INTRAVENTOUS IMMUNE GLOBULIN

General Information

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

The various commercially available manufactured products may also differ in their plasma pool size, steps to improve immunoglobulin 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 many 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 reactive with pathogens that help facilitate their destruction or mediate their neutralization.

For patients with autoimmune or inflammatory dysfunction the mechanism(s) of effect of IVIG are not clear and multiple mechanisms may be at work.2 It is also not clear if the mechanism(s) of effect in one disease is similar or overlapping with effects in other 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).3,4 The primary molecular target(s) of IVIG remains to be 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 table at https://blood.ca/sites/default/files/Intravenous_Immune_Globulins_Table_2017-04-04.pdf.

Indications

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

- Primary immune deficiency,
- Immune thrombocytopenic purpura (ITP),
- Secondary immune deficiency states,
- Chronic inflammatory demyelinating polyneuropathy (CIDP),
- Guillain-Barré Syndrome (GBS),
- Multifocal Motor Neuropathy (MMN).

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 can account for a significant proportion of IVIG use in many provinces. Overall utilization trends by population and province are available at https://www.blood.ca/en/hospitals/plasma-products.
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. There are four Canadian evidence-based practice guidelines to aid transfusion services and clinicians. These guidelines are published in Transfusion Medicine Reviews as:

1. Guidelines on the use of intravenous immune globulin for hematologic conditions. (Note: Currently under review for updates).
2. Guidelines on the use of intravenous immune globulin for neurologic conditions. (Note: Currently under review for updates).

Contraindications

Most manufacturers state that IVIG is contraindicated for individuals with selective IgA deficiency who have anti-IgA antibodies and in patients known to have had anaphylactic or severe systemic responses to IVIG previously. These individuals may be successfully treated with subcutaneous immune globulin therapy. There are also reports of patients with demonstrated IgG anti-IgA antibodies tolerating intravenous (IV) infusions of immune globulin. There is no requirement to routinely test for IgA deficiency prior to IVIG therapy.

Dosing and Administration

Dosing for IVIG infusion is dependent on the clinical indication. Generally, the immune replacement dose is 0.4g/kg every 3–4 weeks whereas the immuno-suppressive dose is 1-2 g/kg over 1-5 days. Local practice guidelines, consensus documents and manufacturer’s recommendations provide more specific information on dose, frequency and duration of therapy for specific indications. Several jurisdictions have also implemented modifications to dosing based on Ideal Body Weight Calculators or absolute dose caps. The reader is referred to their local policies for more details.

IVIG may be issued from the hospital transfusion service in individual vials or as a pooled product.

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.

Protocols for IVIG infusion can 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 ranges from 0.8% to 81%. 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
Minor side effects are quite common with IVIG infusion and are often infusion rate related. 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, viral transmission, transfusion-related acute lung injury (TRALI) and thromboembolic events—are fortunately 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.\textsuperscript{16} 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.\textsuperscript{17,18}

Patients receiving immune globulin 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 further guidance, please refer to the Canadian Immunization recommendations on the Public Health Agency of Canada website.\textsuperscript{19}

**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.\textsuperscript{20,21} IVIG associated hemolysis has been defined by the IVIG Hemolysis Pharmacovigilance Group of Canada as:

A drop in hemoglobin of at least 10g/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,
- hemoglobinemia,
- hemoglobinuria

Or the presence of significant spherocytosis and no alternate etiology for the anemia.\textsuperscript{22}

Many case series have described IVIG associated hemolysis as having a higher occurrence rate in patients receiving high doses.\textsuperscript{21,22,23} The higher prevalence in non group O patients appears to implicate isohemagglutinins. Some manufacturers are now providing IVIG products that are isohemagglutinin depleted to minimize risk. Since the risk of hemolysis appears highest when a high isohemagglutinin titre product is administered to a blood group A or AB recipient at doses of 2 g/kg or higher\textsuperscript{24} some Canadian jurisdictions have implemented prospective hemolysis monitoring processes for these patients.

**Aseptic Meningitis:** Aseptic meningitis secondary to IVIG appears to be dose related, with the majority of reported cases receiving immunomodulatory doses of 2g/kg/cycle.\textsuperscript{25} 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.\textsuperscript{27} The majority of patients recover within 5 days of symptom onset and tolerate subsequent infusions, but the recurrence of
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symptoms with subsequent infusions has also been reported.\textsuperscript{28}

**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.\textsuperscript{12, 22} The use of subcutaneous administration of immunoglobulin may be one effective substitute in patients with a history of anaphylactic or severe allergic reactions who require future immune globulin therapy.\textsuperscript{9} Others recommend the use of IgA-depleted products in those with confirmed anti-IgA antibodies and prior confirmed reactions.\textsuperscript{31}

**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 immunoglobulin products.\textsuperscript{32, 33} 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 8 days following.\textsuperscript{34} 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 immune globulin products should also be administered at the lowest feasible dose and an infusion rate appropriate for the indication and patient condition.

**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 immunoglobulin 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.\textsuperscript{35} As it pertains to decreasing the frequency and duration of infection in patients with primary immune deficiency, SCIG and IVIG are considered equally effective.\textsuperscript{8} 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 table located at https://blood.ca/sites/default/files/Subcutaneous_Immune_Globulins_Table_2017-04-04.pdf.

**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.


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Contraindications

The main contraindication for SCIG is a history of anaphylactic or severe allergic reactions to immune globulin preparations. However, this is often a reason for switching a patient from intravenous to the 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 100-150 mg/kg per week but should not exceed 20 mL/hr per site. 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 the lowest dose acceptable for managing symptoms of immune deficiency.

Storage

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

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.

RH IMMUNE GLOBULIN

Product Description

Rh immune globulin (RhIG) is a freeze-dried preparation of human immune globulin of the IgG class with antibody specificity directed against the Rh (D) antigen. This product is prepared from pooled human plasma derived from donors who selectively make high titers of anti-D. RhIG is not antigen affinity-purified and can be expected to contain background levels of some other IgG antibodies. Although most RhIG 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), 1500 IU (300 µg) and 5000 IU (1000 µg) anti-D.

See the package insert for additional product specific details.

Indications [references 36-38]

There are two broad categories of clinical use:

Category 1. Prevention of alloimmunization to the Rh (D) antigen:

i  Prophylaxis for Rh hemolytic disease of the newborn during pregnancy:
All Rh-negative mothers at 28 week gestation, unless they have pre-existing immune anti-D or a fetus known to be Rh(D) negative. A repeat dose may be considered if the fetus remains in utero after 40 week gestation.
  - If an anti-D is detected and may represent passive anti-D from prior RhIG prophylaxis
All Rh-negative mothers of Rh-positive or weak D positive babies within 72 hours of delivery. If more than 72 hours elapse prior to RhIG administration, RhIG should not be withheld but should be administered as soon as possible up to 10 days after delivery.
  - At time of delivery, additional doses may be recommended if the initial fetal-maternal hemorrhage screen is positive and a quantitative test demonstrates a fetal/maternal hemorrhage of greater than 30 mL of fetal blood (or 15 mL of fetal red blood cells).

ii  Rh (D) negative pregnant women following:
    - spontaneous or therapeutic abortion
    - threatened abortion
    - amniocentesis, cordocentesis or chorionic villus sampling;
    - ectopic pregnancy or molar pregnancy
    - stillbirth or intrauterine death
    - obstetrical manipulations which may result in a transplacental hemorrhage;
    - and blunt abdominal trauma.

iii  Prophylaxis against anti-D formation following transfusion: RhIG administration should be considered whenever Rh-positive platelets or red cells are transfused to an Rh-negative recipient. Most jurisdictions recommend RhIG administration should be provided 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 RhIG administration. Some of these factors would include the volume of Rh mismatched red cells transfused, availability of Rh negative red cell support in the event of hemolysis, renal function and clinical status of the patient.

Category 2. Immune thrombocytopenic purpura

Administration of RhIG for the purposes of ITP differs from its other uses in that the patient must be Rh (D) antigen positive and must have an intact and functional spleen.

Contraindications

**For Category 1. Prevention of Rh (D) alloimmunization**

- Rh (D) positive individuals;
- Rh (D) negative women who are Rh (D) alloimmunized as evidenced by a positive antibody screening test and a demonstrated allo geneic 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 RhIG 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 RhIG administration is undertaken in this setting, it should be under monitored conditions with available treatment for anaphylaxis.

**For Category 2. Immune Thrombocytopenic Purpura**
Rh-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 RhIG.

Dose and Administration

For Category 1. Prevention of alloimmunization to the Rh (D) antigen:

- WinRho SDF™ Rh immune globulin can be administered by either an intravenous or intramuscular route for prevention of Rh (D) alloimmunization.
  - For obstetrical indications, the standard dose in Canada is 1500 IU (300 µg).
  - In postpartum settings with a Rh positive infant, higher doses may be required depending on the results of fetal maternal hemorrhage assessment.
  - However, if the gestational age can be confirmed to be less than 20 weeks, a 600 IU (120 µg) dose may be sufficient if administered within 72 hours of a potentially sensitizing event.
  - For post red cell exposure, the dose may vary depending on the route of administration and may range between 90 to 120 IU per mL of Rh (D) 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 1500 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 3000 IU (600 µg) every 8 hours until the total dose can be administered. In this setting monitoring for hemolysis and consideration of repeat Rh (D) negative red cell transfusion in symptomatic patients may be required.

For Category 2: Immune thrombocytopenic purpura

- WinRho SDF™ Rh immune globulin (RhIG) is most commonly administered by an intravenous route but some jurisdictions and published evidence support subcutaneous administration. 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™ Rh immune globulin (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

These 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 which process is used is dependent on the individual manufacturer’s production process.

Contraindications for hyperimmune globulins include:

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

Hepatitis B Immune Globulin

For the names and product specific details of the Hepatitis B Immune Globulin (HBIG) products carried by Canadian Blood Services Please refer to the table located at https://www.blood.ca/sites/default/files/Hospitals/CustomerLetters2010/HBIGComparisonTable.pdf

Other Hyperimmune Globulins

<table>
<thead>
<tr>
<th>Product Name</th>
<th>Indication</th>
<th>Dose and Administration</th>
</tr>
</thead>
<tbody>
<tr>
<td>Varicella-Zoster Immune Globulin</td>
<td>Prevention or reduction in severity of maternal infections in pregnant</td>
<td>The recommended adult dose is 125 IU/10 kg body weight up to a maximum dose of 625 IU.</td>
</tr>
<tr>
<td>(VariZIG™)</td>
<td>women that have had a significant exposure to the Varicella Zoster Virus</td>
<td>Each vial contains approximately 125 IU of anti-VZV.</td>
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<td>providing that the exposed individual does NOT have known immunity to the</td>
<td>VariZIG™ can be given by intravenous (IV) or intramuscular (IM) administration.</td>
</tr>
<tr>
<td></td>
<td>varicella zoster virus (secondary to either vaccination or previous</td>
<td>VariZIG™ should be administered as soon as possible but at least within 96 hours of</td>
</tr>
<tr>
<td></td>
<td>infection).</td>
<td>exposure. However, the efficacy after this time frame has not been established.</td>
</tr>
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<td></td>
<td></td>
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</tr>
<tr>
<td>Intramuscular Immune Globulin</td>
<td>Passive immunization using IMIG may be considered for immediate post</td>
<td>Please refer to the product monograph for specific dosing recommendations for each specific</td>
</tr>
<tr>
<td>(GamaSTAN® S/D)</td>
<td>exposure prophylaxis when vaccines for active immunization are not</td>
<td>disease exposure.</td>
</tr>
<tr>
<td></td>
<td>available or are contraindicated due to the exposed individual’s age or</td>
<td>GamaSTAN® S/D is administered intramuscularly preferably in the anterolateral aspects of</td>
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<td></td>
<td>underlying medical condition.</td>
<td>the upper thigh and the deltoid muscle of the upper arm. The gluteal region should not</td>
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<td></td>
<td></td>
<td>be used routinely as an injection site because of the risk of injury to the sciatic nerve.</td>
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<td></td>
<td></td>
<td>Doses over 10 mL should be divided and injected into several muscle sites to reduce</td>
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<td>local pain and discomfort.</td>
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</tbody>
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**Product Name** | **Indication** | **Dose and Administration**
---|---|---
Cytomegalo-virus 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: 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

**REFERENCES**

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.

The recommendations do not replace the need in some cases to consult an expert in Transfusion Medicine to provide optimal patient care.

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228-30.e1. [http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3129450/]
30. Burks A, Sampson H, Buckley R. Anaphylactic Reactions after Gamma Globulin Administration in Patients...
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