

*Canadian Agency for
Drugs and Technologies
in Health*

*Agence canadienne
des médicaments et des
technologies de la santé*



CADTH OPTIMAL USE REPORT

PILOT PROJECT

Optimal Therapy Recommendation
for the Use of Solvent/Detergent-Treated
Human Plasma

MAY 2011

Supporting Informed Decisions

This report is prepared by the Canadian Agency for Drugs and Technologies in Health (CADTH). This report contains a comprehensive review of existing public literature, studies, materials, and other information and documentation (collectively the “source documentation”) available to CADTH at the time it was prepared, and it was guided by expert input and advice throughout its preparation.

The information in this report is intended to help health care decision-makers, patients, health care professionals, health systems leaders and policy-makers make well-informed decisions and thereby improve the quality of health care services.

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TABLE OF CONTENTS

| | |
|---|-----------|
| RECOMMENDATION | 1 |
| CONTEXT, SCOPE, AND KEY FINDINGS | 2 |
| Context | 2 |
| Scope and Key Findings..... | 3 |
| BACKGROUND..... | 5 |
| SUMMARY OF APPROACH AND EVIDENCE..... | 5 |
| Clinical Effectiveness..... | 5 |
| Cost-Effectiveness | 6 |
| Other Values and Preferences | 8 |
| Additional Context and Panel Discussion Points..... | 9 |
| APPENDIX A: TABLE OF EVIDENCE CONSIDERED BY THE PANEL OF EXPERTS..... | 10 |
| APPENDIX B: ADVERSE REACTIONS ASSOCIATED WITH S/D PLASMA AND RELEVANT COMPARATORS..... | 11 |
| APPENDIX C: PANEL OF EXPERTS | 12 |
| APPENDIX D: ABBREVIATIONS..... | 15 |
| REFERENCES..... | 16 |

1 RECOMMENDATION

The Canadian Agency for Drugs and Technologies in Health's (CADTH's) Panel of Experts recommends that solvent/detergent-treated human plasma* (S/D plasma) be considered for certain patients:

- who require a high volume of transfusions annually because they have:
 - thrombotic thrombocytopenic purpura (TTP)** or,
 - hemolytic uremic syndrome (HUS) with associated factor H deficiency or,
 - clotting factor deficiencies for which specific licensed concentrates may not be readily available (e.g., factor V, factor XI, factor XIII),
- and who:
 - have experienced an allergic reaction to frozen plasma (FP) or,
 - have a pre-existing lung disorder or,
 - need FP but a blood group compatible product is not available in a timely manner.

* In this document, S/D plasma refers to the product (current trade name: Octaplas) manufactured by Octapharma Pharmazeutika Produktionsges m.b.H (Vienna, Austria) and distributed in Canada by Octapharma Canada Inc. (Scarborough, Ontario) (DIN: 02270013).

** In this document, TTP includes both congenital and acquired forms.

Of Note:

After careful consideration, the Panel of Experts noted the following:

- There is evidence of suboptimal clinical use of FP; a recent audit found that 28.6% of the FP transfusions in Ontario were deemed inappropriate.¹
- There is a need for a national system of active post-marketing surveillance and monitoring to prevent inappropriate use of FP and S/D plasma and acquire further knowledge on the tolerability and safety of S/D plasma in a timely fashion. The Panel recommends that all physicians participate in such a system, although only hematologists would be able to prescribe S/D plasma. It was also noted that the development of such a surveillance and monitoring system is currently under consideration by Health Canada and the Public Health Agency of Canada.²
- Accurately determining the differential diagnosis of transfusion-related acute lung injury (TRALI) (versus other lung events) may be challenging to clinicians given that there are often a multitude of contributing factors. It is also difficult to predict which patients are at risk of developing TRALI.
- Increased use of S/D plasma may be required should a new blood pathogen (particularly an enveloped virus) emerge (e.g., West Nile virus).
- The Panel recommendation is based on the current level of knowledge regarding the comparative effectiveness and safety of S/D plasma versus FP.

2 CONTEXT, SCOPE, AND KEY FINDINGS

Context

Canadian jurisdictions (except Québec) must make a decision on the provision of S/D plasma to clinicians and patients. If funding is approved, the Canadian Blood Services (CBS) will be responsible for the storage and distribution of this blood product in nine provinces and three territories.

An initial review of S/D plasma was conducted by CBS in 2009/2010, with additional input through the National Advisory Committee on Blood and Blood Products (NAC). In the fall of 2010, Canadian jurisdictions, through the Provincial/Territorial Blood Liaison Committee (PTBLC), sought further input from CADTH.

In response, CADTH initiated a pilot project and convened a Panel of Experts to evaluate the clinical and cost-effectiveness of S/D plasma versus standard plasma and to also consider the ethical implications of providing S/D plasma under certain criteria. These criteria were established by PTBLC and CBS on the basis that there exist chronic hematological conditions for which treatment involves administering a high volume of plasma transfusions. Three specific populations were selected by PTBLC and CBS for this pilot project, namely:

- patients with TTP
- patients with HUS
- patients with clotting factor deficiencies for which specific licensed concentrates may not be readily available (e.g., factor V, factor XI, factor XIII).

The recommendation process involved five Panel meetings, as well as a public call for feedback. The Panel of Experts reviewed the literature and considered feedback comments in developing the recommendation.

Conditions for which the recommendation was developed are not commonly encountered. The annual incidence rate of suspected TTP-HUS is about 11.3 per million people; for idiopathic TTP-HUS, the annual incidence rate is estimated at 4.5 per million.³ Based on the current Canadian population of 34 million persons,⁴ it may therefore be projected that approximately 150 to 400 cases per year of TTP-HUS occur in Canada. The estimated incidence rate for factor XI deficiency is one per 100,000 persons.⁵ Extrapolating this rate to the Canadian population, roughly 340 cases may be expected annually. Both factor V deficiency and factor XIII deficiency are rare conditions. The estimated incidence rate for factor V deficiency is one person in one million;⁶ this represents about 34 cases annually in Canada. Factor XIII deficiency is another rare disease; it has been estimated that less than 10 Canadians have been diagnosed with this condition.⁷

Scope and Key Findings

In developing this recommendation, the Panel of Experts answered the following questions:

- 1) What is the clinical effectiveness of S/D plasma versus standard plasma in high-risk populations; i.e., patients who require a high volume of transfusions annually because they have one of the following indications: TTP, HUS, or clotting factor deficiencies for which specific licensed concentrates may not be readily available (e.g., factor V, factor XI, factor XIII)?**

The Panel of Experts considered the results from a systematic review of 15 studies involving 2,235 patients (173 patients from randomized controlled trials [RCTs] and 2,062 patients from observational studies [including one safety study involving 343 patients], as well as one multinational hemovigilance study involving 947 incident reports). The objective of this systematic review was to assess the effectiveness and safety of S/D plasma in relation to other FP products for multiple indications including liver disease, liver transplantation, cardiovascular surgery, TTP, coagulation disorders, obstetric and gynecologic emergencies, and neonatal intensive care.

Key findings suggest that:

- S/D plasma is effective in improving coagulation test results in a number of patient groups.
- The evidence available comparing S/D plasma to standard plasma is limited both in quality and quantity for most indications included in the systematic review, except for TTP for which more evidence is available for FP (compared with other plasma treatments) than S/D plasma (compared with FP). Overall, it appears that S/D plasma is not substantially different from standard plasma in the treatment of TTP, HUS, and coagulation disorders for which specific licensed concentrates may not be readily available.
- The use of S/D plasma, compared with standard plasma, is associated with a lower risk of serious allergic reactions, citrate reactions, and TRALI.

The Panel of Experts noted that:

- The quality of evidence available is low (based on conventional standards).
- There is a low absolute risk of transfusion-related adverse events for both FP and S/D plasma.
- The risks of emerging unknown pathogens are more likely to be prevented with S/D plasma.

- 2) What is the cost-effectiveness of S/D plasma versus standard plasma in high-risk populations; i.e., patients who require a high volume of transfusions annually because they have one of the following indications: TTP, HUS, or clotting factor deficiencies for which specific licensed concentrates may not be readily available (e.g., factor V, factor XI, factor XIII)?**

The Panel of Experts considered the results of an economic analysis which showed that the incremental cost-effectiveness ratio (ICER) (which takes into account the cost differential between FP and S/D plasma, as well as the potential additional clinical benefits of S/D plasma versus FP and patient preferences regarding such benefits) is very high

(\$934,000/quality-adjusted life-year [QALY]) and does not meet conventional thresholds for economically attractive health interventions.

- 3) What are the ethical issues and associated service delivery implications of using S/D plasma in selected patients; i.e., patients who require a high volume of transfusions annually because they have one of the following indications: TTP, HUS, or clotting factor deficiencies for which specific licensed concentrates may not be readily available (e.g., factor V, factor XI, factor XIII)?**

During the deliberations, the Panel of Experts consistently identified the following considerations (in no order of preference) as most important:

- the non-maleficence/precautionary principle (the importance of taking due precaution to not cause harm to patients)
- the principle of beneficence (the need for demonstrable evidence of product efficacy versus FP)
- the principle of distributive justice (the need to account for what is socially just regarding the allocation of goods in a society)
- the principle of opportunity costs
- the greater good to society
- limitations in available economic and infrastructure resources
- the principle of accessibility for a product that has met the minimum standards set out by Health Canada.

The Panel of Experts took a pragmatic approach to the recommendation process, recognizing that it is reasonable, within the Canadian health care system, to recommend a product for certain patient populations knowing it is not possible for it to be available to all. In the case of plasma products, the Panel of Experts acknowledged that the overall transfusion risks are low, but, for patients targeted by the recommendation, risks are higher given the high volume of plasma transfusions they receive. It is therefore reasonable to provide access to these patients, considering the following:

- From a clinical perspective, there is no high-quality evidence indicating that the use of S/D plasma leads to better treatment of TTP, HUS or clotting factor deficiencies for which specific licensed concentrates may not be readily available (e.g., factor V, factor XI, factor XIII) than the use of FP.
- From an economic perspective, the use of S/D plasma is not cost-effective, based on traditionally accepted cost per QALY standards and current knowledge of outcomes and resource use.
- From an ethical perspective, the non-maleficence or precautionary principle requires that a potentially safer treatment be made available whenever possible. It is acknowledged that the S/D process is potentially associated with a reduction in the risk of serious adverse effects, including the risk of transmitting viral infections (including emerging pathogens), TRALI, and allergic reactions.

3 BACKGROUND

Octaplas is a form of virus-inactivated FP prepared using an S/D treatment of 1% tri-nitro-butyl phosphate (TNBP) and 1% Triton X-100 for four hours at 30°C. As a consequence of its means of preparation, this S/D-treated human plasma product reduces the risk of transfusion-related viral infections. S/D plasma has been described as being associated with an improved safety profile as compared with standard FP, based on reduced rates of transfusion-associated allergic reactions, TRALI, transmission of infections from lipid-enveloped viruses (human immunodeficiency virus [HIV], hepatitis B virus [HBV], and hepatitis C Virus [HCV]). (Note: The S/D process does not affect non-enveloped viruses (hepatitis A virus [HAV] and parvovirus B19 [P-B 19]). Health Canada granted the notice of compliance for this product on August 11, 2005 (DIN: 02270013). It is supplied in bags of 200 mL containing 45 mg/mL to 70 mg/mL human plasma proteins (frozen). The administration of S/D plasma must be based on ABO-blood group compatibility. In emergency cases, S/D plasma for blood group AB can be regarded as universal plasma, as it can be given to all patients. The acquisition cost is \$140.00 per unit (2007 data).

4 SUMMARY OF APPROACH AND EVIDENCE

The Panel of Experts considered the scientific information reviewed by CBS, NAC, and other stakeholders involved in the initial review of S/D plasma led by CBS in 2009/2010, along with additional information prepared by CADTH. (See Table 1 Appendix A for a listing of the evidence considered by the Panel of Experts).

Clinical Effectiveness

The Panel of Experts considered the assessment of clinical data from a systematic review of 15 studies involving 2,235 patients (173 patients from RCTs and 2,062 patients from observational studies [including one safety study involving 343 patients], as well as one multinational hemovigilance study involving 947 incident reports). The objective of this systematic review was to assess the effectiveness and safety of S/D plasma in relation to other alternatives including fresh FP, and other FP products for multiple indications including liver disease, liver transplantation, cardiovascular surgery, TTP, coagulation disorders, obstetric and gynecologic emergencies, and neonatal intensive care.

Key findings from this systematic review suggest that:

- S/D plasma is effective in improving coagulation test results in a number of patients groups.
- The evidence available comparing S/D plasma to standard plasma is limited both in quality and quantity for most indications included in the systematic review, except for TTP for which more evidence is available for FP (compared with other plasma treatments) than S/D plasma (compared with FP). Overall, it appears that S/D plasma is not substantially different from standard plasma in the treatment of TTP, HUS, and coagulation disorders for which specific licensed concentrates may not be readily available.
- The use of S/D plasma, compared with standard plasma, is associated with a lower risk of serious allergic reactions, citrate reactions, and TRALI (Table 2 in Appendix B). The Panel of Experts noted that there is a low absolute risk of transfusion-related adverse events for both standard plasma and S/D plasma.

Key outcomes considered by the Panel of Experts during the deliberations were (in no order of preference):

- the need for comparable efficacy to FP regarding treating the primary condition (restoring normal hemostasis, comparable bleeding outcomes, treatment of underlying disorder, and associated sequela)
- the effect on laboratory parameters
- the risks of acute allergy and anaphylactoid reactions
- risks of TRALI
- risks of transmission of known pathogens
- risks of transmission of emerging pathogens
- risks of thromboembolic complications
- safety of the supply.

The Panel of Experts noted that the quality of evidence available was low (based on conventional standards). Due to the heterogeneity of the studies included for review, a meta-analysis was not possible. Also, the number of adverse events reported in the studies was low, which limited the ability to determine potential differences in the rate of such effects between products. The Panel of Experts further noted that the prevalence of TRALI reported in the studies, particularly in hemovigilance studies, may not accurately reflect the real prevalence of this adverse effect given that accurately determining the differential diagnosis of TRALI (versus other lung events) may be challenging to clinicians as there are often a multitude of contributing factors. It is also difficult to predict which patients are at risk of developing TRALI.

Other limitations of the systematic review, as reported by its authors, include:

- the strength of their conclusions was limited by the paucity of rigorous research evaluating S/D plasma
- the study designs used were hypothesis-generating in nature, which further limits the strength of their conclusions
- given a meta-analysis was not feasible, it was not possible to assess publication bias using funnel plots and therefore that technique could not be used to help rule out the possibility that there exist unpublished studies that may alter the conclusions of the systematic review.

Additional observations made by the Panel of Experts include:

- The baseline risk of severe adverse effects (i.e., viral transmission, TRALI) is low.
- The risks of emerging unknown pathogens are more likely to be prevented with S/D plasma.
- Although the quantity and quality of the clinical evidence is poor, the Panel of Experts acknowledged that the feasibility of conducting a large RCT is difficult because of the low prevalence of the conditions of interest.

Cost-Effectiveness

The Panel of Experts considered an updated economic evaluation comparing the cost-effectiveness of S/D plasma and FP in reducing the risk of transmitting viruses. The economic model constructed represents six possible transfusion-related complications (including five types of viral infection [HAV, HBV, HCV, HIV, P-B19] and TRALI) in hypothetical cohorts of 50-

year-old patients (with a one-year mortality rate of 20%) each receiving a four-plasma unit course of treatment.

Key findings from the cost-effectiveness analysis are that S/D plasma treatment (i.e., four units per patient) is more costly than FP (\$566 versus \$385) and produces only a small increase in QALY (12.4786 versus 12.4784). The baseline incremental cost per QALY gained was \$934,000. Accounting for the different (generally very low) prevalence rates reported for TRALI, sensitivity analysis reported that the lowest incremental cost per QALY is \$215,000. Other sensitivity analyses showed that age (35-year-old versus 50-year-old versus 65-year-old) had an influence on the cost per QALY, as did the unit cost of S/D plasma. However, these do not change the conclusion that S/D plasma is not a cost-effective use of health care resources, based on traditionally accepted cost per QALY standards and the current state of knowledge on likely clinical and resource use implications of the two strategies.

There are a number of limitations to the economic analysis reported by its authors: the cost of treating chronic infectious conditions used in the economic analysis was adopted from Canadian studies with different costing methodologies; the utility estimates were obtained from Canadian and non-Canadian studies, with variation in settings and methods; although sensitivity analyses were conducted to minimize the impact of how these estimates were obtained, uncertainty around estimates could not be ruled out.

From a budget impact perspective, the Panel of Experts determined that the cost per treatment with S/D plasma is approximately 47% more expensive than with FP (Table 3). It should be noted that patients may require several treatments annually depending on the condition they have.

| Table 3: Cost of Plasma Treatment | | | |
|--|-----------------------|--------------------------------------|--------------------------------|
| Product | Unit Cost (\$) | Number of Units per Treatment | Cost per Treatment (\$) |
| S/D plasma | 141.40 | 10 | 1,414.00 |
| FP | 96.00 | 10 | 960.00 |

FP = frozen plasma; S/D = solvent/detergent.

* Source of cost information: CADTH Technology Report, March 2011⁸.

It was also estimated that providing access to S/D plasma to populations targeted by the recommendation would result in net additional expenditures in the order of \$5 million to the Canadian blood system (excluding Québec), barring unforeseeable changes impacting factors such as the unit cost for S/D plasma, the demand level, and distribution costs.

Observations made by the Panel of Experts included the following:

- The clinical evidence to populate the model is weak.
- S/D plasma is more costly per unit than FP, resulting in additional costs of \$181 per person (model assuming four plasma units per person).
- The QALY gained on average was small; i.e., 0.0002.
- The ICER is very high and does not meet conventional thresholds for economically attractive health interventions.
- The model was not specific to TTP or HUS and did not account for other potential transfusion-related consequences; e.g., thromboembolic complications due to lack of clinical data available.

- The cost-effectiveness analysis does not consider costs associated with acquisition and time lag nor consequences (e.g, severe adverse events, potential for legal action) associated with the unavailability of FP; for example, when there is a need for a specific blood group (e.g., B or AB). The Panel of Experts acknowledges, however, that these considerations are unlikely to change the overall results of the cost-effectiveness analysis.
- It is very difficult for the cost-effectiveness analysis to take into account the benefits of preventing emerging pathogens from entering the blood system.
- Other measures to improve the selection process for plasma products, independent of the choice of product, have been put in place in recent years that have contributed to reducing the rate of adverse events, including TRALI.

Other Values and Preferences

During the deliberations, the Panel of Experts consistently identified the following as most important considerations (in no order of preference) when comparing S/D plasma to standard plasma:

- The importance of taking due precaution to not cause harm to patients or, in more general ethical terminology, non-maleficence/precautionary principle (e.g., safety is paramount/Krever Inquiry legacy)
- The need for demonstrable evidence of product efficacy versus FP or, in more general ethical terminology, beneficence (i.e., taking actions that serve the best interests of patients)
- The need to account for what is socially just regarding the allocation of goods in a society or, in more general ethical terminology, distributive justice (e.g., should S/D plasma be provided for all or only a subset of individuals, are there differences in cases which would justify providing S/D plasma to some individuals but not to others?)
- Principle of opportunity costs such as whether the funds for providing S/D plasma can be used elsewhere in the health system with greater impact or whether the questionable benefits in safety do not warrant the increase in cost to the health system
- The greater good to society. Examples of related issues include:
 - Will stocking S/D plasma impose a net financial burden on CBS and result in constraints to other areas of the blood supply?
 - Are treatment costs within the accepted societal norms?
 - What is society generally willing to accept in terms of the risks associated with health interventions?
- Limitations in available economic and infrastructure resources (it would be difficult to replace all FP use with S/D plasma)
- The principle of accessibility for a product that has met minimum standards as set out by Health Canada.

Additional Context and Panel Discussion Points

- In developing this recommendation, the Panel of Experts also considered the Krever Inquiry report, which described the Canadian and international situation related to transfusion-related infections, and the recognition that Canadians remember this experience and highly value the need to have a safe blood system. This report resulted from the contamination of the Canadian blood supply with HIV and HCV, resulting in thousands of people in Canada becoming infected in the late 1970's and early 1980's.
- The Panel of Experts acknowledged that the recommendation is based on the current level of knowledge regarding the comparative effectiveness and safety of S/D plasma versus FP.
- There is potential benefit from using a standardized plasma product; i.e., a product that is manufactured based on accepted standards for volume and content. The S/D plasma manufacturing process ensures standardized volume and concentration of coagulation factors in each unit. S/D plasma undergoes steps that ensure the removal of enveloped viruses as well as removal of prions and other impurities.
- There is a need to account for future risk of plasma-related infection and implement measures to reduce such risks.
- From a risk management perspective of the blood supply, adding another plasma product to the CBS inventory may improve the security of the blood supply; e.g., if there is a shortage of FP supply or during catastrophic situations.
- The Panel of Experts acknowledged the importance of making information on plasma derivatives available to the public, and the need for physicians to be able to provide advice to their patients on when S/D plasma may be an option. This statement is consistent with the Krever Inquiry report, which noted the importance for individuals to have information about the risks inherent in the use of blood components to ensure informed decision-making. The Krever Inquiry report also noted the importance of making information about policy and management of the blood supply publicly available.
- The Krever Inquiry report stated that reducing risk associated with the use of blood products to zero is not feasible (achievable). Other measures need to be put in place to mitigate the risk of adverse effects (e.g., TRALI, risk of pathogens).
- There is a low, absolute risk of transfusion-related adverse events for both standard plasma and S/D plasma.
- Some of the ethical issues raised by the ethical assessment report, in particular those related to economics, were considered to be tangential to the Panel's deliberations. Other elements of the report, however, contributed to the identification of ethical issues considered in the development of the optimal use recommendation, along with the contribution of the ethicist panelist.
- S/D plasma may potentially be associated with a reduction in risk of emerging pathogens (known and unknown), particularly enveloped viruses, although baseline risk is low.
- S/D plasma may potentially be associated with an increased risk in non-enveloped pathogens because of pooling of plasma from multiple donors, although baseline risk is low.
- All donors are from North America for both FP and S/D plasma (US only).

APPENDIX A: TABLE OF EVIDENCE CONSIDERED BY THE PANEL OF EXPERTS

| Table 1: Evidence Considered by the Panel of Experts |
|--|
| Original scientific evidence considered by NAC |
| Hutton B, Tinmouth A, Chatelain E, Fergusson D. A systematic review of clinical, laboratory and safety outcomes associated with use of Octaplas in multiple clinical indications. Ottawa: Canadian Blood Services: unpublished data, 2007 Jul. |
| Membe S, Coyle D, Husereau D, Cimon K, Tinmouth A, Normandin S. Octaplas compared with fresh frozen plasma to reduce the risk of transmitting lipid-enveloped viruses: an economic analysis and budget impact analysis. Ottawa: Canadian Agency for Drugs and Technologies in Health; 2009. (Technology report; no. 107). |
| Coyle D. Octaplas compared to fresh frozen plasma to reduce the risk of transmitting lipid-enveloped viruses: supplementary analyses relating to risk of infection from an unknown virus. Ottawa: Canadian Agency for Drugs and Technology in Health; 2009 Feb 17. (Health technology assessment rapid review). |
| Klein HG, Anderson D, Bernardi MJ, Cable R, Carey W, Hoch JS, et al. Pathogen inactivation: making decisions about new technologies. Report of a consensus conference. <i>Transfusion</i> . 2007 Dec;47(12):2338-47. |
| Webert KE, Cserti CM, Hannon J, Lin Y, Pavenski K, Pendergrast JM, et al. Proceedings of a Consensus Conference: pathogen inactivation-making decisions about new technologies. <i>Transfus Med Rev</i> . 2008 Jan;22(1):1-34. |
| AuBuchon JP, Birkmeyer JD. Safety and cost-effectiveness of solvent-detergent-treated plasma. In search of a zero-risk blood supply. <i>JAMA</i> . 1994 Oct 19;272(15):1210-4. |
| Transfusion Related Acute Lung Injury (TRALI) - The Canadian (CBS) Experience. Ottawa: Canadian Blood Services: unpublished data, 2011 Jan 17. |
| Updated scientific evidence considered by the Panel of Experts |
| Assessment: Initiating the distribution of Octaplas (S/D plasma). Ottawa: Canadian Blood Services: unpublished data, 2010 Apr 7 (Redacted). |
| Kokolo M, Tinmouth A, Fergusson D. Addendum to a systematic review of clinical, laboratory and safety outcomes associated with use of Octaplas in multiple clinical indications. Ottawa: Canadian Agency for Drugs and Technologies in Health; 2011. (CADTH Optimal Use Report). |
| Kekewich M and Foreman T. Ethical assessment: Open vs restricted access and optimal use of solvent detergent treated plasma (Octaplas). Ottawa: Canadian Agency for Drugs and Technologies in Health; 2011. |
| Membe S, Coyle D, Husereau D, Cimon K, Tinmouth A, Normandin S. Octaplas compared with fresh frozen plasma to reduce the risk of transmitting lipid-enveloped viruses: an economic analysis and budget impact analysis. Ottawa: Canadian Agency for Drugs and Technologies in Health; 2009. (Technology report; no 107). [amended 2011 Mar]. |
| Kleinman S, Chan P, Robillard P. Risks associated with transfusion of cellular blood components in Canada. <i>Transfus Med Rev</i> . 2003 Apr;17(2):120-62. |
| Product monograph: Octaplas solvent detergent (S/D) treated human plasma liquid (200mL). Vienna, Austria: Octapharma Pharmazeutika Produktionsges m.b.H.; 2010 Apr 13. |
| O'Shaughnessy DF, Atterbury C, Bolton MP, Murphy M, Thomas D, Yates S, et al. Guidelines for the use of fresh-frozen plasma, cryoprecipitate and cryosupernatant. <i>Br J Haematol</i> . 2004 Jul;126(1):11-28. |
| Liumbruno GM, Sodini ML, Grazzini G, Tuscan Transfusion System. Recommendations from the Tuscan Transfusion System on the appropriate use of solvent/detergent-inactivated fresh-frozen plasma. <i>Blood Transfus</i> . 2008 Jan;6(1):25-36. |
| Kleinman S, Cameron C, Custer B, Busch M, Katz L, Kralj B, et al. Modeling the risk of an emerging pathogen entering the Canadian blood supply. <i>Transfusion</i> . 2010 Dec;50(12):2592-606. |

NAC = National Advisory Committee on Blood and Blood Products.

APPENDIX B: ADVERSE REACTIONS ASSOCIATED WITH S/D PLASMA AND RELEVANT COMPARATORS

Table 2: Adverse Reactions Associated with S/D Plasma and Relevant Comparators⁹

| Study | Product | Allergic Reactions | Death | HAV | HBV | HCV | HIV | Line Infection | Other Infections | TRALI | TACO | Thrombosis | Other |
|--|----------------|--------------------|-------|-----|-----|-----|-----|----------------|------------------|--------------------|------|------------|--|
| Scully (2007) [*] | S/D plasma | 3.1% | 0 | 0 | 0 | 0 | 0 | 22 | NR | 0 | NR | 1 | Citrate reactions: 6.9% [*] |
| | CPP | 9.3% [*] | 0 | 0 | 0 | 0 | 0 | | NR | 0 | NR | | Citrate reactions: 18% [*] |
| Flesland (2007) ^{**} | S/D plasma | 5/100,000 | NR | 0 | NR | NR | NR | NR | NR | 0 | NR | NR | Total transfusion reactions: 10.1/100,000 Serious transfusion reactions: 7.6/100,000 Serious allergic reactions: 2.5/100,000 |
| | FFP | NR | NR | NR | NR | NR | NR | NR | NR | 1.5 to 8.8/100,000 | NR | NR | Serious allergic reactions: 3.7 to 5.6/100,000 |
| Vaara (2010) ^{**} [*] | S/D plasma | 0 | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR |
| | FFP/wet plasma | 19/1,135 | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR |

CPP = cryoprecipitate-poor plasma; FFP= fresh-frozen plasma; HAV = hepatitis A virus; HBV = hepatitis B virus; HCV = hepatitis C virus; HIV=human immunodeficiency virus; NR = not reported; S/D = solvent/detergent; TRALI=transfusion-related acute lung injury; TACO= Transfusion-associated circulatory overload. * Statistically significant difference.

^{*}Scully M, et al. Vox Sang. 2007 Aug;93(2):154-8.

^{**}Flesland O. Intensive Care Med. 2007 Jun;33 Suppl 1:S17-S21.

^{***}Vaara I, et al. Lakartidningen. 2010 Jan 20;107(3):106-7.

APPENDIX C: PANEL OF EXPERTS

CADTH Panel of Experts

The CADTH Panel of Experts is an expert advisory body to CADTH, comprising eight Core Members from current CADTH expert advisory committees and six Specialist Experts appointed to provide their expertise in recommending the optimal use of S/D plasma. Two of the Core Members are Public Members who bring a lay perspective to the committee. The remaining six Core Members hold qualifications as physicians, pharmacists, or health economists, or have other relevant qualifications, with expertise in one or more areas such as, but not limited to, family practice, internal medicine, institutional or community clinical pharmacy, pharmacoeconomics, clinical epidemiology, drug utilization expertise, methodology, affecting behaviour change (through health professional and/or patient and/or policy interventions), and critical appraisal. Five of the Specialist Members have expertise in hematology and/or transfusion medicine, and one Specialist Member has expertise in medical ethics.

The Panel of Experts developed the optimal use recommendation with the aim of contributing to optimal health outcomes and fostering a sustainable health care system for Canadians. The Panel of Experts considered the practical needs of policy-makers, health care providers, and consumers in implementing and using the recommendation toward the promotion of optimal practices. The overall perspective used by the Panel of Experts in producing the recommendation was that of public health care policy-makers in pursuit of optimizing the health of Canadians within available health care system resources.

5

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Conflict of Interest

No members declared any conflicts of interest. Conflict of Interest Guidelines are posted on the CADTH website.

APPENDIX D: ABBREVIATIONS

| | |
|------------|---|
| CADTH | Canadian Agency for Drugs and Technologies in Health |
| CBS | Canadian Blood Services |
| DIN | drug identification number |
| FP | frozen plasma |
| HAV | hepatitis A virus |
| HBV | hepatitis B virus |
| HCV | hepatitis C virus |
| HIV | human immunodeficiency virus |
| HUS | hemolytic uremic syndrome |
| ICER | incremental cost-effectiveness ratio |
| NAC | National Advisory Committee on Blood and Blood Products |
| P-B 19 | parvovirus B19 |
| PTBLC | Provincial / Territorial Blood Liaison Committee |
| QALY | quality-adjusted life-year |
| RCT | randomized controlled trials |
| S/D Plasma | solvent/detergent-treated human plasma |
| TNBP | tri-nitro-butyl phosphate |
| TTP | thrombotic thrombocytopenic purpura |
| TRALI | transfusion-related acute lung injury |

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