 3.

### Autologous Donations

Autologous donor samples are typically tested as described previously. Syphilis and anti-HBcore are not mandatory tests for autologous donations.<sup>15</sup> Autologous units found to be repeat reactive, but negative/indeterminate on confirmatory/supplemental testing for any of the transmissible disease markers will be labelled as “Biohazard” and providing all other requirements are met, may be released with the approval of both Canadian Blood Services and recipient’s physician. In addition, syphilis confirmatory positive units may also be released with “Biohazard” labelling.

### Directed Donations

Directed donations are donations made by a donor chosen for or by the recipient. This type of donation is offered in specific and limited cases and may be given only by parents or legal guardians to their minor children. A directed plasma unit must meet all the standards required for **FP**.

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The *Circular* as a whole or in part cannot be considered or interpreted as an expressed or implied warranty of the safety or fitness of the described blood or blood component when used for their intended purpose. Attention to the specific indications for blood components is needed to prevent inappropriate transfusion.

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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.<sup>22</sup>