

### Plasma Components

This component information addresses:

- Apheresis Fresh Frozen Plasma
- Frozen Plasma CPD
- Cryosupernatant Plasma CPD
- Cryoprecipitate CPD

### Composition and properties

**Apheresis Fresh Frozen Plasma (FFPA)** is collected by apheresis in approximately 70 – 90 mL of either trisodium citrate or ACD-A anticoagulant and is frozen within 8 hours of collection. The component label clearly indicates the anticoagulant used. FFPA contains both labile clotting factors V and VIII, plus all non-labile coagulation factors.

**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 frozen within 24 hours of collection. FP is not labelled as leukoreduced as some units may contain  $\geq 5 \times 10^6$  leukocytes/unit. FP contains all coagulation factors at levels similar to the levels in FFPA with the exception of the labile factors, V and VIII, which may be slightly reduced in FP.

**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:  
 CPD (citrate phosphate dextrose) anticoagulant contains citric acid 3.27 g/L, sodium citric 26.3 g/L, sodium acid phosphate 2.51 g/L, dextrose 25.5 g/L.  
 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.  
 Tri-sodium citrate anticoagulant contains sodium citrate 40 g/L and citric acid to adjust pH.  
 For approximate procoagulant and anticoagulant factor concentrations in some of these components, see [www.transfusionmedicine.ca](http://www.transfusionmedicine.ca).

| Plasma Component       | Volume (mL)<br>Mean $\pm$ 2 SD                  | Factor VIII (IU/mL)<br>Mean $\pm$ 2 SD | Fibrinogen (mg)<br>Mean $\pm$ 2 SD |
|------------------------|---|--|------------------------------------|
| FFPA                   | ACD-A: 226 $\pm$ 45<br>n = 1469                 | 1.28 $\pm$ 0.68<br>n = 1392            | N/A                                |
|                        | Trisodium citrate:<br>497 $\pm$ 56<br>n = 22292 |  |                                    |
| FP                     | 287 $\pm$ 32<br>n = 2633                        | 1.00 $\pm$ 0.60<br>n = 2351            | N/A                                |
| Cryosupernatant Plasma | 282 $\pm$ 37<br>n = 1155                        | N/A                                    | N/A                                |
| Cryoprecipitate        | 11 $\pm$ 3<br>n = 1057                          | N/A                                    | 408 $\pm$ 258<br>n = 1057          |

Quality criteria that must be met:  
 FFPA: Factor VIII:  $\geq 0.70$  IU/mL in  $\geq 75\%$  of units tested; FFPA (ACD-A): Volume:  $\pm 10\%$  labelled volume in all 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, Rh type and unexpected antibodies against red cell antigens. ABO group is indicated on the component label. Rh type may also be indicated on the label.

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, HCV and West Nile virus (WNV)]
- 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) 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

FFPA, FP, Cryosupernatant Plasma and Cryoprecipitate may be stored in di-ethyl hexyl phthalate (DEHP) or non-DEHP plasticized bags depending on the manufacturer<sup>1</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>2</sup>

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

- FFPA and Cryosupernatant Plasma: store at  $1 - 6^{\circ}\text{C}$  and transfuse within 24 hours.
- FP: 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 FFPA and FP act as plasma protein supplements and plasma volume expanders. Both plasma components contain all clotting factors. FP levels of factor V and factor VIII may be reduced compared to levels in FFPA.

Transfused Cryosupernatant Plasma provides a source of plasma with reduced levels of von Willebrand factor including high molecular weight multimers.<sup>3</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.

FFPA 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,
- 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.<sup>4</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

FFPA, FP and Cryosupernatant Plasma must be ABO-compatible; for Cryoprecipitate, ABO compatibility is preferred. Rh 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 FP may significantly increase over time during storage at 1 – 6°C for 120 hours. 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>1,5</sup>

Some clotting factor activity in thawed FP may be significantly lost during storage for up to 120 hours.<sup>6,7</sup>

Do not use FFPA 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>8</sup> or for pathogens that are either not recognized or for which there is no donor screening test.

| Virus | Residual risk                  |                         |
|-------|--------------------------------|-------------------------|
|       | Per million donations (95% CI) | Per number of donations |
| HIV   | 0.13 (0.05-0.28)               | 1 in 7.8 million        |
| HCV   | 0.43 (0.27-0.66)               | 1 in 2.3 million        |
| HBV   | 6.55 (3.90-10.29)              | 1 in 153,000            |
| HTLV* | 0.23 (0.04-0.83)               | 1 in 4.3 million‡       |

\*95 percent CI is not available for HTLV window period, the listed numbers in brackets are the range.

‡This estimate represents potentially infectious units released into inventory. The risk to recipients would be much lower due to universal leukoreduction.

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. Canadian Standards Association requires reporting of adverse events associated with blood component quality (e.g. bacterial contamination) to Canadian Blood Services.<sup>10,11</sup> For further information, refer to the Canadian Standards Association, *Blood and Blood Components and Transfusion Transmitted Injuries Surveillance System*.<sup>10,12</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 #11.   |
| 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 FFPA, 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

| Modification | Description  | Indication            | Storage  | Benefits   | Adverse events  |
|--------------|--|-----------------------|--|--|-----------------|
| Divided      | One unit of plasma divided into two smaller units. | Neonates and infants. | Once thawed, 1 - 6°C: transfuse within 24 hours. | Reduced donor exposure if both units transfused to the same patient. | As per Table 3. |

No medications or solutions, with the exception of 0.9% sodium chloride injection, may be added to or infused through the same tubing with the plasma components. In particular, the addition of commonly used solutions such as D5W (5% dextrose in water) or additives such as calcium (e.g. in Lactated Ringers), should never be added to, or administered concurrently through the same vascular access as blood or blood components. Co-administration of platelets, red cells or 5% albumin can be performed at the discretion of the recipient's physician.

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

## Autologous Donations

Autologous donor samples are typically tested as described previously. Syphilis and anti-HBcore are not mandatory tests for autologous donations<sup>10</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.

## References

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14. Popovsky, MA. Transfusion reactions. 3<sup>rd</sup> ed. Bethesda (MD): AABB; 2007.
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17. Health Products and Food Branch Inspectorate, Annex to the GMP guidelines, good manufacturing practices for schedule D drugs, Part 2, human blood and blood components, December 1, 1999.

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>17</sup>