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BACKGROUND

Immune globulin (Ig) products are generated from plasma collected from a large number of carefully screened donors. Ig products may be used as replacement therapy for immunodeficiency patients or as immunomodulatory therapy for autoimmune and alloimmune disorders. Ig products include intravenous Ig (IVIg), subcutaneous Ig (SCIg), RhD Ig (RhIg) and hyperimmune globulins.

INTRAVENOUS IMMUNE GLOBULIN

General information

IVIg products are sterile solutions or lyophilized concentrates of human immune globulin G (IgG) that have been processed to remove multimers and aggregates of IgG, allowing intravenous infusion. The distribution of IgG subclasses in IVIg products is similar to normal plasma. Depending on the method of preparation, some products may contain trace amounts of immune globulin A (IgA) and immune globulin M (IgM).

The various commercial products may differ in their plasma pool size, steps to improve Ig yields, removal of contaminants, pathogen inactivation processes, and stabilizing or preservative agents added. Although those variables alter the final product, the clinical relevance of such modifications has not been widely established, which has resulted in different products being used interchangeably.¹

The mechanism of effect of IVIg has not yet been clearly resolved for any disease. In the case of patients with primary immune deficiency, IVIg is considered to mediate its beneficial effects by providing an array of IgG antibodies that help facilitate the destruction or neutralization of reactive pathogens.

For patients with autoimmunity or inflammation the mechanism or mechanisms of effect of IVIg are not clear.^{2,3} It is also not clear if the mechanisms of effect are similar or overlapping in different diseases. In animal models of autoimmunity, there is some evidence suggesting the induction of anti-inflammatory activity by dendritic cells and/or blockade of Fc receptors in the reticuloendothelial system (RES).^{4,5} The primary molecular targets of IVIg have not yet been definitively established.

Product description

For the names and product-specific details of the various IVIg products carried by Canadian Blood Services, please refer to the [Plasma Protein Products](#) page on www.blood.ca.

Indications

The licensed indications for IVIg in Canada vary slightly by product but currently include:

- Primary immune deficiency (PID),
- Immune thrombocytopenic purpura (ITP),
- Secondary immune deficiency (SID) states,
- Chronic inflammatory demyelinating polyneuropathy (CIDP),
- Guillain-Barré syndrome (GBS),
- Multifocal motor neuropathy (MMN).

<https://professionaleducation.blood.ca/en/transfusion/guide-clinique/immune-globulin-products>

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Chapter 4: Immune Globulin Products

IVIg is often used as an off-label therapy for diseases that may have an immune-mediated or unknown pathogenic mechanism. This off-label use accounts for a significant proportion of IVIg use in most Canadian provinces. Overall utilization trends by population and province are available on the [Plasma Protein Products](#) page of www.blood.ca.

In the attempt to ensure appropriate utilization of IVIg, many jurisdictions across Canada have developed policies and practices that may dictate specific prerequisites and an authorization process prior to the release of products. The Prairie Collaborative Immune Globulin Utilization Management Framework Project has recently developed an evidence-based framework to aid transfusion services and clinicians.⁶

Contraindications

There is no requirement to routinely test for IgA deficiency prior to IVIg therapy. Most manufacturers state that IVIg is contraindicated for individuals with selective IgA deficiency who have anti-IgA antibodies, but these individuals may be successfully treated with SCIg therapy.⁷ There are also reports of patients with demonstrated IgG anti-IgA antibodies tolerating IVIg infusions.⁸ For patients who have had anaphylactic or severe systemic responses to IVIg previously, consideration may be given to the use of solvent-detergent treated products.

Dosing and administration

Dosing for IVIg infusion is dependent on the clinical indication. Generally, the immune replacement dose is 0.4–0.6 g/kg every 3–4 weeks. One additional dose of 0.4 g/kg may be given in the first month of therapy if the serum IgG level is markedly reduced. The immunosuppressive dose is 1–2 g/kg over 1–5 days, and some conditions may require ongoing maintenance therapy, usually given monthly, with efforts made to reduce the dose or extend the treatment interval if/as the patient’s clinical response permits. Local practice guidelines, consensus documents and manufacturer’s recommendations provide more specific information on dose, frequency and duration of therapy for specific indications.

The National Advisory Committee on Blood and Blood Products (NAC) and several provincial health authorities and blood offices recommend IVIg dosing based on adjusted body weight calculators (e.g. Ontario,⁹ Alberta,¹⁰ Nova Scotia,¹¹ British Columbia¹²) and/or absolute dose caps. The reader is referred to the online dose calculators provided (see references above and Table 1) and to local policies for additional details.

Table 1. Adjusted body weight dosing calculations⁶

| |
|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Unless otherwise indicated, use adjusted body weight for dosing calculations in overweight or obese adults as follows: |
| <p>Dosing Weight is an adjusted body weight (of overweight or obese patients): Dosing Weight = IBW + [0.5 x (Actual - IBW)] Note: If actual body weight is less than IBW, then Dosing Weight = actual body weight.</p> |
| <p>Ideal Body Weight (IBW), Devine formula is: IBW (male) = 50.0 kg + 2.3 kg (each inch over 5 feet) IBW (female) = 45.5 kg + 2.3 kg (each inch over 5 feet)</p> |
| In most circumstances, dosing for children is calculated based on actual body weight. |

IVIg must be administered intravenously at an infusion rate specified by the ordering physician. Complications during administration of IVIg may be related to infusion rate. Reactions can be prevented or controlled in many cases by slowing the infusion rate.

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Chapter 4: Immune Globulin Products

Protocols for IVIg infusion vary by institution but are based upon the following principles:

- Start with a slow infusion rate (e.g. 0.01 ml/kg/minute) and monitor vital signs frequently.
- As tolerated, increase the infusion rate at regular intervals with progressively less frequent monitoring of vital signs.

The patient's response to the infusion will dictate an individualized maximum tolerable rate of infusion that may be lower than the manufacturer's recommendation.

Adverse events

The prevalence of IVIg-associated adverse events reported in the literature varies widely.¹³⁻¹⁶ Patients receiving immune replacement therapy appear to have a much lower frequency of side effects than do patients who are receiving IVIg as a treatment for immune-mediated or systemic inflammatory disorders.¹⁷

Minor side effects are quite common with IVIg infusion and are often related to infusion rate. These reactions include headache, chills, fever, malaise, anxiety, chest pain, nausea, pruritus, and rash. The majority of these side effects will resolve with slowing or stopping the IVIg infusion. If recurrent, they can typically be managed by providing premedication or switching to an alternate manufacturer's product. The more serious and potentially fatal adverse events — including hemolysis, aseptic meningitis, anaphylaxis, viral transmission, transfusion-related acute lung injury (TRALI) and thromboembolic events — are rare. Since the implementation of donor testing and routine viral inactivation processes, the currently licensed products are considered safe with respect to transmission of human immunodeficiency virus (HIV) and the hepatitis viruses.¹⁸ Cases of IVIg-associated TRALI reactions have been reported and may be increasing as a result of TRALI mitigation strategies that divert plasma from female donors to fractionation processing.^{19, 20}

Patients receiving Ig products may have reduced response to immunization with parenteral live virus vaccines but IVIg has minimal interference or interaction with inactivated viruses, live oral vaccines, live intranasal vaccines and the Bacillus Calmette–Guérin (BCG) vaccine. For guidance, please refer to the [Canadian Immunization Guide](#) from the Public Health Agency of Canada.²¹

Hemolysis: IVIg administration commonly results in a positive direct antiglobulin test (DAT) and, in up to 3% of cases, contributes to clinically significant hemolytic events.^{22, 23} IVIg-associated hemolysis has been defined by the IVIg Hemolysis Pharmacovigilance Group of Canada as:

A drop in hemoglobin of at least 10 g/l and a positive DAT within 10 days following IVIg infusion with supporting evidence of hemolysis as indicated by at least two of:

- increased reticulocyte count,
- increased lactate dehydrogenase level,
- low haptoglobin level,
- increased unconjugated bilirubin level,

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Chapter 4: Immune Globulin Products

- hemoglobinemia,
- hemoglobinuria,

or the presence of significant spherocytosis and no alternate etiology for the anemia.²⁴

Many case series have described IVIg-associated hemolysis as having a higher occurrence rate in patients receiving high doses.^{23, 25, 26} The lower prevalence in group O patients appears to implicate isohemagglutinins.²⁷ Some manufacturers are now providing IVIg products that are isohemagglutinin-depleted to minimize risk. The risk of hemolysis appears highest when a product with a high isohemagglutinin titre is administered at doses of 2 g/kg or higher to a blood group A or AB recipient;²⁸ some Canadian jurisdictions have implemented prospective hemolysis monitoring processes for these patients.

Aseptic meningitis: Aseptic meningitis secondary to IVIg appears to be dose-related; the majority of reported cases received immunomodulatory doses of 2 g/kg/cycle.²⁹ Meningeal signs and symptoms typically present within 6 to 48 hours of the infusion. On examination, the cerebrospinal fluid demonstrates elevated protein levels, normal to low glucose levels, and a leukocyte pleocytosis with negative cultures.³⁰

The majority of patients recover within five days of symptom onset and tolerate subsequent infusions, but some patients report the recurrence of symptoms with subsequent infusions.³¹

Anaphylaxis: Severe anaphylactic and allergic reactions have been reported in association with IVIg. Some of these reactions have occurred in patients with IgA deficiency and IgA antibodies but there is debate regarding the significance of IgG versus IgE anti-IgA, the role of complement activation, and the persistence of the reactivity.^{8, 32, 33} The use of SClg may be one effective substitute in patients with a history of anaphylactic or severe allergic reactions who require future Ig therapy.⁷ Others recommend the use of IgA-depleted products in those with confirmed anti-IgA antibodies and prior confirmed reactions.³⁴

Thromboembolic events: Health Canada and the Food and Drug Administration (FDA) have both issued safety warnings regarding the potential of thromboembolic complications with non-hyperimmune Ig products.^{35, 36} Reported thromboembolic complications include stroke, transient ischemic attacks, deep-vein thromboses, pulmonary emboli, retinal vein occlusion, and retinal artery infarcts. These thrombotic complications can occur during the IVIg infusion or up to eight days following.³⁷ Patients with cardiovascular risk factors, advanced age, prolonged immobilization and those with a history of thromboembolic events are considered at a higher risk although thrombosis may occur in the absence of any identifiable risk factors. High-risk patients should be carefully monitored and adequately hydrated prior to the IVIg administration. The Ig products should also be administered at the lowest feasible dose and an infusion rate appropriate for the indication and patient condition.

The BC Provincial Blood Coordinating Office (PBCO), in collaboration with immunologists and transfusion medicine physicians and with support from the [BloodTechNet program](#), developed a mobile app to support the diagnosis, treatment and monitoring of patients with primary immunodeficiency disease (PID). The app contains diagnostic and treatment algorithms, a dose calculator to determine IVIg or SClg dose, a dose adjustment calculator and links to references of interest. The PID Toolkit can be downloaded for [Apple](#) or [Android](#).

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SUBCUTANEOUS IMMUNE GLOBULIN

General information

In Canada, subcutaneous immune globulin (SCIg) is predominantly used as replacement therapy for primary and secondary immunodeficiency patients. Since these patients require lifelong therapy with Ig replacement, many may have better quality of life parameters with SCIg use instead of IVIg. These benefits may include improved side effect profiles, no need for vascular access, increased convenience due to home / self-administration and easier travel.³⁸ As it pertains to decreasing the frequency and duration of infection in patients with primary immune deficiency, SCIg and IVIg are considered equally effective.³⁹ As with any blood product managed at home, the use of SCIg should be under the oversight of a comprehensive care clinic to ensure appropriate training for patients / caregivers with respect to administration, proper handling / storage and monitoring for adverse effects.

Product description

For the names and product-specific details of the SCIg products carried by Canadian Blood Services, please refer to the [Subcutaneous Immune Globulins](#) table located at www.blood.ca.

Indications

The licensed indication for SCIg is currently restricted to replacement therapy for primary and secondary immunodeficiency. Some early clinical trials are underway with use of these products in patients with neurologic disorders to allow for home administration.

Contraindications

The main contraindication for SCIg is a history of anaphylactic or severe allergic reactions to Ig preparations. However, this is often a reason for switching a patient from intravenous to subcutaneous forms. Some, but not all, products advise against use in those with known anti-IgA. One product recommends against use in patients with hyperprolinemia.

Dose and administration

For initiation of replacement therapy in patients with primary immunodeficiency, SCIg should be started at a dose of 100–500 mg/kg per week³⁹ but should not exceed 20 ml/h per site (Hizentra) or 60 ml/h/site (Cuvitru). One additional dose of 0.4 g/kg may be given in the first month of therapy if the serum IgG level is markedly reduced.

If transitioning from IVIg, the easiest calculation is to take the monthly total IVIg dose and divide by 4 to obtain the weekly SCIg dose followed by titration to achieve an IgG trough level of at least the lower limit of the age-specific serum IgG reference range, or as needed to achieve clinical effectiveness.

Storage

The storage temperature ranges from 2–25°C but the product expiry may differ with some products if stored at room temperature. Please consult each product monograph for maximal time at each temperature range.

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Adverse events

The adverse event profile with SCIg is similar to that of IVIg with the addition of discomfort from subcutaneous injection. Please refer to the above section.

ORAL IMMUNE GLOBULIN

General information

Oral Ig may be considered for persistent, proven *Norovirus* or *Rotavirus* in immunosuppressed transplant recipients where reduction of immunosuppression is contraindicated.⁶

Dose and administration

Single oral doses of 25 mg to 45 mg are given four times daily, for at least 2 days, to a maximum total dose of 360 mg.

RH IMMUNE GLOBULIN

Product description

Rh immune globulin (Rhlg) is a freeze-dried preparation of human immune globulin of the IgG class with antibody specificity directed against the RhD antigen. This product is prepared from pooled human plasma collected from donors who selectively make high titers of anti-D. Rhlg is not antigen affinity-purified and can be expected to contain background levels of some other IgG antibodies. Although most Rhlg products have high purity without high-levels of complement activity, some products will contain residual antibodies against other Rh antigens.

The available vial sizes include: 600 IU (120 µg), 1,500 IU (300 µg) and 5,000 IU (1,000 µg) anti-D. See the package insert for additional product specific details. See [Chapter 12](#) of this *Guide* for more information on Rhlg.

Indications⁴⁰⁻⁴²

There are two broad categories of clinical use:

Category 1. Prevention of alloimmunization to the RhD antigen

- i. Prophylaxis for RhD hemolytic disease of the newborn during pregnancy. See [Chapter 12](#) of this *Guide* for more information.
- ii. Prophylaxis against anti-D formation following transfusion. Rhlg administration should be considered whenever Rh-positive platelets or red blood cells are transfused to an Rh-negative recipient. Most jurisdictions recommend Rhlg administration for female patients of child-bearing potential (less than 45 years of age) receiving Rh-positive blood components. However, additional risk benefit determinations may be required prior to Rhlg administration. Some of these factors would include the volume of Rh mismatched red blood cells

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Chapter 4: Immune Globulin Products

transfused, availability of Rh-negative red blood cell support in the event of hemolysis, renal function and clinical status of the patient.

Category 2. Immune thrombocytopenic purpura

Administration of Rhlg for ITP differs from its other uses in that the patient must be RhD-positive and must have an intact and functional spleen.

Contraindications

For Category 1: Prevention of alloimmunization to the RhD antigen

- RhD-positive individuals;
- RhD-negative women who are RhD alloimmunized as evidenced by a positive antibody screening test and a demonstrated allogeneic anti-D; and
- Individuals with a history of anaphylactic or other severe reactions to immune globulin or plasma products.
- The manufacturer also recommends avoidance in patients with IgA deficiency. However, no IgA-depleted Rhlg products are currently available in Canada. Reports of successful intramuscular administration in patients with anti-IgA antibodies exist. In these rare situations, a risk benefit discussion with each patient is recommended. If Rhlg administration is undertaken in this setting, it should be under monitored conditions with available treatment for anaphylaxis.

For Category 2: Immune thrombocytopenic purpura

- RhD-negative patients;
- Patients with prior splenectomy; or
- Individuals with a history of anaphylactic or other severe reactions to immune globulin or plasma products.
- The manufacturer also recommends that it should not be used in patients with secondary ITP, patients with evidence of autoimmune hemolytic anemia (Evan's syndrome), patients with systemic lupus erythematosus (SLE), patients with anti-phospholipid antibody syndrome and patients with underlying cardiac, renal or hepatic co-morbidities that would be predisposed to complications of acute hemolysis induced by Rhlg.

Dose and administration

For Category 1: Prevention of alloimmunization to the RhD antigen

- Rhlg (usually supplied in Canada as WinRho SDFä) can be administered by either an intravenous or intramuscular route for prevention of RhD alloimmunization. It should be administered within 72 hours of a potentially sensitizing event. However, even if delayed, it should be given as soon as the need is recognized, up to 28 days.
 - For obstetrical indications, see Chapter 12 of this Guide.
 - For transfusion-associated red blood cell exposure, the dose may vary depending on the route of administration and may range between 90 to 120 IU per ml of RhD-positive red blood cells (whole blood dosing 45-60 IU) with the intramuscular dosing at the higher end of the scale. A common rule of thumb is 1,500 IU (300 µg) for each 15 ml of red cells or 30 ml of whole blood.
 - For larger volume exposures, intravenous administration may require multiple doses of 3,000 IU (600 µg) every 8 hours until the total dose can be administered. In this setting monitoring for hemolysis and consideration of repeat RhD-negative red blood cell transfusion in symptomatic patients may be required.

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Chapter 4: Immune Globulin Products

For Category 2: Immune thrombocytopenic purpura

- RhIg is most commonly administered by an intravenous route but some jurisdictions and published evidence support subcutaneous administration.⁴³ Intramuscular administration is not recommended for this indication due to the risk of bleeding.
- Dosing will vary between 25–75 µg/kg depending on the patient’s baseline hemoglobin and local practice.
- Monitoring of hemoglobin concentration post administration should be undertaken to detect significant hemolysis.

Storage

The storage temperature ranges from 2–8°C. The product must be used within four hours of reconstitution.

Adverse events

WinRho SDF™ RhIg has a serious warning and precautions label regarding the risk of severe hemolysis when used for immune thrombocytopenic purpura – see contraindications above. Otherwise, the adverse event profile is similar to that of other immune globulins.

HYPERIMMUNE GLOBULINS

General information

Hyperimmune globulin fractionation products are created from pools of human plasma specifically chosen for high titers of antibodies with selected specificities. Each product undergoes viral inactivation procedures but the process used is dependent on the individual manufacturer.

Contraindications

- IgA deficiency;
- Previous severe or allergic reaction to the product; and
- Any condition that would contraindicate intramuscular injections.

Hepatitis B immune globulin

For the names and product specific details of the Hepatitis B Ig products carried by Canadian Blood Services, please refer to the [Hepatitis B Immune Globulin Comparison](#) table at www.blood.ca.

Other hyperimmune globulins

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| Product name | Indication | Dose and administration |
|--------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Varicella-Zoster Immune Globulin (VariZIG™) | Prevention or reduction in severity of maternal infections in pregnant women that have had a significant exposure to the varicella zoster virus (VZV) providing that the exposed individual does NOT have known immunity to the varicella zoster virus (secondary to either vaccination or previous infection). | The recommended adult dose is 125 IU/10 kg body weight up to a maximum dose of 625 IU. Each vial contains approximately 125 IU of anti-VZV. VariZIG™ can be given by intravenous (IV) or intramuscular (IM) administration. VariZIG™ should be administered as soon as possible but at least within 96 hours of exposure. However, the efficacy after this time frame has not been established. |
| Intramuscular Immune Globulin (GamaSTAN® S/D) | Passive immunization using IMIg may be considered for immediate post exposure prophylaxis when vaccines for active immunization are not available or are contraindicated due to the exposed individual's age or underlying medical condition. | Please refer to the product monograph for specific dosing recommendations for each specific disease exposure. GamaSTAN® S/D is administered intramuscularly preferably in the anterolateral aspects of the upper thigh and the deltoid muscle of the upper arm. The gluteal region should not be used routinely as an injection site because of the risk of injury to the sciatic nerve. Doses over 10 ml should be divided and injected into several muscle sites to reduce local pain and discomfort. |
| Cytomegalovirus Immune Globulin (Cytogam™) | Cytomegalovirus Immune Globulin Intravenous (Human) is primarily indicated for solid organ transplant recipients who are seronegative for CMV but are receiving an organ from a CMV seropositive donor to mitigate the development of primary (1°) cytomegalovirus disease. In transplants of organs other than kidneys, concomitant therapy with ganciclovir may be administered. | The maximum recommended total dosage per infusion is 150 mg/kg. The product should be administered intravenously according to the following schedule but should not exceed a rate of: <ul style="list-style-type: none"> • Within 72 hours of transplant: 150 mg/kg • 2 weeks post transplant: 100 mg/kg • 4 weeks post transplant: 100 mg/kg • 6 weeks post transplant: 100 mg/kg • 8 weeks post transplant: 100 mg/kg • 12 weeks post transplant: 50 mg/kg • 16 weeks post transplant: 50 mg/kg |

For all products discussed in this chapter, please refer to the manufacturer's product monograph for the most up-to-date information on indications, dosing, administration, and potential side effects. For more information about the Ig products available through Canadian Blood Services, see the [Plasma Protein Products](#) page at www.blood.ca.

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CONTINUING PROFESSIONAL DEVELOPMENT CREDITS

Fellows and health-care professionals who participate in the Canadian Royal College's Maintenance of Certification (MOC) Program can claim the reading of the Clinical Guide to Transfusion as a continuing professional development (CPD) activity under Section 2: Self-learning credit. The reading of one chapter is equivalent to **two credits**.

We're here to answer your questions about the Clinical Guide to Transfusion. We'd also appreciate your ideas on how to improve the Guide. Please contact us through the [Clinical Guide feedback form](#).

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Chapter 4: Immune Globulin Products

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