NAC RECOMMENDATIONS FOR THE USE OF SOLVENT-DETERGENT PLASMA IN CANADA

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ACRONYMS

S/D Plasma	Solvent-Detergent Human Plasma
FP	Frozen Plasma
MHP	Massive Hemorrhage Protocol
NAC	National Advisory Committee on Blood and Blood Products
RBC	Red Blood Cell
TTP	Thrombotic Thrombocytopenic Purpura

SUMMARY OF REVISIONS

May 2026

General	Formatting updates.
Section 4.2	Updates to recommendation *(f) Use of thawed S/D Plasma in massive hemorrhage protocol* to address and provide guidance regarding precipitate formation during thawing.
References	Updated.

1.0 BACKGROUND

On March 27, 2023, the restrictions on the use of Octaplasma Solvent-Detergent Human Plasma (S/D Plasma) in Canada (outside the province of Québec) was removed. Prior to this date, S/D Plasma was restricted to specific patient groups as recommended by Canada's Drug Agency (previously known as Canadian Agency for Drugs and Technologies in Health).[1] The restrictions on the use of S/D Plasma were based on clinical evidence showing no difference in effectiveness as compared to regular frozen plasma (FP), and a substantial increase in cost associated with S/D Plasma as compared to FP.[2] In July 2022, Canadian Blood Services announced a transition to pathogen-reduced platelet and plasma components as an additional layer of safety to the blood supply system in Canada. The first phase in the implementation of pathogen-reduced plasma is the transition from FP and S/D Plasma with a target of 80% of all transfused plasma to be S/D Plasma by September 2023. The second phase (planned for 2024-25) is to replace the remaining 20% of FP with pathogen-reduced FP using the same technology (Intercept Blood System) currently in use to produce pathogen-reduced platelets.

S/D Plasma has been used in Canada since 2011 on a restricted basis, and in many European countries (Netherlands, Finland, Sweden, Norway, United Kingdom) as the primary plasma product with no concerns for either clinical efficacy or safety. S/D Plasma is made from large pools of plasma that undergo pathogen inactivation using a solvent-detergent process and is then divided into 200 mL units. As a result of the manufacturing process, S/D Plasma units have relatively standard or uniform levels of coagulation factors. The levels for all clotting factors are similar to those in FP with the exception of lower protein S and anti-plasmin levels. The pooling of units for S/D Plasma results in decreased allergic reactions[3-6] and possibly a reduction in transfusion-related acute lung injury reactions.[7]

The transition to S/D Plasma represents a significant change in hospital transfusion practice in Canada. While S/D Plasma and FP have the same clinical indications, there are some differences in the products themselves and the packaging of the product, which are important for health care practitioners and hospital transfusion medicine services. Further information from Canadian Blood Services on S/D Plasma and the transition to this product can be found at here.[8]

This document from the National Advisory Committee on Blood and Blood Products (NAC) provides additional clinical recommendations regarding the indications, dosing, and use in special populations.

2.0 INDICATIONS

The main indication for plasma transfusion is the replacement of deficient coagulation factor(s) in patients with active bleeding, or prior to a surgery or invasive procedures. Specific guidelines and recommendations for the use of plasma transfusion have been previously published.[9,10]

In general, most patients who would be treated with FP can receive S/D Plasma, these would include the following indications:

- 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;
- 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; and,
- Patients with thrombotic thrombocytopenic purpura (TTP).

There are a limited number of specific contraindications to S/D Plasma:

- Patients with IgA deficiency and documented anti-IgA antibodies. These patients will also potentially have allergic reactions to regular FP and should only receive FP from IgA deficient donors. IgA deficiency alone (no anti-IgA antibodies) is not a contraindication as most patients with this relatively common deficiency do not form antibodies and will not have an adverse reaction to blood components;[11] and,
- Patients with severe deficiency of protein S. S/D Plasma has significantly lower levels of protein S as compared to FP, which may result in an increased risk of blood clots. If these patients with severe deficiencies of protein S require a plasma transfusion, they should receive FP.

3.0 SPECIAL POPULATIONS

3.1 Pediatrics

Based on limited data, S/D Plasma and FP should be considered equally effective in pediatric patients and can be used interchangeably. Two studies which included 91 pediatric patients receiving S/D Plasma did not identify any safety concerns.[12, 13] A secondary analysis of a large multinational study identified 62 pediatric critical care patients who received S/D Plasma; there was no difference in the reduction in the INR compared to patients receiving FP and S/D Plasma was associated with reduced mortality.[14] Adoption of S/D Plasma for routine use in other jurisdictions has also not identified any concerns with pediatric patients.[5]

3.2 Neonatology

Based on limited data, there is no reason to expect differences in clinical efficacy with S/D Plasma as compared to FP. A retrospective study included 41 neonate patients and reported no clinical or safety concerns with S/D Plasma.[15] One non-published study reported no adverse events in 55 neonates receiving S/D Plasma.[16] The reduction in adverse transfusion reactions associated with S/D Plasma may be advantageous.

3.3 Pregnancy

Based on limited clinical data, S/D Plasma and FP can be considered equally effective in pregnant patients and can be used interchangeably. A retrospective study including 37 obstetrical patients reported no clinical or safety concerns.[15] Adoption of S/D Plasma for

routine use including obstetrics and gynecology patients also did not identify any clinical concerns in gynecology or obstetrical patients.[5]

3.4 Geriatrics

S/D Plasma and FP should be considered equally effective in geriatric patients and can be used interchangeably. While there are no studies of evaluating S/D Plasma specifically in geriatric patients, there are no physiologic reasons that S/D Plasma would be less effective or have increased adverse effects in geriatric patients. The reduction in adverse events associated with S/D Plasma may be considered advantageous in this patient group who would be at greater risk of adverse outcomes associated with a transfusion reaction.

3.5 Liver transplantation/liver disease

S/D Plasma and FP can be considered equally effective in patients undergoing liver transplantation or coagulopathy associated with liver disease and can be used interchangeably. Three randomized controlled trial studies (n=115) evaluated S/D Plasma in patients with coagulopathy associated with liver disease or liver transplant patients.[17-19] There were no differences in clinical efficacy or adverse events.

3.6 Thrombotic Thrombocytopenic Purpura

Clinical studies have shown that S/D Plasma is effective and safe when used as part of plasmapheresis treatments in patients with TTP.[20-22] No clinical studies have compared the effectiveness of S/D Plasma to FP or cryosupernatant. In the 2 clinical trials evaluating cryosupernatant in TTP patients, there was no evidence of improved outcomes as compared to FP.[23, 24] The reduction in adverse events and lower risk of transfusion transmitted infections with S/D Plasma may be considered advantageous in patients receiving large volume plasma transfusions as part of plasmapheresis treatment.

4.0 DOSING, PREPARATION, AND INFUSION CONSIDERATIONS

An important factor in the dosing of S/D Plasma is the smaller unit volumes. FP units, which are made from individual blood donations, vary in size with an average volume of 289mL (± 16mL)[25] and have more variability in coagulation factor levels as each unit is from an individual donor. Overall, the mean concentration of coagulation factors in S/D Plasma and FP are similar,[26] but as a pooled blood product, the concentrations are more uniform in S/D Plasma.

4.1 Recommendations for Dosing

The correct dose of plasma is determined by either weight-based dosing (hemodynamically stable patients) or ratio-based dosing (massively bleeding patients):

(a) For the correction of coagulation factor levels in patients with acute bleeding, or prior to surgery or invasive procedures, the recommended dose for FP is 10-15mL/kg,[9,27] which is the volume required to increase coagulation factors levels above the minimum

hemostatic threshold of 30%.[27] Given the similarity in coagulation factor levels, this dose is also appropriate for S/D Plasma. In pediatric patients weighing less than 40kg, the plasma is usually ordered in mL/kg. For larger pediatric patients and adult patients, plasma is usually ordered in units. As S/D Plasma is supplied in a smaller standard 200mL bag compared to an average 289mL per unit of FP, a larger number of units of S/D Plasma may be required to deliver a therapeutic dose of plasma. Most adult patients (60-90kg) will require 4-6 units of S/D Plasma or 3-4 units of FP to achieve hemostatic levels of coagulation factors. The prescribed dose of plasma should be guided by the clinical situation and coagulation results.

(b) NAC recommends that the number of plasma units prescribed in massive hemorrhage protocols (MHPs) be the same whether S/D Plasma or FP is used. For patients with massive hemorrhage requiring transfusion support, resuscitation with fixed ratio of FP to red blood cells (RBCs) is commonly used.[28] This practice is based on observational studies that report improved outcomes in military patients with massive hemorrhage secondary to trauma. While a high transfusion ratio of FP:RBC has been recommended in trauma patients requiring massive transfusion, the ideal ratio is unknown.[29] In clinical practice, there is variability in the volumes of the FP and RBC units transfused, and often the desired ratio of FP:RBC units is not achieved. As a result, there is significant inherent variability in the actual volumes of plasma and RBCs transfused. FP:RBC ratios of 1:1 to 1:3 have been recommended as sufficient to provide hemostatic levels of coagulation factors in trauma patients.[30] Additionally, no benefit has been demonstrated for higher FP:RBC ratios in the resuscitation of patients with non-traumatic massive hemorrhage, who represent the majority of MHP activations in the civilian setting. Therefore, based on the limited evidence available, NAC does not recommend increasing the initial ratio of plasma to RBC units in MHPs when using S/D Plasma despite the lower volume of S/D Plasma units. However, as per recent recommendations, patients requiring massive transfusion require frequent monitoring of coagulation tests and should be transitioned to laboratory guided administration of blood components as soon as possible.[28]

4.2 Recommendations for Preparing and Infusing

(c) Administration rate

A maximum infusion rate of 1mL/kg/min is recommended in the S/D Plasma product monograph.[16] In most clinical situations, the infusion rate for plasma will be much lower than the maximum recommended infusion rate. For a 70kg patient, the maximum rate would allow for an infusion of one unit of S/D Plasma in three minutes. Infusion rates above this rate would only be seen when a rapid infuser, which can infuse at rates up to 750-1000mL/min, is used.

The concern related to higher infusion rates is due to the citrate anticoagulant in S/D Plasma and the potential for citrate toxicity. However, the risk of citrate toxicity is not different for S/D Plasma as compared to regular FP. The concentration of citrate in S/D

Plasma is 17mM/L which is similar to the calculated estimate for FP (17-25mM/L) [Unpublished data, Canadian Blood Services]. Therefore, S/D Plasma and FP have a similar risk for citrate toxicity during high volume rapid infusion.

Rapid infusions of plasma only occur in the setting of a massive hemorrhage. In this setting a fixed ratio of RBCs and FP is recommended to decrease the coagulopathy associated with trauma and possibly decrease mortality. The risk of citrate toxicity will be reduced by ongoing rapid blood loss, which includes the loss of citrate, and giving added calcium as part of MHP. Based on current clinical practice recommendations for trauma, infusing plasma at rates above 1mL/kg would be considered standard practice where the benefit of the rapid infusion outweighs the potential risk for citrate toxicity. NAC recommends that S/D Plasma and FP can be used interchangeably in this setting.

(d) Temperature for thawing and infusion

The product monograph for S/D Plasma recommends that during thawing S/D Plasma should not be warmed above 37°C.[16] This follows current practice for FP, and the temperature requirement does not represent a change in laboratory practice.

The rationale provided for this maximum temperature of 37°C as the optimal temperature for the constituents of blood is not clear. As measured by in-vitro coagulation studies, there is evidence for increased coagulation activity of whole blood with hyperthermia. However, the mechanisms suggested for the increased coagulation activity is related to tissue factor, which is almost exclusively extravascular, and not due to proteins found in plasma or the cellular components of whole blood.[31]

With regards to blood warmers and rapid infusion devices, there are no specific recommendations for temperature for S/D Plasma or FP. Rapid infusers currently used to infuse blood products including plasma may be set at temperatures up to 41°C. Given the short period of infusion for most rapid infusion devices, the temperature of the plasma is unlikely to significantly exceed 37°C. The exception is the Belmont infusion device, which heats the plasma through magnetic induction. However, even if the temperature of the plasma increases above 37°C, any increase in temperature will be transient and the infused plasma will very quickly equilibrate with the recipient's body temperature, thereby negating any potential adverse effects of a short temperature excursion. Importantly, any changes in coagulation protein activity due to increased temperatures would be seen in both FP and S/D Plasma. Thus, the potential for any adverse impact on the function of coagulation proteins from using a blood warmer that increases the temperature of plasma above 37°C would be negligible, and they would be identical for S/D Plasma and FP.

(e) Reconstituted whole blood

Reconstituted whole blood is made by mixing plasma and RBCs and is used primarily for neonatal exchange transfusion and priming cardiac bypass circuits. The product monograph states that S/D Plasma can be mixed with RBCs and platelets.[16] Health Canada does not consider mixing RBCs and S/D Plasma to be a transformation activity as per the *Blood Regulations*; while S/D Plasma is classified as a drug, mixing it with RBCs falls under

the practice of medicine.[32] The use of either S/D Plasma and FP for reconstituted whole blood is scientifically and medically appropriate, and both products should be considered interchangeable for this use.

(f) Use of thawed S/D Plasma in massive hemorrhage protocol

The use of S/D Plasma is indicated for the treatment of massive bleeding, including activations of MHPs. Many large trauma centres maintain thawed plasma units for MHP activations to decrease the time needed to issue plasma. S/D Plasma can be thawed and stored at 2-8°C as per the product monograph or 1-6°C for 5 days and maintain hemostatic capability;[33] therefore, it can used as a thawed plasma product in MHP activations. However, as outlined in communications from Octapharma,[34] precipitates can form during thawing of frozen S/D Plasma. Many centres have noted precipitates in S/D Plasma when it is stored as thawed plasma leading to higher wastage rates. The manufacturer has recommended secondary rewarming to "dissolve" the precipitates, but the rewarming procedure is not Health Canada approved or included in the product monograph. Rewarming could also delay issuing plasma during a MHP activation, which negates the goal of maintaining thawed plasma. Further, based on quality improvement studies[35] and clinical practice, rewarming may not consistently "dissolve" all precipitates. As nursing/medical staff may refuse to transfuse S/D Plasma if they see precipitates resulting in additional delays in administering plasma during a massive hemorrhage and potentially increasing wastage of S/D Plasma.

As reports of precipitates in S/D Plasma vary among institutions, NAC recommends monitoring wastage rates of S/D Plasma due to precipitates, particularly when used as a thawed product. If higher rates of wastage are noted due to precipitates in S/D Plasma, then transfusion medicine services should consider using thawed plasma manufactured by Canadian Blood Services for the initiation of MHPs to reduce wastage while being mindful that not all Canadian Blood Services manufactured plasma available at this time provides the benefits of pathogen reduction. However, a pathogen inactivated psoralen treated plasma from Canadian Blood Services is available for ordering across all Canadian sites. The use of thawed plasma manufactured by Canadian Blood Services in MHPs may result in individual hospitals not meeting the target of S/D Plasma representing a minimum of 80% of all transfused plasma in Canada, but avoiding discards of thawed S/D Plasma due to precipitate formation outweighs the need to meet this target at individual hospitals.

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