Getting Started with Your Immunotherapy (Ig)

Please read through this booklet to learn about immunodeficiency disorders, what GAMMAGARD does, how to use it, how to store it, as well as important information on safety, warnings and side effects.
Part I

Disease Information for Patients Receiving GAMMAGARD LIQUID

Your Doctor has prescribed GAMMAGARD LIQUID to treat one of the following conditions:

**Primary Immunodeficiency** - Used as replacement therapy in primary immunodeficiency syndromes (PID) such as:
- Congenital agammaglobulinaemia and hypogammaglobulinaemia
- Common variable immunodeficiency or severe combined immunodeficiency - Wiskott Aldrich syndrome

**Secondary Immunodeficiency** - Replacement therapy in secondary immunodeficiency syndromes (SID) such as:
- B-cell chronic lymphocytic leukemia
- Pediatric HIV infection
- Allogeneic bone marrow transplantation

**Idiopathic Thrombocytopenic Purpura (ITP)**

**Multifocal Motor Neuropathy (MMN)**
- Used as maintenance therapy to improve muscle strength and disability in adult patients with MMN.6

Next is a brief description of these conditions, what causes them and primary symptoms.

*Part II of this booklet provides you with information on GAMMAGARD LIQUID and addresses key questions such as how to use the drug appropriately, what it contains, common side effects and potential warnings or contraindications.*
What is Primary Immunodeficiency?
The immune system is composed of a variety of cells, especially white blood cells, and proteins, for which one of the principal functions is microbial defense. A deficit in the immune system can therefore lead to unusually severe or uncommon recurrent infections. Immune deficits (immunodeficiency) may be primary or secondary. Primary immunodeficiencies, often genetic, are caused by problems in the formation of the immune system itself and not by external factors.¹

How does a Primary Immunodeficiency present?
One must suspect an immune deficit in the context of infections that are recurrent, atypical, severe, or that do not respond well to standard treatments. A family history or growth delay and failure to thrive in the infant may also lead to this diagnosis.¹

Although relatively rare, primary immune deficiencies are numerous:
• Prevalence is more common than originally thought. It is estimated that as many as 1 in every 1,200–2,000 people may have some form of primary immunodeficiency.²
• Primary immunodeficiency diseases can occur in individuals of any age. The original descriptions of these diseases were in children. However, as medical experience has grown, many adolescents and adults have been diagnosed with primary immunodeficiency diseases.²
• In addition to an increased susceptibility to infection, people with primary immunodeficiencies may also have autoimmune diseases in which the immune system attacks their own cells or tissues as if these cells were foreign, or non-self.²
• All PI disorders result from a defect in one or more of the elements or functions of the normal immune system such as T-cells, B-cells, NK cells, neutrophils, monocytes, antibodies, cytokines or the complement system.²
Because the most important function of the immune system is to protect against infection, people with primary immunodeficiency diseases have an increased susceptibility to infection. This may include too many infections, infections that are difficult to cure, unusually severe infections, or infections with unusual organisms. The infections may be located anywhere in the body. Common sites are the sinuses (sinusitis), the bronchi (bronchitis), the lung (pneumonia) or the intestinal tract (infectious diarrhea).

Primary immunodeficiency is different from secondary immunodeficiency conditions, which are not hereditary but acquired and autoimmune conditions, in which a person's immune system attacks his or her own body. Rather, primary immunodeficiency is usually inherited or caused by errors in the genes of the cells that make up the immune system.

**How does one diagnose an immunodeficiency?**
The diagnosis is suspected by history. Following this, very specific testing might be ordered by the allergist-immunologist. Sometimes the tests are sent to specialized centres. It is important to test for the number and function of certain cells (ex: white blood cells) and proteins (ex: antibodies and complement proteins) in the blood. It is possible that the doctor will also run radiological tests or genetic tests.

**What is Secondary Immunodeficiency (SID)?**
As discussed in the previous section, a deficit in the immune system can lead to unusually severe or uncommon recurrent infections. Secondary immune deficiencies (or acquired deficiencies) are more frequent than primary immune deficiencies and are problems of the immune system that are not genetic and which are caused by external factors.

Secondary immune deficiencies are common and can occur as part of another disease or as a consequence of certain medications. The most well-known example of a secondary immune deficiency is the immunodeficiency caused by the Human
Immunodeficiency Virus, or HIV. HIV attacks certain cells in the immune system and prevents them from carrying out their proper functions against microbes. When the immune system is sufficiently weakened, infected people catch atypical and severe infections. This is then called the Acquired ImmunoDeficiency Syndrome, or AIDS. AIDS at this time is often treated by a specialized multidisciplinary team.\(^3\)

Regardless of the root cause, recognition of the secondary immune deficiency and provision of immunologic support can be helpful. The types of support offered are comparable to what is used for primary immune deficiencies.\(^2\)

**What is Multifocal Motor Neuropathy (MMN)?**

MMN (Multifocal Motor Neuropathy) is a rare disorder in which focal areas of multiple motor nerves are attacked by one’s own immune system. Typically, MMN is slowly progressive, resulting in asymmetrical weakness of a patient’s limbs. Patients frequently develop weakness in their hand(s), resulting in dropping of objects or sometimes inability to turn a key in a lock. The weakness associated with MMN can be recognized as fitting a specific nerve territory. There is essentially no numbness, tingling, or pain.\(^4\)

**What causes MMN?**

MMN is associated with increased levels of specific antibodies to GM1, a ganglioside or sugar-containing lipid found in peripheral nerve. Antibodies normally protect individuals from viruses and bacteria, but may under certain circumstances bind to and facilitate an immune attack on the peripheral nerve. These antibodies have been detected with newer assays in almost all of MMN patients. Even if these antibodies do not cause the nerve damage, they may be an important marker for disease and facilitate diagnosis.\(^4\)

The prevalence of this very rare disease is estimated to be 0.6 cases in every 100,000 people.\(^4\) Its onset is progressive over time, causing increased disability that reflects the greater
number of nerve sites involved. The clinical course of MMN is chronically progressive without remission.⁴

**People with MMN may have symptoms that include:** ⁴,⁷
- Difficulty gripping objects
- Spasms or cramps usually in one arm or leg
- Wrist drop (when the wrist cannot be extended), foot drop (difficulty lifting the front part of the foot)
- MMN is asymmetric and affects the right and left side of the body differently.⁴
- Other symptoms can include twitching, or small random dimpling of the muscle under the skin which neurologists call fasciculations.⁴

**What is Primary Immune Thrombocytopenia (ITP)?** ⁵
Idiopathic Thrombocytopenic Purpura (ITP) is a disorder that can lead to easy or excessive bruising and bleeding. The bleeding results from unusually low levels of platelets - the cells that help blood clot.

Idiopathic Thrombocytopenic Purpura, which is also called immune thrombocytopenia, affects children and adults. Children often develop ITP after a viral infection and usually recover fully without treatment. In adults, the disorder is often long term.⁵
**Symptoms** - Idiopathic Thrombocytopenic Purpura (ITP) may have no signs and symptoms. When they do occur, they may include:

- Easy or excessive bruising (purpura)
- Superficial bleeding into the skin that appears as a rash of pinpoint-sized reddish-purple spots (petechiae), usually on the lower legs
- Bleeding from the gums or nose
- Blood in urine or stools or unusually heavy menstrual flow

**Causes** - In some people thrombocytopenia is caused by the immune system mistakenly attacking and destroying platelets. If the cause of this immune reaction is unknown, the condition is called idiopathic thrombocytopenic purpura. Idiopathic means “of unknown cause”.

In most children with ITP, the disorder follows a viral illness, such as the mumps or the flu. It may be that the infection triggers the immune system malfunction.

In people with ITP, antibodies produced by the immune system attach themselves to the platelets, marking the platelets for destruction. The spleen, which helps your body fight infection, recognizes the antibodies and removes the platelets from your system. The result of this case of mistaken identity is a lower number of circulating platelets than is normal.
Part II
Medication Information for Patients Receiving GAMMAGARD LIQUID (Immune Globulin Intravenous (Human), [IGIV] 10%)

About This Medication – Read this for safe and effective use of your medicine

This section is based on part III of a three-part “Product Monograph” published when GAMMAGARD LIQUID was approved for sale in Canada and is designed specifically for patients. This section of the leaflet is a summary and will not tell you everything about GAMMAGARD LIQUID. Contact your healthcare professional about your medical condition and treatment and ask if there is any new information about GAMMAGARD LIQUID or if you have any questions about the drug.6

Note – The previous section on Disease Information discusses what conditions are treated with GAMMAGARD LIQUID.6

How does GAMMAGARD LIQUID work?
GAMMAGARD LIQUID belongs to a class of medicines called immunoglobulins. These medicines contain human antibodies, which are also present in your blood. Antibodies help your body to fight infections. Immunoglobulins are used in patients who do not have enough antibodies in their blood and tend to get frequent infections. They can also be used in patients who need additional antibodies for the treatment of certain inflammatory disorders.6
You must not use GAMMAGARD LIQUID if:
• You are hypersensitive (allergic) to immunoglobulins or to the other ingredients of GAMMAGARD LIQUID.
• You have an immunoglobulin A deficiency (lack of IgA antibodies), you may have antibodies against immunoglobulin A in your blood. Since GAMMAGARD LIQUID contains small amounts of immunoglobulin A (average concentration of 37 mcg/mL), you might develop an allergic reaction.6

What are the ingredients in GAMMAGARD LIQUID?
• The active substance is human normal immunoglobulin.
• GAMMAGARD LIQUID contains 10% (100 mg/mL) of human protein of which at least 98% is immunoglobulin G (IgG).
• GAMMAGARD LIQUID is a 10% solution (100 mg/mL) for intravenous infusion. The solution is clear or slightly opalescent and colourless or pale yellow.
• Nonmedicinal ingredients - The other ingredients are glycine and water for injections.
• GAMMAGARD LIQUID does NOT contain sucrose.6

Gammagard Liquid is available in the following package sizes
• 1 g in 10 mL • 2.5 g in 25 mL • 5 g in 50 mL • 10 g in 100 mL
• 20 g in 200 mL • 30 g in 300 mL 6

Directions for proper use
GAMMAGARD LIQUID is intended for intravenous administration (infusion into a vein). It is given to you by your doctor. Dosage will vary depending on your condition and your bodyweight. The following instructions are to help your doctor administer the best dose for you.6
Recommended dose and dose adjustment

<table>
<thead>
<tr>
<th>Indication</th>
<th>Dose</th>
<th>Frequency of Injections</th>
</tr>
</thead>
<tbody>
<tr>
<td>Replacement therapy in primary immunodeficiency</td>
<td>Starting dose: 0.4 – 0.8 g/kg BW Thereafter: 0.2 – 0.8 g/kg BW</td>
<td>Every 2 – 4 weeks to obtain IgG trough level of at least 4 – 6 g/L</td>
</tr>
<tr>
<td>Replacement therapy in secondary immunodeficiency</td>
<td>0.2 – 0.4 g/kg BW</td>
<td>Every 3 – 4 weeks to obtain IgG trough level of at least 4 – 6 g/L</td>
</tr>
<tr>
<td>• Allogeneic bone marrow transplantation</td>
<td>0.5 g/kg</td>
<td>Every week from day -7 up to 3 months after transplantation</td>
</tr>
<tr>
<td>• Treatment of infestations and prophylaxis of</td>
<td>0.5 g/kg</td>
<td>Every month until antibody levels return to normal</td>
</tr>
<tr>
<td>• Graft-versus host disease</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Idiopathic Thrombocytopenic Purpura (ITP)</td>
<td>0.8 – 1 g/kg BW or 0.4 g/kg BW/d</td>
<td>On day 1, possibly repeated once within 3 days</td>
</tr>
<tr>
<td>Multifocal Motor Neuropathy (MMN)</td>
<td>0.5 – 2.4 g/kg</td>
<td>Every month based on clinical response</td>
</tr>
</tbody>
</table>

BW = bodyweight  d = day

Additional dosing instructions
At the beginning of your infusion you will receive GAMMAGARD LIQUID at a slow rate (0.5 mL/kg of bodyweight/hour for 30 minutes). Depending on how comfortable you are, your doctor may then gradually increase the infusion rate to a maximum of 8 mL/kg of bodyweight/hour.

For treatment of Multifocal Motor Neuropathy (MMN), human normal immunoglobulin should be infused intravenously at an initial rate of 0.5 mL/kg BW/hr. If well tolerated, the rate of administration may gradually be increased to a maximum rate of 5.4 mL/kg BW/hr.

What to do if you have missed a dose?
Contact your Immunology Clinic or Nurse and make arrangements to take GAMMAGARD LIQUID at the earliest available opportunity.

What is the risk of overdose and what to do if you suspect an overdose?
If you receive more GAMMAGARD LIQUID than you should, your blood may become too thick (hyperviscose). This could particularly happen when you are a patient at risk, e.g. an elderly patient or a patient having problems with your kidneys.
If you believe that you have taken too much GAMMAGARD LIQUID, contact your healthcare provider, hospital emergency department or regional Poison Control Centre immediately, even if there are no symptoms.6

What are possible side effects from using GAMMAGARD LIQUID?
These are not all the possible side effects that you may feel when taking GAMMAGARD LIQUID. If you experience any side effects not listed here, contact your healthcare professional. Like all medicines, GAMMAGARD LIQUID can have side effects. However, possible side effects may be reduced by slowing the infusion rate.6

- General reactions such as chills, headaches, fever, vomiting, allergic reactions, nausea, joint pain, low blood pressure and moderate lower back pain have been experienced occasionally.6
- Rarely, cases of a sudden fall in blood pressure were observed, and in isolated cases allergic reactions (anaphylactic shock), even in patients who have shown no reactions to previous infusions. Symptoms for an immediate allergic reaction are bronchitis or asthma, flu-like symptoms, pink eye, generalized rash, skin oedema (angiooedema), dizziness and collapse.6
- Cases of temporary meningitis (reversible aseptic meningitis), isolated cases of temporary decrease of red blood cells (reversible haemolytic anaemia/haemolysis) and rare cases of eczema-like symptoms (transient cutaneous reactions) have been observed with immunoglobulin products.6
- An increase in blood creatinine content and kidney failure has also been observed.6
- Very rarely, cases of blood clot formation in the veins (thromboembolic reactions) resulting in cardiac infarction, stroke, lung embolism, and deep vein thrombosis have been reported.6
- This is not a complete list of side effects. If you notice any side effects not mentioned in this booklet, please contact your doctor or pharmacist.6
How often do serious side effects happen and what to do about them?

<table>
<thead>
<tr>
<th>Serious side effect</th>
<th>Likelihood</th>
<th>Talk with your Doctor or Pharmacist</th>
<th>Stop taking drug &amp; call the Doctor or Pharmacist</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anaphylactic shock</td>
<td>Rare</td>
<td>✓ in all cases</td>
<td>Yes</td>
</tr>
<tr>
<td>Renal insufficiency</td>
<td>Rare</td>
<td>✓ in all cases</td>
<td>Yes</td>
</tr>
<tr>
<td>Reversible aseptic meningitis</td>
<td>Rare</td>
<td>✓ in all cases</td>
<td>Yes</td>
</tr>
<tr>
<td>Thromboembolic events (blood clots)</td>
<td>Rare</td>
<td>✓ in all cases</td>
<td>Yes</td>
</tr>
</tbody>
</table>

This is not a complete list of side effects. For any unexpected effects while taking GAMMAGARD LIQUID contact your healthcare professional.\(^6\)

**Serious Warnings and Precautions**

*You should discuss the risks and benefits of this product with your healthcare professional.* Immune Globulin Intravenous (IGIV) products have been reported to cause disease of the kidneys, failure of the kidneys, damage to the tubes inside of the kidneys, thromboembolic events and death.\(^6\)

People with an increased risk of kidney damage include those with any degree of existing kidney disease, diabetes, age greater than 65, dehydrated, have an overwhelming infection, have abnormal proteins in their blood, or patients receiving drugs known to damage the kidneys. Especially in these people, IGIV products should be administered at the lowest possible concentration and as slowly as is practical. While these reports of kidney disease and failure of the kidneys have been associated with the use of many of the licensed IGIV products, those containing sucrose produced more kidney problems than expected. People with increased risk to blood clots in their veins or arteries include those that have high blood pressure, diabetes mellitus, history of blood vessel disease or previous clots, acquired or inherited increased numbers or activity of platelets which help the blood clot, prolonged periods of not moving, such as lying in bed, increased activity of the proteins that make blood clot, conditions, obesity, advanced age, use of estrogens, long term catheters that go into a central vein, and other cardiovascular risk factors. Thrombosis may occur even in the absence of known risk factors.\(^6\)

**GAMMAGARD LIQUID does not contain any sucrose.**\(^6\)
Potential interactions and cautions about vaccines

- Please inform your healthcare provider if you are taking, or have recently taken any other medicines, even those not prescribed, or if you have received a vaccination during the last six weeks.\(^6\)

- Infusion of immunoglobulins like GAMMAGARD LIQUID may impair the effect of some live virus vaccines such as measles, rubella, mumps and chicken pox vaccines. Therefore, after receiving immunoglobulins you may have to wait up to 3 months before receiving your live-attenuated vaccine. You may have to wait for up to 1 year after receiving immunoglobulins before you receive your measles vaccine.\(^6\)

- GAMMAGARD LIQUID contains a wide variety of different antibodies, some of which can affect blood tests. If you have a blood test after receiving GAMMAGARD LIQUID, please inform the person taking your blood or your doctor about your infusion.\(^6\)

How do I store GAMMAGARD LIQUID?  \(^6\)

- Keep out of the reach and sight of children.\(^6\)
- **Refrigeration storage:** Store in a refrigerator (2°C – 8°C) for up to 36 months.
- **Room temperature storage:** Within the first 24 months from the date of manufacture, GAMMAGARD LIQUID may be stored for a single period of up to 12 months at room temperature (below 25° C). After this period, unused product must be discarded.
- Do not freeze.
- Do not use after the expiry date stated on the label.
- Keep the container in the outer carton in order to protect from light.\(^6\)

The total storage time of GAMMAGARD LIQUID depends on the point of the time the vial is transferred to room temperature. If GAMMAGARD LIQUID is stored at room temperature (below 25° C), the date on which carton is removed from refrigerated storage and the new expiry date must be recorded in the area provided on the carton.\(^6\)
The new expiry date will be the shorter of: 24 months from the date of manufacture (indicated on the carton); or 12 months from the date removed from refrigeration. Once removed from refrigeration and stored at room temperature GAMMAGARD LIQUID must be used or discarded and may not be returned to refrigerated storage. *Example: If the product is taken out of the refrigerator after 3 months, it can be stored for 12 months at room temperature, and the total storage time is 15 months.*

**If you want more information about GAMMAGARD LIQUID**
- The full product monograph, prepared for health professionals can be found at [www.shirecanada.ca](http://www.shirecanada.ca)
- Or by calling the sponsor, Shire Canada at: 1-800-268-2722
REFERENCES:

1. The Association of Allergists and Immunologists of Québec website www.allerg.qc.ca AAIQ 2016, authors - Nha Uyen Nguyen-Luu, MD FRCPC, Hugo Chapdelaine, MD FRCPC.


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