

## Human Intravenous Immunoglobulin (IVIG) Replacement Therapy Fact Sheet

**Brand Names: US** Bivigam; Carimune NF; Cuvitru; Flebogamma DIF; GamaSTAN S/D; Gammagard; Gammagard S/D Less IgA; Gammagard S/D [DSC]; Gammaked; Gammaplex; Gamunex-C; Hizentra; Hyqvia; Octagam; Privigen

**Brand Names: Canada** Cuvitru; Gamastan S/D; Gammagard Liquid; Gammagard S/D; Gamunex; Hizentra; IGIVnex; Octagam 10%; Panzyga; Privigen

### Key Points

- IVIG is not a panacea; it's a treatment used only under a doctor's care for recurrent, serious infections
- It's expensive and scarce
- It can have serious side effects (see below)
- It is a good option for some patients with WM

### Introduction

Waldenstrom's macroglobulinemia (WM) is a non-Hodgkin lymphoma and cancer of the immune system that is defined by high levels of IgM in the blood and WM cells (also known as lymphoplasmacytic cells) in the bone marrow. There are five basic immunoglobulins (Ig) or antibodies, proteins that help the body fight infections: IgG, IgA, IgM, IgD, and IgE. Many patients with WM have low levels of the "uninvolved" immunoglobulins IgA and IgG, which persist despite treatment of the disease. These low immunoglobulin levels do not always result in repeated, serious infections, but lower levels of IgA and IgG might be associated with disease progression to WM in individuals who have IgM-MGUS. Furthermore, recurrent or severe infections, especially sinusitis or pneumonia, can be seen in many patients with WM.

### How does this happen in patients with WM and what are these immunoglobulins?

IgM is the first antibody to respond during infection. Even though high levels of monoclonal (identical antibodies from one cell line) IgM are found in WM, it is not totally understood if these clones of IgM still respond to infection in the usual manner. IgA plays a crucial role in the immune function of the mucous membranes, such as the respiratory tract and the gastrointestinal tract. IgG is the most common type of antibody found in the serum portion of the blood and extracellular fluid, making it the principal immunoglobulin that offers protection from viruses, bacteria, and fungi. About

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70% of patients with WM have low levels of IgG even at the time of diagnosis. Most WM-directed treatments drag down the IgG to an even lower level. Whether due to the non-Hodgkin lymphoma itself or as a side effect of treatment, the functions of the immune system are decreased, and that makes many patients with WM more prone to repeated and/or serious infections. Patients with WM who have repeated, serious sinus or bronchial infections requiring antibiotics are the group that benefits the most from human intravenous immunoglobulin (IVIG) replacement therapy. The IV stands for intravenous and the IG for immunoglobulin G (IgG or gammaglobulin). Some patients are born with low IgG, IgA and IgM levels (primary hypogammaglobulinemia). WM patients with chronically low levels of both IgA and IgG have secondary hypogammaglobulinemia.

### **When is IVIG given?**

It cannot be overemphasized that not all patients with low levels of IgG and/or IgA have recurrent or severe infections. Furthermore, recurrent or serious infections can occur without low levels of IgG or IgA due to other reasons, such as neutropenia (low levels of another type of white blood cell that fights infection) or T-cell suppression. Hunter et al. found low IgG and IgA in WM patients despite response to treatment, including complete remissions. Questions that oncologists consider include what type of infections the patients are getting, how frequently they are getting the infections, and are they occurring during the winter months? IVIG often is indicated for those patients who have low levels of IgG and who suffer recurrent infections – usually sinus and bronchial during the winter months. Also especially affected are those patients in whom prophylactic antibiotics (those intended to prevent disease) have failed with repeated infections, patients having recurrent infections despite appropriate vaccinations, or those with severe infections requiring intravenous antibiotics or hospitalization. If the infections occur just during the winter months, then the monthly IVIG might be stopped in the spring when the high risk of infections has passed. It is important to note that clinical trials are lacking for patients with WM and who have received IVIG. It is also not certain how much IgG to prescribe. There have been some recommendations, but sometimes the patient requires a higher dose. It is a judgment call by your oncologist, sometimes in consultation with an infectious disease specialist or an immunologist.

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### **What is IVIG and how is it given?**

IVIG is a therapy that has been around for decades and is used to treat patients with many different types of illnesses. IVIGs are products that can be hung in a bag for liquid administration into the veins. Because there are millions of different germs and no one person has antibodies to all the germs, the best way to make sure the IVIG has a wide variety of antibodies is to pool the human plasma (part of the blood) from a lot of people, meaning these bags contain IgG antibodies from 10,000-50,000 healthy human donors. The products typically contain more than 95 percent unmodified IgG, and only trace amounts of immunoglobulin A (IgA) or immunoglobulin M (IgM). It is manufactured in accordance with World Health Organization standards, so the result is a highly purified IgG with a high record of safety. Companies who produce immunoglobulins add different stabilizers (e.g., sucrose, glucose, maltose) or they may use amino acids, such as glycine or proline to prevent clumping of the IgG molecules within the IVIG. The sodium content of different products also varies. Products for intravenous use (i.e., medications that are liquids administered directly into veins by a syringe or intravenous catheter) are referred to as intravenous immunoglobulins (IVIG), while products for subcutaneous use (administered by injection under the skin) are referred to as subcutaneous administration (SCIG) by health care providers. There is also an intramuscular (injection deep into the muscle) form of the product. IVIG in all its forms is very expensive. If given monthly over a year, the annual cost could be \$40,000-\$50,000.

It is important to understand that the immunoglobulin that is given partly replaces what the body should be making, but it does not stimulate the patient's own immune system to make more immunoglobulin. Most immunoglobulins, whether produced by the patient's own immune system or given in the form of IVIG replacement, are used up or "metabolized" by the body within 3-4 weeks and must be replenished. When IVIG infusions are given once a month directly into a vein, there generally is a very high "peak" IgG level in the blood right after the dose is given and a lower IgG level in the blood at the "trough" just before the next dose is due. Comparatively, SCIG (subcutaneous Ig) is injected relatively slowly, directly under the skin. Because small amounts are often given more frequently and because the immunoglobulin is absorbed more slowly, the peak and trough phenomenon associated with IVIG may not be

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observed with SCIG. Patients who have side effects from high peaks of IgG or feel “washed out” or weak before their next IVIG dose is due may prefer SCIG. SCIG therapy may be an alternative for those patients who have difficulty getting venous access and/or who have serious, negative reactions to IVIG. Patients must be committed to this therapy and should not “skip” doses or change their regimen without consulting their health care team.

### **What do I need to tell my health care team before I start IVIG replacement therapy?**

Inform the team if you are allergic to any drugs like this one, or any other drugs, foods, or other substances (i.e. latex). Talk with the team about whether to get certain vaccines, as injection of vaccines at the same time IVIG therapy is being administered may raise the chance of an infection or can cause the vaccine not to work as well. If you are pregnant or breast feeding you should discuss the use of this therapy and its benefits vs. risks to your baby with your health care team. For intramuscular (IM) injection, tell the team if you have low platelet levels. For intravenous injection (IV), tell the health care team if you are not able to break down fructose. Some of these immunoglobulin products have sorbitol. If you are on a low-sodium or sodium-free diet, talk with your doctor, as some of these products have sodium. If you have high blood sugar (diabetes), talk with your doctor about which glucose tests are best to use. Make sure everyone on the rest of your health care team knows that you are on IVIG. This includes doctors, nurses, pharmacists, and dentists.

### **What are the risks of IVIG replacement therapy?**

Most patients tolerate IVIG well. Adverse (negative) reactions to IVIG are reported to occur in up to 5 to 10 percent of all IVIG infusions. Adverse reactions are uncommon in patients receiving IVIG on a regular schedule.

#### Potential symptoms due to treatment:

- Flu-like symptoms may accompany the use of IVIG, especially in patients with active bacterial infections and WM. Other symptoms may resemble those that accompany the onset of infection in individuals with intact immune function. These symptoms may include chills, fever, flushing, flu-like muscle pain, joint pain, general discomfort, nausea, vomiting, and/or headache.

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- Headaches are more common in patients with a history of migraines.
- Symptoms may be especially pronounced if the patient is receiving IVIG for the first time. Patients with WM should receive appropriate antibiotics for any existing infections before receiving IVIG for the first time or if several months have elapsed since a patient's last intravenous therapy. In such cases, the delay need only last for a day or two, providing there is reasonable evidence that the infection is responding and under control (e.g., absence of severe fever or other acute symptoms). However, the initiation of IVIG should not be delayed further in patients who have an infection that has not responded to routine antimicrobial therapy.
- These symptoms may be minimized by giving the IVIG slowly. Giving acetaminophen or a nonsteroidal anti-inflammatory drug (NSAID), such as ibuprofen and/or short-acting steroids before the IVIG also may help and are often standard procedure.
- If symptoms still occur, management generally involves temporarily interrupting the infusion and/or treating specific symptoms. Other transfusion reactions are rare but may occur. Managing these reactions is beyond the scope of this fact sheet.

### Potential side effects and reactions due to treatment, and how to adjust for them:

- Potentially serious reactions occur in 1 to 6 percent of patients. The most serious risks of IVIG are thrombosis (blood clots), renal (kidney) dysfunction, and acute renal failure.
- The risk of adverse reactions increases with higher doses of IVIG.
- Many of the known negative side effects are most likely to occur during the first infusion, or the first infusion of a new product after changing brands.
- More than half of reactions occur within the first few hours of the infusion.
- Changing from a well-tolerated product to another product should be avoided when possible, and changes should not be made without the knowledge of the health care team.

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- Patients initiating IVIG therapy, or those switching between products, should be observed closely by a clinician who is familiar with the signs and symptoms of IVIG reactions. Slow infusion rates, with gradual stepwise increases, are suggested for new patients or when products are changed.

### Other possible considerations:

- Severe kidney problems have been observed in connection with human immunoglobulin therapy. Such problems are more common in people using products that have sucrose. Risk to the kidneys may be exacerbated if you already have existing kidney problems, high blood sugar (diabetes), fluid loss (dehydration) or low blood volume, a blood infection, or proteins in the blood that are not normal. The chance may also be raised if you are 65 or older, or if you take other drugs that may harm the kidneys.
- For patients with WM who have hyperviscosity there may be an increased risk of negative side effects. Thromboembolic complications (deep vein thrombosis, pulmonary embolism) may occur due to hyperviscosity, especially in patients having such risk factors as advanced age, previous thromboembolic events, immobilization, diabetes mellitus, high blood pressure, dyslipidemia (high triglyceride concentration, low high-density lipoprotein cholesterol/HDL-C, and decreased concentration of low-density lipoprotein cholesterol/LDL-C) or those receiving high-dose IVIG in a rapid infusion rate or excessive dose. However, negative side effects can also occur in individuals who lack predisposing factors. Case reports have described the use of IVIG for cold agglutinin disease, but the efficacy has not been well characterized.
- Lung problems, such as transfusion-related acute lung injury (TRALI), have happened with this drug. Call your doctor right away if you have trouble breathing, shortness of breath, or a cough that is new or worsening.
- This drug may raise the chance of a very serious brain problem called aseptic meningitis. Call your doctor right away if you experience a headache, fever, chills, very upset stomach or throwing up, stiff neck, rash, bright lights that bother your eyes, sleepiness, or confusion.
- Arrhythmias, such as supraventricular tachycardia and bradycardia, have been reported in patients with a history of heart disease during and after

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immunoglobulin infusion. Although it is not fully understood whether arrhythmia is directly related to immunoglobulin infusion, cardiac monitoring during IVIG infusion is recommended in patients with a history of cardiac disorders.

### **Is There Anything Else I Need to Know?**

Vaccines may not work as well in the days directly after the IVIG is given because the IVIG may block the immune system from responding appropriately to the vaccine. However, it is important to get certain vaccines, and you are better protected if you get them than if you do not. Discuss the best timing with your doctor.

Keep records of the lot number and date you received your IVIG infusions. This is important for keeping track of which products worked best for you and for testing if you think you had a side effect related to the IVIG.

If a specific brand of IVIG is working well for you, it is safer not to substitute a different brand.

### **Final Notes**

The goal of IVIG replacement therapy is to provide defense against infection, but not all infections can be prevented. Due to the diversity of clinical and biological features observed in patients with WM, the treatment approach to infections is often personalized for each patient and then modified as necessary. Not all patients with infections and WM are candidates for IVIG.

Having chronically low IgG levels does not automatically mean that one is a candidate for IVIG therapy. In many cases, a WM patient with low IgG levels can continue to lead an otherwise healthy life, and will not be impacted by chronic sinusitis, lung infections, pneumonia, etc. In fact, many patients do well either with no related treatment, or with mere careful observation by one's medical team and judicious use of vaccines or antibiotics when necessary.

In cases where infections and adverse health persist due to low immunoglobulin levels, one should consult with their medical team and assess whether immunoglobulin replacement therapy is appropriate at that time.

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**NOTE: The information in this fact sheet is intended to be helpful and educational, but it does not constitute an endorsement by the IWMF and is not meant to be a substitute for professional medical advice.**

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