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Octaplas Compared with Fresh Frozen Plasma to Reduce the Risk of Transmitting Lipid-Enveloped Viruses: An Economic Analysis and Budget Impact Analysis

Supporting Informed Decisions

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Canadian Agency for Drugs and Technologies in Health

Octaplas Compared with Fresh Frozen Plasma to Reduce the Risk of Transmitting Lipid-Enveloped Viruses: An Economic Analysis and Budget Impact Analysis

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Authorship

As lead author, Stephen Membe led the project protocol development, supervised the literature review, wrote the initial draft, revised the report, and prepared the final version of certain sections of the report for publication.

Doug Coyle developed the economic model, conducted the economic analysis and prepared the final version of section 6 of the report for publication.

Karen Cimon worked with Stephen Membe to evaluate the articles' relevance, assess their quality, extract data, and organize the report.

Alan Tinmouth provided clinical expertise and contributed to the draft document and its subsequent revisions.

Sarah Normandin was responsible for the design and execution of the literature search strategies, writing the section and associated appendix on literature searching, and verifying and formatting the bibliographic references.

Don Husereau reviewed the report and contributed to the discussion and background.

EXECUTIVE SUMMARY

The Issue

Risk of transmitting viruses such as hepatitis A (HAV), parvovirus B19 (P-B19), HIV/AIDS, hepatitis B (HBV), and hepatitis C (HCV) through blood transfusions, along with transfusion-related acute lung injury (TRALI), have driven an increasing number of measures aimed at improving the safety of transfusion therapy. Octaplas — solvent-detergent-treated fresh frozen plasma (SD-FFP) — is a pooled blood product treated with the aim of reducing the risk of transmitting lipid-enveloped viruses (HBV, HCV, and HIV) and TRALI. Health Canada recently licensed Octaplas. The widespread implementation of Octaplas may have significant public health and economic implications.

Objectives

This study investigates the cost-effectiveness of Octaplas against standard FFP and its budgetary impact to the health care system. Specifically, the study answers the following research questions:

- What is the cost-effectiveness of Octaplas versus standard frozen plasma (FP or FFP)?
- What is the budget impact if Octaplas replaced a proportion of the FFP used in Canada (excluding Quebec), or if it replaced a proportion of the FFP cryosupernatant plasma (CSP) used in the treatment of thrombotic thrombocytopenic purpura in Canada?

Methods

Literature searches were conducted to obtain necessary economic and clinical data. All search strategies were developed by the Information Specialist (SN), with input from the project team, and underwent an internal peer review by another Information Specialist. Using data from the literature, two analyses were conducted. First, a Markov decision cost-utility analysis model was constructed to represent six possible transfusion-related complications (HAV, HIV, HBV, HCV, P-B19, and TRALI) in hypothetical cohorts of patients receiving an average of four units of FFP versus Octaplas. The results were presented as incremental cost per quality-adjusted life-years (QALYs). Second, a decision analytical time-series cost-effectiveness model was built. The cost equation in the model included treatment costs and incremental cost of Octaplas; whereas, the effectiveness equation included difference in survival years between interventions. The outcome of the model was cost per life-year saved.

Results

The results of the economic evaluation showed that Octaplas is more costly than FFP and is associated with negligible increases in both QALYs and life years. For a 50-year-old patient, the incremental cost per QALY gained was $934,000 and the incremental cost per life-year gained was $1.3 million. Results were insensitive to changes in parameter estimates.

Budget Impact Analysis

The incremental cost (additional budget) to the health care system resulting from switching 100% of the total demand of all forms of plasma to Octaplas would be about C$16.5 million per year. When Octaplas replaces all forms of FFP, plasma from ongoing donations would go for fractionation; hence, enabling the health care system to potentially save about C$3 million per year (in absolute terms) from purchasing much-needed intravenous immunoglobulin (IVIg) and albumin. In relative terms, the health care system would incur a yearly net loss of about C$13.5 million.

Should Octaplas replace CSP only, the health care budget would have to increase by C$2 million, hence enabling the health care system to potentially save about C$300,000 per year (in absolute terms) from purchases of IVIg and albumin. In relative terms, the health care system would incur a yearly net loss of about C$1.7 million.

Conclusions

Octaplas is associated with only a minimal reduction in disease burden at a higher cost than standard FP or FFP. The high incremental cost per QALY results from low transfusion-related risks for FP or FFP engineered by advances in the safety measures of blood transfusion, such as testing, donor screening, and deferral. Switching to Octaplas may increase the volume of much-needed IVIg and albumin. However, overall, in relative terms, the health care system incurs a net loss, as it could purchase the added volume of IVIg and albumin at lower total cost from its current suppliers.

ABBREVIATIONS

AIDS	acquired immunodeficiency syndrome
AP	apheresis plasma
BIA	budget impact analysis
CEA	cost-effectiveness analysis
CUA	cost-utility analysis
CSP	cryosupernatant plasma
FFP	fresh frozen plasma
FP	frozen plasma
HAV	hepatitis A virus
HBV	hepatitis B virus
HBsAg	hepatitis B surface antigen
HBcAb	hepatitis B core antibody
HCV	hepatitis C virus
HIV	human immunodeficiency virus
ICER	incremental cost-effectiveness ratio
IVIg	intravenous immunoglobulin
LYS	life-year saved
NAT	nucleic acids testing
P-B19	parvovirus B19
QALY	quality-adjusted life-year
SD-FP	solvent-detergent frozen plasma
SD-FFP	solvent-detergent fresh frozen plasma
TRALI	transfusion-related acute lung injury
TTP	thrombotic thrombocytopenic purpura

TABLE OF CONTENTS

APPENDICES – available from CADTH's website www.cadth.ca

1 INTRODUCTION

1.1 Background

In Canada, plasma is collected from volunteer blood donors. The plasma is frozen and either stored for transfusion or shipped to the US for processing to make fractionated blood products, predominantly intravenous immunoglobulin (IVIg). The plasma for transfusion is available as either frozen plasma (FP), frozen within 24 hours of collection; or fresh frozen plasma (FFP), frozen within eight hours of collection. FP and FFP can be used interchangeably. Each unit of FFP or FP made from a whole blood donation is approximately 200 mL to 250 mL, and contains 2 mg per mL to 4 mg per mL of fibrinogen and approximately 1 IU per mL of all clotting factors (except factor VIII, which is slightly lower in FP). FFP or FP units collected on an apheresis machine are approximately 500 mL in volume, but are otherwise similar in composition.

The risk of transmitting viruses such as hepatitis A virus (HAV), parvovirus B19 (P-B19), HIV/AIDS, hepatitis B virus (HBV), and hepatitis C virus (HCV) through blood transfusions, along with transfusion-related acute lung injury (TRALI), have driven an increasing number of measures aimed at improving the safety of transfusion therapy. Screening potential donors, undertaking laboratory tests for blood-borne infectious diseases, and implementing blood conservation measures such as preoperative autologous blood donations are among the safety measures.[1]

Solvent-detergent treatment of FFP (SD-FFP) is pooled blood product that is treated with the aim of reducing the risk of transmitting lipid-enveloped viruses (HBV, HCV, and HIV) and TRALI. There are no SD-FP products currently available in Canada. A different SD-FP (Vitex) was manufactured in the US and was available in Canada, but it is no longer being manufactured. Octaplas is a SD-FP manufactured in Europe and was introduced there in 1992. It received Health Canada approval in 2005.

1.2 Technology Overview

Solvent-detergent virus processes inactivate encapsulated viruses such as HBV, HCV, and HIV. Non-encapsulated viruses, bacteria, and prions are not specifically targeted by solvent-detergent techniques. For SD-FP, small batches of FFP are pooled (up to 1,520 donors) and then undergo a solvent-detergent process. Octaplas is a form of solvent-detergent, virus-inactivated FFP, prepared by Octapharma, using a solvent-detergent treatment of 1% trinitrobutyl phosphate and 1% Triton X-100, for four hours at 30ºC. Residual solvent-detergent reagents are removed through both oil extraction and reverse-phase chromatography on C18 resin, and the plasma is subsequently re-frozen in 200 mL aliquots to match specific blood types. In addition, the product undergoes multiple size exclusion filtrations at 0.2 microns during the manufacturing process. Through such preparation processes, Octaplas is associated with reduced risk of bacterial contamination and possibly non-infectious complications, including TRALI.[2] In addition, the manufacturer of Octaplas reports prion clearance associated with the manufacturing process.

1.3 Current Fresh Frozen Plasma Utilization in Canada

Approximately 200,000 units of FFP and FP are transfused annually in Canada (Appendix 3), which represents approximately 60,000 patients per year who receive the transfusions. In 1997, the Canadian Expert Working Group outlined the indications for FFP. These included[3]:

- patients with acquired deficiencies of multiple coagulation factors with active bleeding, or who are undergoing preparation for surgical or invasive procedures
- patients with thrombotic thrombocytopenic purpura (TTP)
- patients with acquired single-factor deficiencies when no alternative therapies are available or are appropriate.

Only limited data are available describing the utilization of FFP. No Canadian studies have

looked at FFP or FP utilization. Studies from the United Kingdom,[4] US,[5] and Australia[6,7] identified surgery, internal medicine, and critical care as the largest users of FFP: critical care patients make up to 40% of all units transfused, with surgery patients at 30% to 40% of all units transfused. Cardiac surgery patients alone account for 10% to 20% of all units transfused. The next largest users are internal medicine patients and emergency room patients, who both use approximately 15% of all FFP units transfused.

There appears to be significant variation in the use of FFP/FP among different health care centres. For example, from a database of all patients receiving red blood cell transfusions at 23 Canadian centres in 1998 to 2000, the proportions of critical care and cardiac surgery patients transfused with FFP varied from 22% to 55% and 28% to 60% respectively.[8] Similar variation has been reported in other studies looking at FFP utilization.[9] Given this variation, it is not surprising that there is a high rate of inappropriate utilization for FFP or FP. The most recent Canadian study reported that 40% of FFP transfusions failed to meet the recent recommendations from the Canadian Expert Working Group.[10]

1.4 Adverse Reactions Associated with Frozen Plasma Transfusions

FP transfusions can be associated with both infectious and non-infectious complications. The associated infectious complications include viral infections (both enveloped and non-enveloped viruses), bacterial infections, parasitic infections, and prion diseases. The non-infectious complications include minor reactions, such as febrile non-hemolytic reactions, allergic/urticarial reactions; and more serious reactions, such as allergic/anaphylactic reactions, transfusion-associated circulatory overload, TRALI, acute hemolytic transfusion reactions, and ABO blood group incompatibility. Some of these adverse events are reduced or eliminated by the pooling of FP units and other manufacturing steps included as part of the solvent-detergent process for Octaplas.

1.4.1 Infectious Complications

The main infectious complications associated with FP transfusions are viral. The current estimated risks for HIV, HCV, HBV, human T-lymphotropic virus, West Nile virus, HAV, and P-B19 from standard blood components, including FP, are provided in Table 1.

To reduce the risk of transfusion-transmitted infections, all blood donations in Canada undergo polymerase chain reaction nucleic acids testing (NAT) for HIV, HCV, and WNV (seasonally in Quebec); and antibody testing for HIV, HCV, HBV (hepatitis B surface antigen [HBsAg] and hepatitis B core antibody [HBcAb]), and human T-lymphotropic virus. During plasma collection and manufacturing for Octaplas, plasma pools are tested by polymerase chain reaction NAT for HIV, HCV, HBV, HAV, and P-B19. In addition, individual plasma donations are tested for antibodies to HIV, HCV, and HBV (HBsAg). The solvent-detergent treatment virtually eliminates the risk of transmitting enveloped viruses (HIV, HCV, HBV), but does not affect non-enveloped viruses. For the non-enveloped viruses (HAV and P-B19), donor exposure is increased with the pooling of plasma units; however, this increased risk for transfusion-transmitted infections is offset by filtration at 0.2 microns (sterile filtration), NAT testing, and the presence of anti-HAV and anti-P-B19 antibodies in the plasma pools. Some of these tests must be "negative" or "non-reactive" to pass, while others, particularly P-B19 testing on the pools (and the units that go into the pool), establish a maximum level of virus that can be present — a threshold. Transfusion-transmitted infections for HAV and P-B19 in Canada are estimated to be very rare for standard blood components,[11] but the true rate is unknown.

Table 1: Estimated Risk of Viral Infections from Standard Blood Components in Canada[11,12]	
Infection	**Risk**
HIV	1:4.7 million
HCV	1:3.1 million
HBV	1:82,000
HTLV	1:4.3 million
WNV	< 1.1 million
HAV	1:10 million
P-B19	1: 10 million

HAV = hepatitis A virus; HBV = hepatitis B virus; HCV = hepatitis C virus; HIV = human immunodeficiency virus; HTLV = human T-lymphotropic virus; P-B19 = parvovirus B19; WNV = West Nile virus.

No reports of HAV or P-B19 infections have been published for solvent-detergent plasma using the current manufacturing and testing procedures, but there are no large epidemiologic studies that have properly evaluated this risk. One small post-surveillance study of SD-FP reported 17 patients seroconverting after receiving SD-FP with P-B19 levels > 7 IU per mL.[13] In 56 recipients of units with levels < 3.5 IU per mL, there were no seroconversions. The current NAT testing was subsequently introduced to avoid the transfusion of these high titre units of SD-FP. As a result, the true relative risks of transfusion transmitted HAV and P-B19 for Octaplas and FP are unknown.

1.4.2 Non-Infectious Complications

TRALI is defined as the development of a new acute lung injury (increased oxygen requirements and bilateral lung infiltrates on chest radiograph, with no evidence of circulatory overload) within six hours of a blood transfusion, and no other risk factors for acute lung injury.[12] The etiology of TRALI has not been clearly elucidated, but the two main postulated mechanisms are passive transfer of donor anti-leukocyte (either anti-HLA or anti-granulocyte antibodies) or biologically active lipids that accumulate in stored blood.[14] TRALI is generally considered to be under-recognized, but the true incidence of this important and serious transfusion reaction is unknown. Current estimates for TRALI vary from 10.5 to 1.4 per 100,000 units transfused although risks may be higher for platelet pools (i.e. 12.1per 100,000 units transfused).[11] As many as 40% of TRALI reactions reported in hemovigilance data are due to FP transfusions.[15]

The pooling of plasma units for solvent-detergent plasma has been hypothesized to reduce or eliminate the risk of TRALI. No prospective studies have evaluated the rates of TRALI following transfusion of solvent-detergent plasma. However, there have been no case reports of TRALI following the transfusion of Octaplas or other solvent-detergent plasma products. Additionally, a recent review of hemovigilance data from four different European countries reported no TRALI events from 1999 to 2003 in Norway, where Octaplas is exclusively used for FP transfusions.[15] In the three other countries that use standard FP, the rates for TRALI following FP transfusions were 1.6 to 8.8 per 100,000 units.[15] While conclusions from hemovigilance are limited due to the passive reporting mechanisms used, these data support the notion that TRALI may be reduced or eliminated with Octaplas.

Allergic (anaphylactic) reactions are characterized by a severe allergic hypersensitivity during, or shortly after, a blood transfusion. This is most commonly due to anti-IgA antibodies in recipients, but may also be due to other antigens in the transfused plasma. The estimated rate of anaphylactic reactions is 1:20,000 to 1:47,000.[16] The pooling of units in the manufacturing process for Octaplas may theoretically decrease the incidence of these reactions, but no evidence for decreased reaction rates were found in a systematic review of prospective studies of Octaplas. A recent report comparing hemovigilance data among different countries also did not suggest a reduced rate of severe immunologic reactions in Norway, where SD-FP

is exclusively used.[15] Similarly, from a systematic review of the literature of Octaplas, there was no evidence of a reduced rate of severe or minor allergic reactions.

Circulatory overload is a serious and seemingly under-recognized complication of FP transfusions. The commonly used doses of two or four units of FP represent a volume of approximately 400 mL to 800 mL of colloid. Transfusing this volume can lead to serious complications associated with fluid overload. Current estimates for circulatory overload following blood transfusion are 1:100 to 1:700 transfusions.[12]

2 THE ISSUE

Health Canada recently licensed Octaplas, which can now be considered as an alternative to standard FFP for certain indications. Since, on average, 200,000 units of FFP are transfused annually in Canada (Appendix 3), the widespread implementation of Octaplas may have significant public health and economic implications. This study investigates the cost-effectiveness position of Octaplas against standard FFP and its budgetary impact to the health care system.

3 RESEARCH QUESTIONS

The study focuses on the following two questions:

- What is the cost-effectiveness of Octaplas versus standard FFP?
- What is the budget impact if Octaplas replaced a proportion of the FFP used in Canada (excluding Quebec), or if it replaced a proportion of the FFP cryosupernatant plasma (CSP) used in the treatment of thrombotic thrombocytopenic purpura in Canada?

4 METHODS

4.1 Literature Search

Literature searches were conducted to obtain necessary economic and clinical data. All search strategies were developed by the Information Specialist (SN), with input from the project team, and underwent an internal peer review by another Information Specialist.

The following databases were cross-searched through the OVID interface: MEDLINE (1950 to September 2007, week 4; In-Process & Other Non-Indexed Citations (October 3, 2007), EMBASE (1996 to 2007, week 39), BIOSIS Previews (1989 to 2007, week 42), Cochrane Database of Systematic Reviews (Issue 3, 2007), Database of Abstracts of Reviews of Effects (Issue 3, 2007), ACP Journal Club (1991 to September/October 2007), and Cochrane Central Register of Controlled Trials (Issue 3, 2007). Parallel searches were run in the Health Economic Evaluations Database (HEED) and PubMed. The search strategy was comprised of both controlled vocabulary, such as the National Library of Medicine's MeSH (Medical Subject Headings), and keywords. The main search concepts included Octaplas, and solvent-detergent-treated plasma, and FFP. Methodological filters were applied to limit retrieval to economic studies from 1990 onward. See Appendix 1 for the detailed search strategies. OVID AutoAlerts were set up, and regular searches were performed in HEED and PubMed to find any new literature.

The websites of health technology assessment and related agencies, professional associations, and other specialized databases were searched, including the University of York NHS Centre for Reviews and Dissemination (NHS CRD). Google and Yahoo search engines were used to search for additional web-based materials and information. Extra searches were conducted for literature published from 2004 onward on the cost of treating HIV, HBV, and HCV, TRALI, and thrombosis complications. Bibliographies and abstracts of key papers and conference proceedings were also reviewed.

4.2 Selection Criteria

Table 2: Selection Criteria

Category	Inclusion Criteria
Study Design	Full or partial economic evaluations
Study Population	Transfusion recipients of all ages
Intervention and Comparator	FFP; Octaplas solvent-detergent-treated plasma
Clinical Outcome Measure	HAV, HBV, HCV, HIV, TRALI, P-B19, HRQoL, QALY, LYS, and health utility
Cost Outcome Measure	Weekly, monthly, or yearly costs associated with treating infection, managing adverse events, medicine, health care resources use, lost time, and quality of life
Incremental Outcome	Incremental cost utility, ICER, and incremental cost per LYS

FFP = fresh frozen plasma; HAV = hepatitis A virus; HBV = hepatitis B virus; HCV = hepatitis C virus; HIV = human immunodeficiency virus; HRQoL = health-related quality of life; ICER = incremental cost-effectiveness ratio; LYS = life-year saved; P-B19 = parvovirus B19; QALY = quality-adjusted life-year; TRALI = transfusion-related acute lung injury.

4.3 Data Extraction Method

One reviewer (SM) used a data extraction sheet to compile the data for each study. The extracted data were checked by a second reviewer (KC). Each study was also summarized.

4.4 Results of Literature Search

The literature searches revealed 173 potentially relevant citations for economic review (Figure 1). A total of 170 articles were excluded due to inappropriate interventions and study design, resulting in six studies retrieved for further scrutiny (three from the original search and three from the grey literature search). Two articles were excluded due to inappropriate interventions, and one was excluded due to inappropriate design; thus resulting in three relevant reports.

5 REVIEW OF ECONOMIC STUDIES

Literature in cost-effectiveness studies was limited, as only three studies were identified as meeting the inclusion criteria; one conducted in 1994, one in 1999, and one in 2003. Study characteristics are detailed in Table 3.

In the 1994 study, using a decision analysis model, AuBuchon and Birkmeyer[17] performed cost-utility analysis (CUA) comparing SD-FP with untreated plasma for hypothetical cohorts of plasma recipients (mean age 65 years). In their calculations, the assumed transfusion infection risk was 30:100,000 units for HCV, 2:100,000 units for HBV, and 1:100,000 units for HIV.

Compared with untreated plasma, a unit of SD-FP produced a net benefit of 35 minutes in quality-adjusted life expectancy, at a cost of about $19. This translated to 147 quality-adjusted life-years (QALYs) at a cost of $142.5 million for 2.2 million plasma units transfused in the US in 1993. The resulting incremental cost per QALY of $289,300 was most responsive to the cost of SD-FP and to the clinical setting of the plasma use. The results of the sensitivity analysis showed that the presence of non-enveloped virus in SD-FP in the ratio of 1:71 million units or more negated the net benefits.

In the 1999 study, Pereira[18] used a Monte Carlo simulation of a Markov model to derive cost and utilities of transfusing SD-FP instead of FFP. Transfusion risk used in the model was 0.2:100,000 units for HIV, 5:100,000 units for HCV, and 1.6:100,000 units for HBV. Base-case results showed that SD-FP infusion prolonged the quality-adjusted survival by one hour and 11 minutes per patient, producing an incremental cost of $2,156,398 per QALY gained. In

sensitivity analysis, the incremental cost-effectiveness ratio (ICER) was responsive to patient's age, cost-difference between interventions, short-term mortality rates, and HIV and HCV transmission rates.

In the 2003 study, Riedler et al.[2] estimated the incremental cost per life-year saved (LYS) for SD-FP compared with untreated FP using a time-series analytical model. Keeping patients' age and short-term mortality rates controlled in the model, the authors applied the incidence rates of 1:2 million units for HIV, 1:625,000 for HCV, 1:200,000 for HBV, and 1:5,000 for TRALI. SD-FP in the model was assumed to have zero transfusion-infection risks. Baseline results showed that SD-FP produced an incremental cost per LYS of £22,728 for neonates, and £98,465 for patients aged 70 years. For patients younger than 48 years of age, the cost-effectiveness ratio was lower at £50,000 per LYS, and less than £30,000 per LYS for patients younger than 21 years old. The cost-effectiveness ratio for patients with no significant morbidity was £12,335 for neonates and £61,692 for patients who were 70 years of age. The results showed that TRALI was the major cost driver, due to its high incidence rates.

Results of the reviewed studies are summarized in Table 4.

6 ECONOMIC EVALUATION

6.1 Methods

Due to lack of reliable utility estimates and the nature of interventions in question, we established that an analysis presenting the results both in aggregated and disaggregated terms would be appropriate. Therefore, an economic model was derived and results are reported in the form of both a cost utility analysis (CUA) and a cost-effectiveness analysis (CEA).

Figure 1: Selected Studies for Economic Review

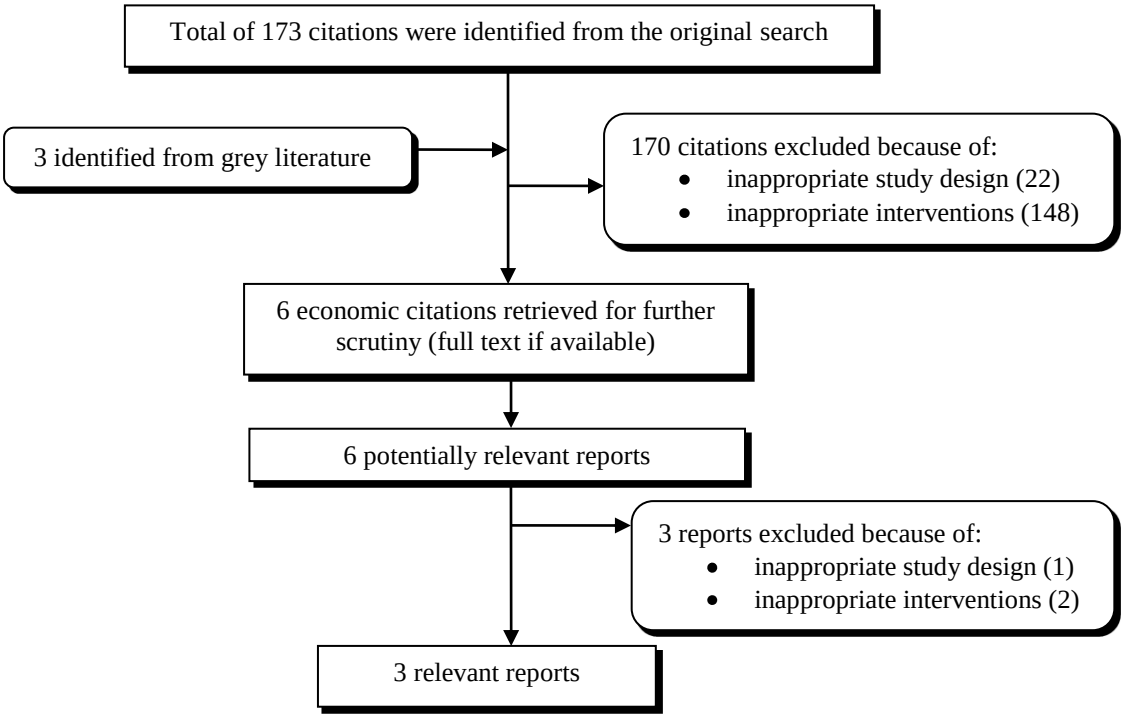


Table 3: Characteristics of Selected Studies				
Author, Year, and Country	**Study Design and Perspective**	**Study Population / Comparator**	**Clinical Outcomes**	**Cost Considered**
AuBuchon and Birkmeyer, 1994[17] US	CUA, public health care payer	Hypothetical cohorts of patients taking SD-FP versus non SD-FP	Virus transmission (HIV, HBV, and HCV)	Evaluation and management of acute hepatitis, HIV infection, and AIDS
Pereira, 1999[18] Spain	CUA, national health care service	Hypothetical patients aged up to 70 years taking FFP versus SD-FP	Virus transmission (HIV, HBV, and HCV)	Unit cost of SD-FP and FP
Riedler et al., 2003[2] UK	CEA, health care payer	Hypothetical patients aged up to 70 years taking FFP versus SD-FP	TRALI	Unit cost of SD-FP and FFP

AIDS = acquired immunodeficiency syndrome; CEA = cost-effectiveness analysis; CUA = cost-utility analysis; FFP = fresh frozen plasma; HBV = hepatitis B virus; HCV = hepatitis C virus; HIV = human immunodeficiency virus; TRALI = transfusion-related acute lung injury; SD-FP = solvent-detergent frozen plasma.

Table 4: Summary of the Results of Reviewed Economic Studies			
Author, Year, and Funding Source	**Study Endpoint**	**Study Results**	**Conclusion**
AuBuchon and Birkmeyer, 1994[17] Funding source not specified	Cost per QALY gained	Compared with FFP, a unit of SD-FP produced a net benefit of 35 minutes of QALYs at $19, with 2.2 million units given annually = $142.5 million per 147 QALYs.	SD-FP produces small benefit and high costs
Pereira, 1999[18] Funded by Octapharma UK	Cost per QALY gained	Virus-inactivated plasma prolonged the QALYs by 1 hour and 11 minutes at a cost-effectiveness ratio of $2,156,398 per QALY.	Virus-inactivated plasma produces little benefit and very high cost due to low current risk of infection with transfusion-transmitted viruses and due to the greater age and poor short-term prognosis of most plasma recipients.
Riedler et al., 2003[2] Funded in part by Ministerio de Sanidad y Consumo, Government of Spain	Cost per LY gained	Cost per LY = £22,728 for neonates and £98,465 for patients aged 70 years. Cost per LY was less than £50,000 for patients < 48 years and less than £30,000 for patients < 21 years. For patients with no significant mobility, cost per LY = £12,335 for neonates and £61,692 for 70-year-olds.	Inclusion of non-infectious complication suggests that SD-FP is cost-effective in patients < 48 years old and in older patients with good clinical prognosis.

FFP = fresh frozen plasma; LY = life-year; QALY = quality-adjusted life-year; SD-FFP = solvent-detergent fresh frozen plasma.

6.1.1 Description of the Model

A Markov decision analysis model was constructed to represent six possible transfusion-related complications (HAV, HIV, HBV, HCV, P-B19, and TRALI) in hypothetical cohorts of patients (with a one-year mortality rate of 20%) receiving an average of four units of Octaplas versus FFP. Other plasma transfusion-related consequences, such as thrombosis complications, were not modelled due to the lack of data.

In each arm of the model, patients received the same volume of units of plasma (four in the base case). Patients can either complete the transfusion safely or experience transfusion-related complications according to assigned probabilities. In the short-run, patients may experience immediate mortality due to both their underlying disease and transfusion-related complications; whereas, in the long-run, they may experience morbidity and mortality due to transfusion-related complications. As patients move from one health state to another, according to respective transitional probabilities, they accumulate QALYs and incur costs-to-treat transfusion-transmitted infections.

6.1.2 Key Model Assumptions

The model makes the following key assumptions. First, a unit of Octaplas is therapeutically equivalent to a unit of FFP. Second, based on previous studies,[2,17,19] Octaplas virtually eliminates the risk of transmission of enveloped viruses (HIV, HBV, and HCV) and non-infectious complications such as TRALI. For HAV and P-B19 it was assumed that the risks associated with Octaplas were the same as those estimated for FFP with sensitivity analysis around this assumption. Third, a patient cannot experience more than one transfusion-related complication. Fourth, patients are at equal and normal life expectancy before receiving infusion (sensitivity is performed to account for differences in prognosis condition before infusion).

6.1.3 Probabilities

The model incorporates relevant estimates governing clinical probabilities for each disease state. Expected values for probabilities with standard errors used for probabilistic analysis are detailed in Table 5. Uncertainty around probabilities was characterized by beta distributions. The estimates were extracted from a systematic review of relevant Canadian studies, identified through the electronic search. In the absence of Canadian data from the literature, non-Canadian data and expert opinion became the last resort. In the model, per unit risk of transmitting hepatitis viruses and TRALI were multiplied by four to derive the risk to an average recipient of four units of plasma.

6.1.4 Utilities

Utility estimates measure health-related quality of life and are used to weigh life expectancy to allow measurement of QALYs. Although both chronic HBV and HCV have similar clinical complications (compensated cirrhosis, decompensated cirrhosis, hepatocellular carcinoma, etc.), the present studies[20-22] estimate utilities for HCV only and we assumed these would be suitable for HBV. Expected values for the utility for each health state with standard errors used for probabilistic analysis are presented in Table 6. Uncertainty around utility estimates was modelled based on the assumption that the uncertainty around disutility takes the form of a lognormal distribution.

6.1.5 Costs

In the model, the costs to acquire four units of plasma were calculated by multiplying respective price per unit of plasma by four. Table 7 displays expected values for costs and standard errors used for probabilistic analysis. Expected annual costs of care for each hepatitis disease state were adopted from recent Canadian studies by Gagnon et al.,[23] Bauch et al.[24] and El Saadany et al.[22] Yearly costs of managing chronic HIV and AIDS in Canada were adopted from Beck et al.[25] When necessary, original costs were adjusted for inflation using consumer price indices for health care, available at http://www.bank-banque-canada.ca Gamma distributions were assigned to all uncertain cost data.

Table 5: Probabilities		
Variable and Source	**Expected Value**	**Standard Error**
Probability of transfusion-transmitted HBV per unit of FFP[12]	0.000012	0.000007
Probability of progression to chronic hepatitis HBV or HCV[22]	0.75	0.089
Probability of progression to rapid liver failure (fulminant death) due to HBV or HCV infection[22]	0.05	0.013
Probability of resolving or curing HBV infections[11]	0.56	0.13
Probability of resolving or curing HCV infections[11]	0.20	0.051
Annual probability of progressing from chronic to compensated cirrhosis HBV or HCV[26]	0.011	0.0043
Annual probability of progressing from chronic to hepatocellular carcinoma HBV or HCV[26]	0.015	0.026
Annual probability of progressing from compensated cirrhosis to esophageal varices HBV or HCV[26]	0.011	0.0043
Annual probability of progressing from compensated cirrhosis to hepatic encephalopathy HBV or HCV[22]	0.004	0.0010
Annual probability of progressing from compensated cirrhosis to ascites HBV or HCV[22]	0.025	0.0066
Annual probability of receiving liver transplant (for both HBV and HCV)[22]	0.03	0.0077
Annual probability of post-liver transplant death (HBV or HCV)[22]	0.15	0.037
Annual probability of hepatic encephalopathy death (HBV or HCV)[22]	0.68	0.17
Annual probability of esophageal varices death (HBV or HCV)[22]	0.40	0.15
Annual probability of ascites death (HBV or HCV)	0.011	0.0043
Annual probability of hepatocellular carcinoma death (HBV or HCV)[22]	0.86	0.13
Annual probability of progressing from compensated cirrhosis to hepatocellular carcinoma[22]	0.015	0.0026
Probability of transfusion-transmitted HCV per unit of FFP[12]	0.00000032	0.00000019
Probability of transfusion-transmitted HIV per unit of FFP[12]	0.00000021	0.00000012
Probability of becoming chronic HIV[27]	0.79	0.10
Probability of progressing from chronic HIV to AIDS[27]	0.052	0.020
Probability of death from AIDS state[27]	0.85	0.11
Probability of transfusion-transmitted TRALI[11]	0.000014	0.000008
Probability of transfusion-related HAV per unit of FFP[11]	0.0000001	0.00000006
Probability of transfusion-related P-B19 per unit of FFP[11]	0.0000001	0.00000006
Probability of acute death from TRALI[28]	0.10	0.037
Short-term mortality rate (patient prognosis condition)[2,17]	0.20	0.17
Short-term mortality rate from HAV[24]	0.0175	0.0045
Probability of hospital recovery from TRALI[28]	0.90	0.14

AIDS = acquired immunodeficiency syndrome; HAV = hepatitis A virus; HIV = human immunodeficiency virus; P-B19 = parvovirus B19; TRALI = transfusion-related acute lung injury.

Table 6: Annual Utilities		
Variable	**Expected Value**	**Standard Error**
Chronic condition (no complications)[22]	0.820	0.150
Compensated cirrhosis[26]	0.800	0.051
Post-liver transplant[22]	0.700	0.089
Stable hepatocellular carcinoma[22]	0.100	0.038
Chronic HIV[18]	0.500	0.130
AIDS [18]	0.250	0.150
Ascites[22]	0.350	0.099
HAV[24]	0.900	0.100
Esophageal varices[22]	0.280	0.066
Hepatic encephalopathy[22]	0.300	0.084
TRALI [29]	0.690	0.100
P-B19 [30]	0.987	0.026

AIDS = acquired immunodeficiency syndrome; FFP = fresh frozen plasma; HAV = hepatitis A virus; HBV = hepatitis B virus; HCV = hepatitis C virus; HIV = human immunodeficiency virus; TRALI = transfusion-related acute lung injury.

Table 7: Annual Costs		
Variable	**Expected Value (standard error)**	
	First Year	**Subsequent Years**
Cost of treating chronic HBV or HCV[22]	$482 (241)	$262 (131)
Cost of treating compensated cirrhosis HBV or HCV[22]	$1,005 (502.5)	$326 (163)
Cost of treating HAV complications[24]	$1,923 (961.5)	$0.00
Cost of liver post-liver transplant (successful liver transplant)[22]	$66,542 (33,271)	$37,854 (37,854)
Cost of treating or managing stable hepatocellular carcinoma[22]	$9,343 (4,671.5)	$7,028 (3,514)
Cost of managing ascites[22]	$6,799 (3,399.5)	$1,302 (651)
Cost of managing hepatic encephalopathy[22]	$10,606 (5,303)	$1,376 (688)
Cost of managing esophageal varices[22]	$24,246 (12,123)	$11,057 (5,528.5)
Per unit average cost of FP, FFP or CSP unit*	$96.00 (Fixed)	
Cost of curing acute hepatitis infection†	$482 (241)	
Cost of treating TRALI[31]	$13,885 (6942.5)	
Cost of managing chronic HIV[25]	$10,065 (5,032.5)	
Cost of managing AIDS[25]	$12,526 (6,263)	
Cost of per unit Octaplas infusion	$141.40 (Fixed)	

AIDS = acquired immunodeficiency syndrome; CSP = cryosupernatant plasma; FP = frozen plasma; FFP = fresh frozen plasma; HAV = hepatitis A virus; HBV = hepatitis B virus; HCV = hepatitis C virus; HIV = human immunodeficiency virus; TRALI = transfusion-related acute lung injury.

*Calculated from plasma price data from Canadian Blood Services (Appendix 2).

†Derived by adding per unit price of Octaplas [C$140.00 (Octapharma Inc.: personal communication, 2007)] and per unit annual carrying cost (C$1.40) calculated from annual plasma utilization data from Canadian Blood Services (Appendix 3).

6.1.6 Sensitivity Analysis

To evaluate the impact of joint uncertainty of model inputs, we performed probabilistic sensitivity analysis (second-order Monte Carlo simulation). In the simulation, costs and outcomes were calculated for each intervention through a random draw of each variable's probability distribution. This was repeated 5 000 times.

In addition deterministic sensitivity analyses were conducted focussing on the the affect of the patient's age (baseline = 50), units of plasma required (baseline = 4), discount rate (baseline = 5%), costs of Octaplas, risks of HIV and HCV, risk of TRALI, underlying disease mortality and risks of HAV and P-B19 associated with Octaplas.

6.2 Base-Case Results

As depicted in Table 8, Octaplas is more costly (C$566 versus C$385) and produces only a modest increase in QALYs (12.4786 versus 12.4784) and life-years (12.4786 versus 12.4784) when compared to FFP. The incremental cost per QALY gained was $934,000 and the incremental cost per life-year gained was $1.3 million.

6.3 Sensitivity Analysis

6.3.1 Probabilistic Sensitivity Analysis

Figure 2 depicts the results of the second-order Monte Carlo simulation, revealing the joint distribution of incremental costs and effects generated in 5,000 simulations on the cost-effectiveness plane. All of the simulated ICERs are located in the upper right quadrant of the cost-effectiveness plane indicating that Octaplas is more effective and more costly. The acceptability curve shows that the probability that Octaplas is cost-effective is 0% for all values of a QALY less than $100,000 and only 6.3% for a value of $500,000

6.3.2 Deterministic Sensitivity Analysis

Results were insensitive to all the assumptions considered within the deterministic sensitivity analysis (Table 9). If the cost per unit cost of Octaplas infusion was $100 (an increase of only $4 over the cost of FFP), the incremental cost per QALY gained would be $77,000.

For all other transition probabilities, costs and utilities imputing the upper and lower values did not lead to ICERs that were less than $70,000 indicating little impact on cost-effectiveness.

Table 8: Base-Case Results

Intervention	FFP	Octaplas
Cost	$385	$566
Life-Years	12.4784	12.4786
QALYs	12.4784	12.4786
Incremental Cost per Life-Year Gained		$1.3 million
Incremental Cost per QALY Gained		$934 000

FFP = fresh frozen plasma; QALYs = quality-adjusted life-year.

Figure 2: Scatterplot of Incremental Costs and QALYs

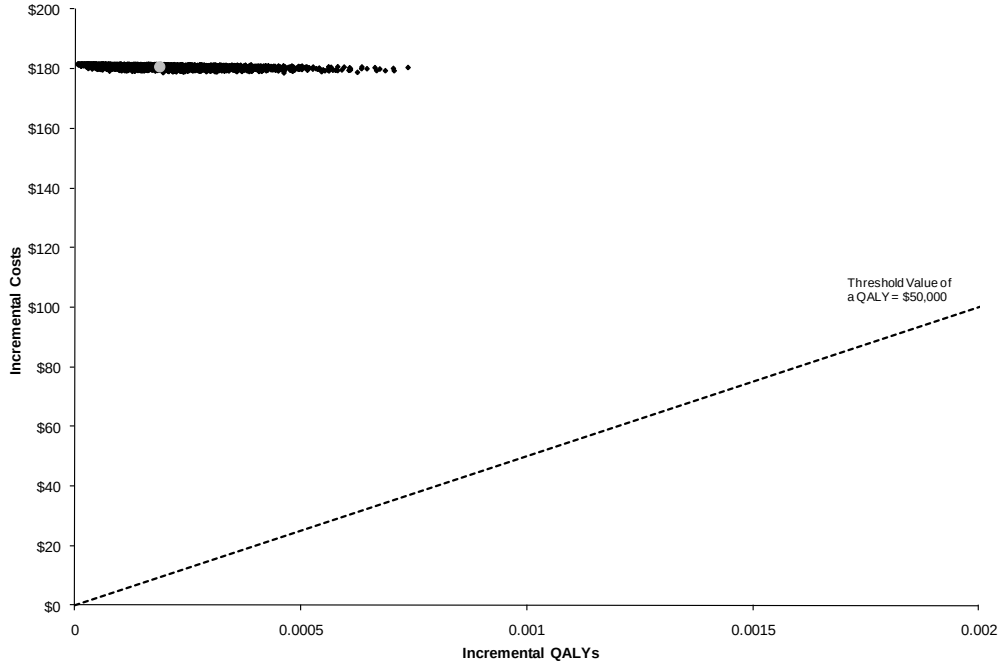


Figure 3: Cost-Effectiveness Acceptability Curve

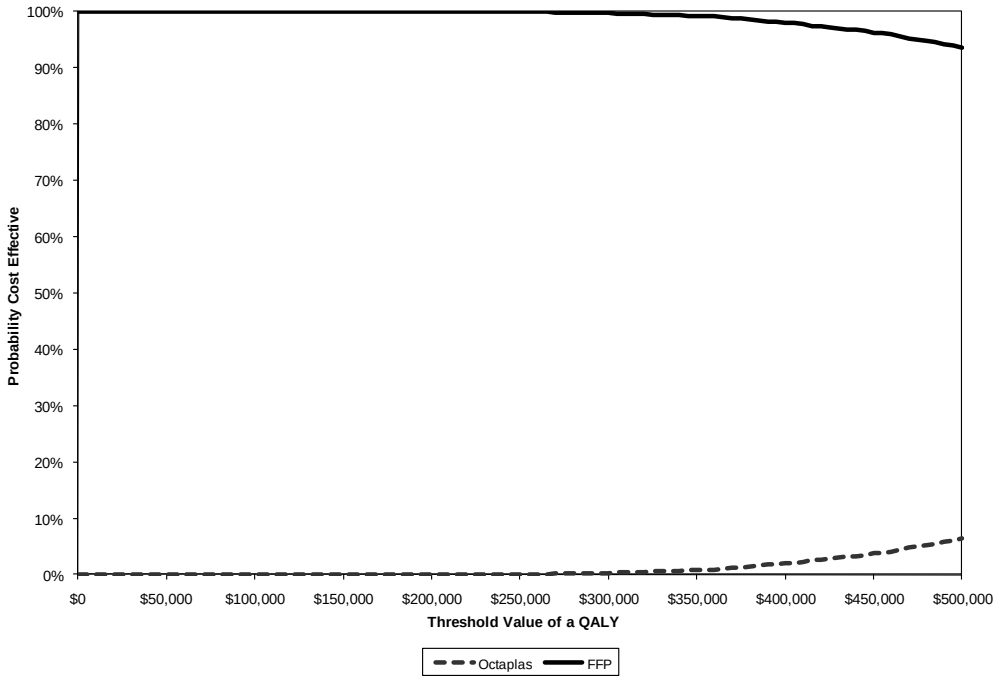


Table 9: Results of Deterministic Sensitivity Analysis	
Scenario	**Incremental Cost per QALY Gained ($)**
Baseline*	934 000
Probability of transfusion related TRALI with plasma = 0.000121	215 000
Probability of acute death from TRALI = 0.015	795 800
Lower risks of HIV (1 in 5million) and HCV (1 in 13 million)	952 900
Discount rate = 0%	453 400
Discount rate = 3%	724 600
Age = 35 years	822 900
Age = 65 years	1 307 800
1 unit of plasma	934 000
10 units of plasma	934 000
Probability of transfusion-related HAV or P-B19 per unit of Octaplas = 0	933 400
Probability of transfusion-related HAV or P-B19 per unit of Octaplas = 0.000152	1 225 500
Unit cost of Octaplas = $125	594 800

FFP = fresh frozen plasma; HAV = hepatitis A virus; P-B19 = parvovirus B19; TRALI = transfusion-related acute lung injury; QALY = quality-adjusted life-year.
*Baseline is for a 50-year-old patient receiving four units of plasma assuming a 5% discount rate and same risk of P-B19 and HAV with Octaplas.

7 BUDGET IMPACT AND BENEFIT ANALYSIS

7.1 Incremental Cost from Switching from Fresh Frozen Plasma to Octaplas

A one-year time-horizon budget impact analysis (BIA) was performed from the health care payer perspective to assess the impact of switching from FFP to Octaplas. Specifically, the analysis focused on the following research questions:

What is the budget impact if Octaplas:

- replaced FFP or FP and apheresis plasma (AP) in Canada (excluding Quebec)
- replaced CSP for treatment of TTP in Canada?

Respective incremental cost for FFP, FP, AP and CSP was calculated using variables shown in Table 10. The incremental cost shows how much the health care budget should increase to have Octaplas replace the current intervention. This was calculated as the difference in total costs between Octaplas and the current intervention. For instance, the incremental cost for a 25% switch from FFP to Octaplas was calculated as:

BIA = [(0.25)*(average annual total FFP units)*(cost per unit FFP)] – [(0.25)*(equivalent total Octaplas units)*(cost per unit Octaplas = per unit price + per unit carrying cost)]

Equivalent total Octaplas units were calculated by converting average annual FFP units to mL and dividing them by Octaplas volume (mL) per unit.

Aggregate results of BIA show that it would cost the health care system an additional $8.2 million and $16.5 million to have Octaplas replace, respectively, 50% and 100% of the total demand for all forms of plasma. It would require an additional $7.2 million and $14.4 million to have Octaplas replace 50% and 100%, respectively, of the total demand for AP, FFP, and FP. If Octaplas replaced 50%, 75%, and 100% of the total demand for CSP, the required additional budget would be $1 million, $1.5 million, and $2 million respectively.
Disaggregated results of BIA are detailed in Tables 11, 12, 13, and 14.

Table 10: Variables Used in Budget Impact Analysis	
Variable	**Estimate and Source**
Average total unit cost of FFP, FP or CSP	C$96[*]
Total unit cost AP	C$267[†]
Average annual FFP, FP or AP units demanded	196,072.33[‡]
Average annual AP units demanded	50,789.67[‡]
Plasma volume per unit of FFP or FP	250 mL[†]
Plasma volume per unit of CSP	238 mL[†]
Octaplas volume per unit	200 mL[32]
Plasma volume per unit of AP	500 mL[†]
Per unit price of Octaplas	$140[**]
Annual carrying cost per Octaplas unit	$1.40[‡]

AP = apheresis plasma; CSP = cryosupernatant plasma; FP = frozen plasma; FFP = fresh frozen plasma.
[*]Calculated using price data from Canadian Blood Services (Appendix 2).
[†] Adopted from Canadian Blood Services (Appendix 2 and 3).
[‡]Calculated from annual plasma utilization data from Canadian Blood Services (Appendix 3).
[**]Octapharma Inc.: personal communication, 2007.

Table 11: Budgetary Impact of Switching from Fresh Frozen Plasma to Octaplas						
	From	**To**	**Total Units in mL**	**Current Cost**		**BIA**
Switching Rate (% of demand)	**FFP Units**	**Octaplas Units**		**Octaplas Cost ($)**	**FFP Cost ($)**	**Increment Cost ($)**
10	9,523.23	11,904.04	2,380,808.33	1,683,231	876,137	807,094
15	14,284.85	17,856.06	3,571,212.50	2,524,847	1,314,206	1,210,641
20	19,046.47	23,808.08	4,761,616.67	3,366,463	1,752,275	1,614,188
25	23,808.08	29,760.10	5,952,020.83	4,208,079	2,190,344	2,017,735
30	28,569.70	35,712.13	7,142,425.00	5,049,694	2,628,412	2,421,282
35	33,331.32	41,664.15	8,332,829.17	5,891,310	3,066,481	2,824,829
40	38,092.93	47,616.17	9,523,233.33	6,732,926	3,504,550	3,228,376
45	42,854.55	53,568.19	10,713,637.50	7,574,542	3,942,619	3,631,923
50	47,616.17	59,520.21	11,904,041.67	8,416,157	4,380,687	4,035,470
55	52,377.78	65,472.23	13,094,445.83	9,257,773	4,818,756	4,439,017
60	57,139.40	71,424.25	14,284,850.00	10,099,389	5,256,825	4,842,564
65	61,901.02	77,376.27	15,475,254.17	10,941,005	5,694,894	5,246,111
70	66,662.63	83,328.29	16,665,658.33	11,782,620	6,132,962	5,649,658
75	71,424.25	89,280.31	17,856,062.50	12,624,236	6,571,031	6,053,205
80	76,185.87	95,232.33	19,046,466.67	13,465,852	7,009,100	6,456,752
85	80,947.48	101,184.35	20,236,870.83	14,307,468	7,447,168	6,860,299
90	85,709.10	107,136.38	21,427,275.00	15,149,083	7,885,237	7,263,846
95	90,470.72	113,088.40	22,617,679.17	15,990,699	8,323,306	7,667,393
100	95,232.33	119,040.42	23,808,083.33	16,832,315	8,761,375	8,070,940
FFP mL per bag/unit		250.00				
Octaplas mL per bag/unit		200.00				

BIA = budget impact analysis; FFP = fresh frozen plasma.

Table 12: Budgetary Impact of Switching from Apheresis Plasma to Octaplas						
	AP Plasma	**Octaplas**	**Total Units in mL**		**Current Cost**	**BIA**
Switching Rate (% of total demand)	**AP Units**	**Octaplas Units**		**Octaplas Cost ($)**	**AP Cost ($)**	**Incremental Cost ($)**
10	5,078.97	12,697.42	2,539,483.33	1,795,414	1,356,084	439,330
15	7,618.45	19,046.13	3,809,225.00	2,693,122	2,034,126	658,995
20	10,157.93	25,394.83	5,078,966.67	3,590,829	2,712,168	878,661
25	12,697.42	31,743.54	6,348,708.33	4,488,536	3,390,210	1,098,326
30	15,236.90	38,092.25	7,618,450.00	5,386,244	4,068,252	1,317,991
35	17,776.38	44,440.96	8,888,191.67	6,283,951	4,746,294	1,537,657
40	20,315.87	50,789.67	10,157,933.33	7,181,658	5,424,336	1,757,322
45	22,855.35	57,138.38	11,427,675.00	8,079,366	6,102,378	1,976,987
50	25,394.83	63,487.08	12,697,416.67	8,977,073	6,780,420	2,196,653
55	27,934.32	69,835.79	13,967,158.33	9,874,780	7,458,462	2,416,318
60	30,473.80	76,184.50	15,236,900.00	10,772,488	8,136,504	2,635,983
65	33,013.28	82,533.21	16,506,641.67	11,670,195	8,814,546	2,855,649
70	35,552.77	88,881.92	17,776,383.33	12,567,903	9,492,588	3,075,314
75	38,092.25	95,230.63	19,046,125.00	13,465,610	10,170,630	3,294,979
80	40,631.73	101,579.33	20,315,866.67	14,363,317	10,848,672	3,514,644
85	43,171.22	107,928.04	21,585,608.33	15,261,025	11,526,714	3,734,310
90	45,710.70	114,276.75	22,855,350.00	16,158,732	12,204,756	3,953,975
95	48,250.18	120,625.46	24,125,091.67	17,056,439	12,882,798	4,173,640
100	50,789.67	126,974.17	25,394,833.33	17,954,147	13,560,841	4,393,306
AP mL per bag/unit		500.00				
Octaplas mL per bag/unit		200.00				

AP = apheresis plasma; BIA = budget impact analysis.

Table 13: Budgetary Impact of Switching from Frozen Plasma to Octaplas						
	From	**To**	**Total Units in mL**	**Current Costs**		**BIA**
Distribution by %	**FP Units**	**Octaplas Units**	**Total mL**	**Octaplas Cost ($)**	**FP Cost ($)**	**Increment Cost ($)**
10	2,332.77	2,915.96	583,191.67	412,317	214,615	197,702
15	3,499.15	4,373.94	874,787.50	618,475	321,922	296,553
20	4,665.53	5,831.92	1,166,383.33	824,633	429,229	395,404
25	5,831.92	7,289.90	1,457,979.17	1,030,791	536,536	494,255
30	6,998.30	8,747.88	1,749,575.00	1,236,950	643,844	593,106
35	8,164.68	10,205.85	2,041,170.83	1,443,108	751,151	691,957
40	9,331.07	11,663.83	2,332,766.67	1,649,266	858,458	790,808
45	10,497.45	13,121.81	2,624,362.50	1,855,424	965,765	889,659
50	11,663.83	14,579.79	2,915,958.33	2,061,583	1,073,073	988,510
55	12,830.22	16,037.77	3,207,554.17	2,267,741	1,180,380	1,087,361
60	13,996.60	17,495.75	3,499,150.00	2,473,899	1,287,687	1,186,212
65	15,162.98	18,953.73	3,790,745.83	2,680,057	1,394,994	1,285,063
70	16,329.37	20,411.71	4,082,341.67	2,886,216	1,502,302	1,383,914
75	17,495.75	21,869.69	4,373,937.50	3,092,374	1,609,609	1,482,765
80	18,662.13	23,327.67	4,665,533.33	3,298,532	1,716,916	1,581,616
85	19,828.52	24,785.65	4,957,129.17	3,504,690	1,824,224	1,680,467
90	20,994.90	26,243.63	5,248,725.00	3,710,849	1,931,531	1,779,318
95	22,161.28	27,701.60	5,540,320.83	3,917,007	2,038,838	1,878,169
100	23,327.67	29,159.58	5,831,916.67	4,123,165	2,146,145	1,977,020
FP ml per bag/unit		250.00				
Octaplas ml per bag/unit		200.00				

BIA = budget impact analysis; FP = frozen plasma.

7.2 Potential Savings from Switching to Octaplas

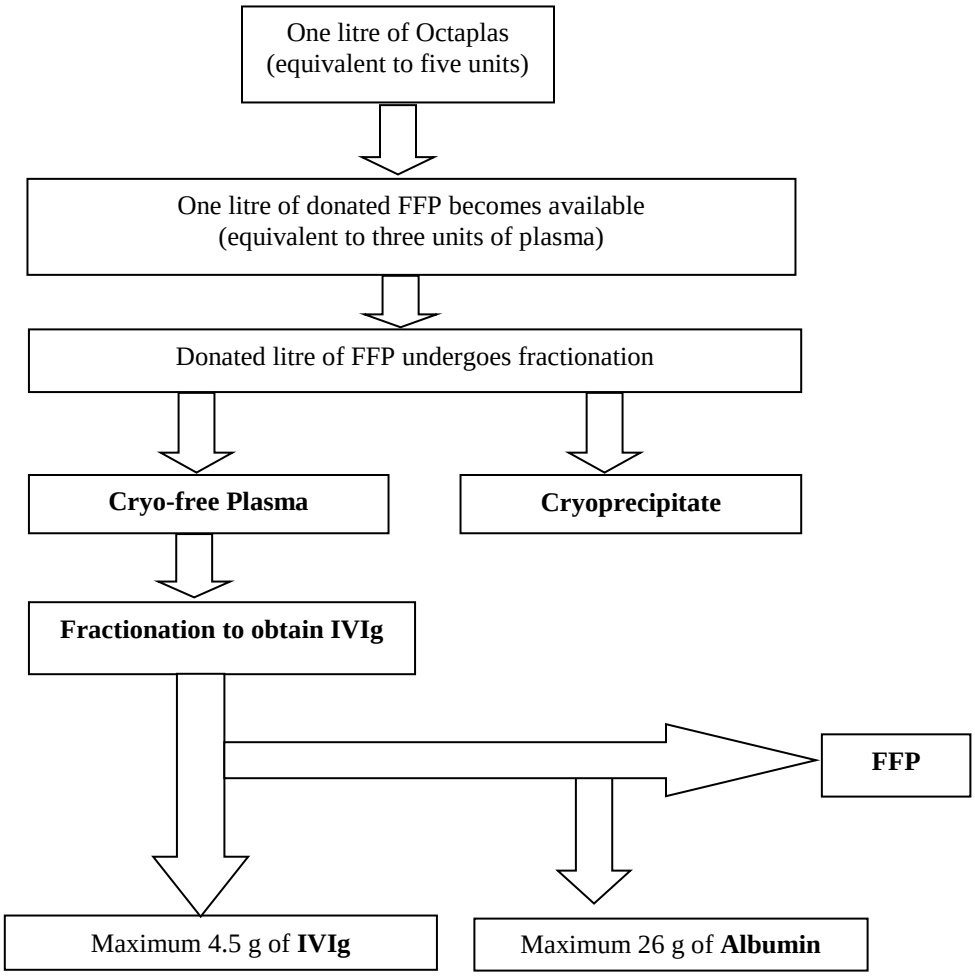
Potential savings resulting from the replacement of FFP, FP, AP, or CSP with Octaplas was calculated under the assumption that each Octaplas litre purchased would free up one litre of donated FFP for fractionation at zero cost (Figure 4). Thus, Canadian Blood Services would continue collecting plasma for fractionation after Octaplas replaced FFP. Each FFP litre going for fractionation would cost the health care system an average of three units of plasma (C$92 x 3 = 276) and yield a maximum of 4.5 g and 26 g of IVIg and albumin respectively.[33] The per gram price for IVIg is C$57.56,[34] and the per gram price of albumin is C$2.42.[35] Aggregate results show that the health care system would save about C$700,000 and C$1.5 million to have Octaplas replace, respectively, 25% and 50% of the total demand for all forms plasma. If Octaplas replaces 75% and 100% of the total demand for all types of plasma, the health care system would save about C$2.2 million and C$3 million respectively. If Octaplas replaces only CSP, potential savings to the health care system would be about C$300,000.

Disaggregated results of potential savings are detailed in Tables 15, 16, 17, and 18.

Table 14: Budgetary Impact of Switching from Cryosupernatant Plasma to Octaplas						
	From	**To**	**Total Units in mL**	**Current Costs**		**BIA**
Switching Rate (% of demand)	**CSP Units**	**Octaplas Units**	**Total mL**	**Octaplas Cost ($)**	**CSP Cost ($)**	**Increment Cost ($)**
10	2,672.27	3,180.00	635,999.47	449,652	248,521	201,131
15	4,008.40	4,770.00	953,999.20	674,477	372,781	301,696
20	5,344.53	6,359.99	1,271,998.93	899,303	497,042	402,262
25	6,680.67	7,949.99	1,589,998.67	1,124,129	621,302	502,827
30	8,016.80	9,539.99	1,907,998.40	1,348,955	745,562	603,392
35	9,352.93	11,129.99	2,225,998.13	1,573,781	869,823	703,958
40	10,689.07	12,719.99	2,543,997.87	1,798,606	994,083	804,523
45	12,025.20	14,309.99	2,861,997.60	2,023,432	1,118,344	905,089
50	13,361.33	15,899.99	3,179,997.33	2,248,258	1,242,604	1,005,654
55	14,697.47	17,489.99	3,497,997.07	2,473,084	1,366,864	1,106,220
60	16,033.60	19,079.98	3,815,996.80	2,697,910	1,491,125	1,206,785
65	17,369.73	20,669.98	4,133,996.53	2,922,736	1,615,385	1,307,350
70	18,705.87	22,259.98	4,451,996.27	3,147,561	1,739,646	1,407,916
75	20,042.00	23,849.98	4,769,996.00	3,372,387	1,863,906	1,508,481
80	21,378.13	25,439.98	5,087,995.73	3,597,213	1,988,166	1,609,047
85	22,714.27	27,029.98	5,405,995.47	3,822,039	2,112,427	1,709,612
90	24,050.40	28,619.98	5,723,995.20	4,046,865	2,236,687	1,810,177
95	25,386.53	30,209.97	6,041,994.93	4,271,690	2,360,948	1,910,743
100	26,722.67	31,799.97	6,359,994.67	4,496,516	2,485,208	2,011,308
CSP ml per bag/unit		238.00				
Octaplas ml per bag/unit		200.00				

BIA = budget impact analysis; CSP = cryosupernatant plasma.

Figure 4: Fractionation Paths and Yields from One Litre of FFP



FFP = fresh frozen plasma; IVIg = intravenous immunoglobulin.

Table 15: Potential Savings (Switching from Fresh Frozen Plasma to Octaplas)									
Switching Rate (% of Demand)	**Octaplas Units/Bags**	**FFP Freed Litres**	**Cost per Freed Litres ($)**	**Yield IVIg Grams**	**IVIg Savings ($)**	**Yield Albumin Grams**	**Albumin Savings ($)**	**Total Savings ($)**	**Net Savings ($)**
10	11,904.04	2,380.81	657,104	10,713.65	616,677	61,901.06	155,793	772,470	115,366
15	17,856.06	3,571.21	985,654	16,070.45	925,015	92,851.46	233,689	1,158,703	173,049
20	23,808.08	4,761.62	1,314,207	21,427.29	1,233,355	123,802.12	311,585	1,544,940	230,733
25	29,760.10	5,952.02	1,642,758	26,784.09	1,541,692	154,752.52	389,481	1,931,173	288,416
30	35,712.13	7,142.43	1,971,311	32,140.94	1,850,032	185,703.18	467,378	2,317,410	346,099
35	41,664.15	8,332.83	2,299,861	37,497.74	2,158,370	216,653.58	545,274	2,703,643	403,782
40	47,616.17	9,523.23	2,628,411	42,854.54	2,466,707	247,603.98	623,170	3,089,877	461,465
45	53,568.19	10,713.64	2,956,965	48,211.38	2,775,047	278,554.64	701,066	3,476,113	519,149
50	59,520.21	11,904.04	3,285,515	53,568.18	3,083,384	309,505.04	778,962	3,862,347	576,832
55	65,472.23	13,094.45	3,614,068	58,925.03	3,391,724	340,455.70	856,859	4,248,583	634,515
60	71,424.25	14,284.85	3,942,619	64,281.83	3,700,062	371,406.10	934,755	4,634,817	692,198
65	77,376.27	15,475.25	4,271,169	69,638.63	4,008,399	402,356.50	1,012,651	5,021,050	749,881
70	83,328.29	16,665.66	4,599,722	74,995.47	4,316,739	433,307.16	1,090,547	5,407,287	807,565
75	89,280.31	17,856.06	4,928,273	80,352.27	4,625,077	464,257.56	1,168,443	5,793,520	865,248
80	95,232.33	19,046.47	5,256,826	85,709.12	4,933,417	495,208.22	1,246,340	6,179,757	922,931
85	101,184.35	20,236.87	5,585,376	91,065.92	5,241,754	526,158.62	1,324,236	6,565,990	980,614
90	107,136.38	21,427.28	5,913,929	96,422.76	5,550,094	557,109.28	1,402,133	6,952,227	1,038,297
95	113,088.40	22,617.68	6,242,480	101,779.56	5,858,431	588,059.68	1,480,029	7,338,460	1,095,980
100	119,040.42	23,808.08	6,571,030	107,136.36	6,166,769	619,010.08	1,557,925	7,724,693	1,153,663

FFP = fresh frozen plasma; IVIg = intravenous immunoglobulin.

Table 16: Potential Savings (Switching from Fresh Frozen Plasma to Octaplas)									
Switching Rate (% of Demand)	**Octaplas Units/Bags**	**FFP Freed Litres**	**Cost per Freed Litres ($)**	**Yield IVIg Grams**	**IVIg Savings ($)**	**Yield Albumin Grams**	**Albumin Savings ($)**	**Total Savings ($)**	**Net Savings ($)**
10	2,915.96	583.19	160,961	2,624.36	151,557	15,162.98	36,694	188,251	27,290
15	4,373.94	874.79	241,441	3,936.54	227,335	22,744.48	55,042	282,377	40,936
20	5,831.92	1,166.38	321,922	5,248.73	303,114	30,325.97	73,389	376,503	54,581
25	7,289.90	1,457.98	402,402	6,560.91	**378,892**	37,907.46	91,736	**470,628**	**68,226**
30	8,747.88	1,749.58	482,883	7,873.09	454,671	45,488.95	110,083	564,754	81,871
35	10,205.85	2,041.17	563,363	9,185.27	530,449	53,070.44	128,430	658,880	95,517
40	11,663.83	2,332.77	643,844	10,497.45	606,228	60,651.93	146,778	753,005	109,162
45	13,121.81	2,624.36	724,324	11,809.63	682,006	68,233.43	165,125	847,131	122,807
50	14,579.79	2,915.96	804,805	13,121.81	**757,785**	75,814.92	183,472	**941,257**	**136,452**
55	16,037.77	3,207.55	885,285	14,433.99	833,563	83,396.41	201,819	1,035,382	150,097
60	17,495.75	3,499.15	965,765	15,746.18	909,342	90,977.90	220,167	1,129,508	163,743
65	18,953.73	3,790.75	1,046,246	17,058.36	985,120	98,559.39	238,514	1,223,634	177,388
70	20,411.71	4,082.34	1,126,726	18,370.54	1,060,899	106,140.88	256,861	1,317,759	191,033
75	21,869.69	4,373.94	1,207,207	19,682.72	**1,136,677**	113,722.38	275,208	**1,411,885**	**204,678**
80	23,327.67	4,665.53	1,287,687	20,994.90	1,212,455	121,303.87	293,555	1,506,011	218,324
85	24,785.65	4,957.13	1,368,168	22,307.08	1,288,234	128,885.36	311,903	1,600,137	231,969
90	26,243.63	5,248.73	1,448,648	23,619.26	1,364,012	136,466.85	330,250	1,694,262	245,614
95	27,701.60	5,540.32	1,529,129	24,931.44	1,439,791	144,048.34	348,597	1,788,388	259,259
100	29,159.58	5,831.92	1,609,609	26,243.63	**1,515,569**	151,629.83	366,944	**1,882,514**	**272,905**

FFP = fresh frozen plasma; IVIg = intravenous immunoglobulin.

Table 17: Potential Savings (Switching from Apheresis Plasma to Octaplas)									
Switching Rate (% of Demand)	**Octaplas Units/Bags**	**FFP Freed Litres**	**Cost per Freed Litres ($)**	**Yield IVIg Grams**	**IVIg Savings ($)**	**Yield Albumin Grams**	**Albumin Savings ($)**	**Total Savings ($)**	**Net Savings ($)**
10	12,697.42	2,539.48	700,897	11,427.68	659,948	66,026.57	159,784	819,733	118,835
15	19,046.13	3,809.23	1,051,346	17,141.51	989,922	99,039.85	239,676	1,229,599	178,253
20	25,394.83	5,078.97	1,401,795	22,855.35	1,319,896	132,053.13	319,569	1,639,465	237,670
25	31,743.54	6,348.71	1,752,244	28,569.19	**1,649,871**	165,066.42	399,461	**2,049,331**	**297,088**
30	38,092.25	7,618.45	2,102,692	34,283.03	1,979,845	198,079.70	479,353	2,459,198	356,505
35	44,440.96	8,888.19	2,453,141	39,996.86	2,309,819	231,092.98	559,245	2,869,064	415,923
40	50,789.67	10,157.93	2,803,590	45,710.70	2,639,793	264,106.27	639,137	3,278,930	475,340
45	57,138.38	11,427.68	3,154,038	51,424.54	2,969,767	297,119.55	719,029	3,688,796	534,758
50	63,487.08	12,697.42	3,504,487	57,138.38	**3,299,741**	330,132.83	798,921	**4,098,663**	**594,176**
55	69,835.79	13,967.16	3,854,936	62,852.21	3,629,715	363,146.12	878,814	4,508,529	653,593
60	76,184.50	15,236.90	4,205,384	68,566.05	3,959,689	396,159.40	958,706	4,918,395	713,011
65	82,533.21	16,506.64	4,555,833	74,279.89	4,289,664	429,172.68	1,038,598	5,328,261	772,428
70	88,881.92	17,776.38	4,906,282	79,993.73	4,619,638	462,185.97	1,118,490	5,738,128	831,846
75	95,230.63	19,046.13	5,256,731	85,707.56	**4,949,612**	495,199.25	1,198,382	**6,147,994**	**891,263**
80	101,579.33	20,315.87	5,607,179	91,421.40	5,279,586	528,212.53	1,278,274	6,557,860	950,681
85	107,928.04	21,585.61	5,957,628	97,135.24	5,609,560	561,225.82	1,358,166	6,967,726	1,010,099
90	114,276.75	22,855.35	6,308,077	102,849.08	5,939,534	594,239.10	1,438,059	7,377,593	1,069,516
95	120,625.46	24,125.09	6,658,525	108,562.91	6,269,508	627,252.38	1,517,951	7,787,459	1,128,934
100	126,974.17	25,394.83	7,008,974	114,276.75	**6,599,482**	660,265.67	1,597,843	**8,197,325**	**1,188,351**

FFP = fresh frozen plasma; IVIg = intravenous immunoglobulin.

Table 18: Potential Savings (Switching from Cryosupernatant Plasma to Octaplas)									
Switching Rate (% of Demand)	**Octaplas Units/Bags**	**FFP Freed Litres**	**Cost per Freed Litres**	**Yield IVIg Grams**	**IVIg Savings ($)**	**Yield Albumin Grams**	**Albumin Savings ($)**	**Total Savings ($)**	**Net Savings ($)**
10	3,180.00	636.00	$175,536	2,862.00	165,280	16,535.99	40,017	205,297	29,762
15	4,770.00	954.00	$263,304	4,293.00	247,921	24,803.98	60,026	307,946	44,642
20	6,359.99	1,272.00	$351,072	5,724.00	330,561	33,071.97	80,034	410,595	59,523
25	7,949.99	1,590.00	$438,840	7,154.99	**413,201**	41,339.97	100,043	**513,244**	74,404
30	9,539.99	1,908.00	$526,608	8,585.99	495,841	49,607.96	120,051	615,892	89,285
35	11,129.99	2,226.00	$614,375	10,016.99	578,481	57,875.95	140,060	718,541	104,166
40	12,719.99	2,544.00	$702,143	11,447.99	661,121	66,143.94	160,068	821,190	119,046
45	14,309.99	2,862.00	$789,911	12,878.99	743,762	74,411.94	180,077	923,839	133,927
50	15,899.99	3,180.00	$877,679	14,309.99	**826,402**	82,679.93	200,085	**1,026,487**	148,808
55	17,489.99	3,498.00	$965,447	15,740.99	909,042	90,947.92	220,094	1,129,136	163,689
60	19,079.98	3,816.00	$1,053,215	17,171.99	991,682	99,215.92	240,103	1,231,785	178,570
65	20,669.98	4,134.00	$1,140,983	18,602.98	1,074,322	107,483.91	260,111	1,334,433	193,450
70	22,259.98	4,452.00	$1,228,751	20,033.98	1,156,963	115,751.90	280,120	1,437,082	208,331
75	23,849.98	4,770.00	$1,316,519	21,464.98	**1,239,603**	124,019.90	300,128	**1,539,731**	223,212
80	25,439.98	5,088.00	$1,404,287	22,895.98	1,322,243	132,287.89	320,137	1,642,380	238,093
85	27,029.98	5,406.00	$1,492,055	24,326.98	1,404,883	140,555.88	340,145	1,745,028	252,974
90	28,619.98	5,724.00	$1,579,823	25,757.98	1,487,523	148,823.88	360,154	1,847,677	267,854
95	30,209.97	6,041.99	$1,667,591	27,188.98	1,570,163	157,091.87	380,162	1,950,326	282,735
100	31,799.97	6,359.99	$1,755,359	28,619.98	**1,652,804**	165,359.86	400,171	**2,052,974**	297,616

FFP = fresh frozen plasma; IVIg = intravenous immunoglobulin.

7.3 Net Gain or Loss from Switching to Octaplas

At each FFP demand level, the net gain or loss to the health care system from switching to Octaplas was calculated as the difference between incremental cost and potential savings from purchasing commercial IVIg and albumin. Incremental cost and potential savings or benefits from switching from FFP to Octaplas was computed in sections 7.1 and section 7.2 respectively. The net gain or loss calculated should not be confused with the concept of net health or monetary benefit. It is a comparison of market value of the added volume of IVIg and albumin resulting from a switch to Octaplas and the additional cost required to switch to Octaplas.

In aggregate there would be yearly net loss of C$13.5 million if Octaplas replaces 100% of the total demand for all forms of plasma. Should Octaplas replace only 50% of the total demand for all types of plasma, the health care system would incur a yearly net loss of C$6.7 million. Switching 75% of total demand for all plasma would lead to a yearly net loss of C$10.1 million.

Table 19 shows disaggregate results of the BIA. If Octaplas replaced CSP, only for treatment of TTP in Canada, the health care system would incur a yearly net loss of between C$171,000 and C$1.7 million.

8 DISCUSSION

The results of the economic evaluation show that Octaplas is both more costly and is associated with minimal health gains compared to FFP. The incremental cost per QALY gained is $934 000, whilst the incremental cost per life-year gained is $1.3 million. The magnitude of the cost-effectiveness ratios is likely due to the minimal risks of transfusions. Although Octaplas reduces the risk of transmission of lipid-enveloped viruses, Canadian data indicate that presently such risks are already reduced to

Table 19: Net Gain or Loss from Switching to Octaplas

Switching rates (% of demand)	FFP ($)	FP ($)	AP ($)	CSP ($)
10	-691,728	-170,412	-320,495	-171,369
15	-1,037,592	-255,617	-480,743	-257,054
20	-1,383,455	-340,823	-640,991	-342,738
25	-1,729,319	-426,029	-801,239	-428,423
30	-2,075,183	-511,235	-961,486	-514,108
35	-2,421,047	-596,440	-1,121,734	-599,792
40	-2,766,911	-681,646	-1,281,982	-685,477
45	-3,112,774	-766,852	-1,442,230	-771,162
50	-3,458,638	-852,058	-1,602,477	-856,846
55	-3,804,502	-937,263	-1,762,725	-942,531
60	-4,150,366	-1,022,469	-1,922,973	-1,028,215
65	-4,496,230	-1,107,675	-2,083,221	-1,113,900
70	-4,842,093	-1,192,881	-2,243,468	-1,199,585
75	-5,187,957	-1,278,086	-2,403,716	-1,285,269
80	-5,533,821	-1,363,292	-2,563,964	-1,370,954
85	-5,879,685	-1,448,498	-2,724,212	-1,456,638
90	-6,225,549	-1,533,704	-2,884,459	-1,542,323
95	-6,571,413	-1,618,909	-3,044,707	-1,628,008
100	-6,917,277	-1,704,115	-3,204,955	-1,713,692

AP = apheresis plasma; CSP = cryosupernatant plasma; FFP = fresh frozen plasma; FP = frozen plasma.

their lowest possible level.[34] For example, with 200,000 FFP units transfused annually in Canada, a transfusion-related HIV incident is likely to occur every 24 years (1:4.7 million units), while an incident of HCV will occur every 16 years (1:3.1 million units). Also, incidence rates for HBV and TRALI in Canada are lower than those reported in previous studies.[2,19]

The results of the sensitivity analysis show that if the per unit cost of Octaplas was reduced from $141.20 to $100 (an incremental cost compared to FFP of only $4 per unit) the incremental cost per QALY gained associated with Octaplas would still be greater than $50,000.

The results of the analysis show that the Octaplas is even less cost effective for elderly plasma recipients who make up the majority of users. The average age of plasma recipients is 65 years.[2,17] In our analysis, the incremental cost per QALY gained from Octaplas for 65-year-old recipients was $1.3 million. Thus, our findings mirror previous studies where technologies to reduce transfusion infections may be more cost-effective for younger recipients.[2,17,18]

The results of the economic evaluations are only as precise as the costs used in the analyses. The costs of treating chronic infection conditions used in our study were adopted from previous Canadian studies with different costing methodologies. However, sensitivity analyses showed that such costs do not influence cost-effectiveness significantly.

Similarly, utility estimates used in the CUA were gathered from Canadian and non-Canadian studies with variation in settings and methods. As a result, there is minimal inconsistency among utility estimates and their respective health states in our CUA. This might have compromised the validity of our findings. However, results were similarly insensitive to changes in these values.

It is important to note that the uncertainty tested through sensitivity analyses in the economic evaluations is known, or aleatory, uncertainty. This describes statistical uncertainty known from variability of input parameters based on current scientific knowledge. Of potentially greater concern in risk management are epistemic or systematic uncertainties from unknown unknowns. What is known is that the risk of infection from any potential future pathogens not susceptible to Octaplas treatment will be potentially amplified by pooling compared with a single-unit approach.

Regarding the budget impact and benefit analysis, we found that, should Octaplas replace 100% of the total demand of CSP, the health care budget would have to increase by C$2 million. Incremental cost (additional budget) to the health care system resulting from switching 100% of total demand of all forms of plasma to Octaplas would cost about C$16.5 million. In return, this amount would enable the health care system to save about C$3 million from purchasing the much-needed IVIg and albumin, given that each litre of FFP freed up by one litre of Octaplas would go for fractionation at zero cost and yield 4.5 g of IVIg and 26 g of albumin.[33,36] While in absolute terms, the health care system would benefit by increasing the volume of IVIg and albumin, this isn't the case in relative terms where there would be a yearly net loss of C$13.5 million.

Yearly net loss can be mainly attributed to the pre-fractionation cost per litre of plasma. Although each five units of Octaplas purchased would free one litre of plasma for fractionation, the pre-fractionation cost of plasma litres (ranging from C$91[FP] to C$267 [AP] per unit] reduces fractionation benefits significantly. In our analysis, we used an average pre-fractionation cost of C$276 per litre (C$92 per unit x three units per litre), which translated to saving C$45.87 per litre. However, this savings would only be realized if we purchase five units of Octaplas; hence, adding C$247 [(C$141.40 – C$92) x 5] to our regular budget for one litre of FFP. As a result, we incur a loss of about C$201 (C$247 – C$45.87) for each plasma litre freed up by a litre of Octaplas. A net benefit would have been possible had we not included the pre-fractionation cost of a plasma litre freed up by five units of Octaplas.

The results of the net gain or loss analysis are limited in terms of assumptions, prices, and fractionation yields used in the analysis. We assumed that FFP freed up by Octaplas would undergo fractionation at zero cost. Other variables being constant, an incremental cost of Octaplas, along with yearly net loss, will increase when such an assumption is relaxed. Also, prices of fractionated products (IVIg and albumin) used in the analysis may not reflect actual contract price. Furthermore, our findings are likely to change due to variations in fractionation yields among fractionators. Currently, yields from one litre of FFP range from 2 g to 4.5 g of IVIg and from 20 g to 26 g of albumin.[33,36,37] In our analysis, we applied upper-bound yield estimates to avoid underestimation.

9 CONCLUSION

Defining effectiveness as QALYs, the results of the economic evaluation showed that, compared with FFP, Octaplas is more costly and with only minimal potential health gains. For treating a 50-year-old patient, the incremental cost per QALY gained from using Octaplas was $934,000 and the incremental cost per life-year gained was $1.3 million. The incremental cost per QALY occurs because currently, transfusion-related risks are low, owing to dramatic advances in the safety measures of blood transfusion. Such measures as testing, donor screening, and deferral have reduced transfusion-related risks significantly.[33]

Switching to Octaplas may increase the volume of much-needed IVIg and albumin. However, the health care system could purchase the added volume of IVIg and albumin at lower total cost from its current suppliers.

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APPENDICES

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