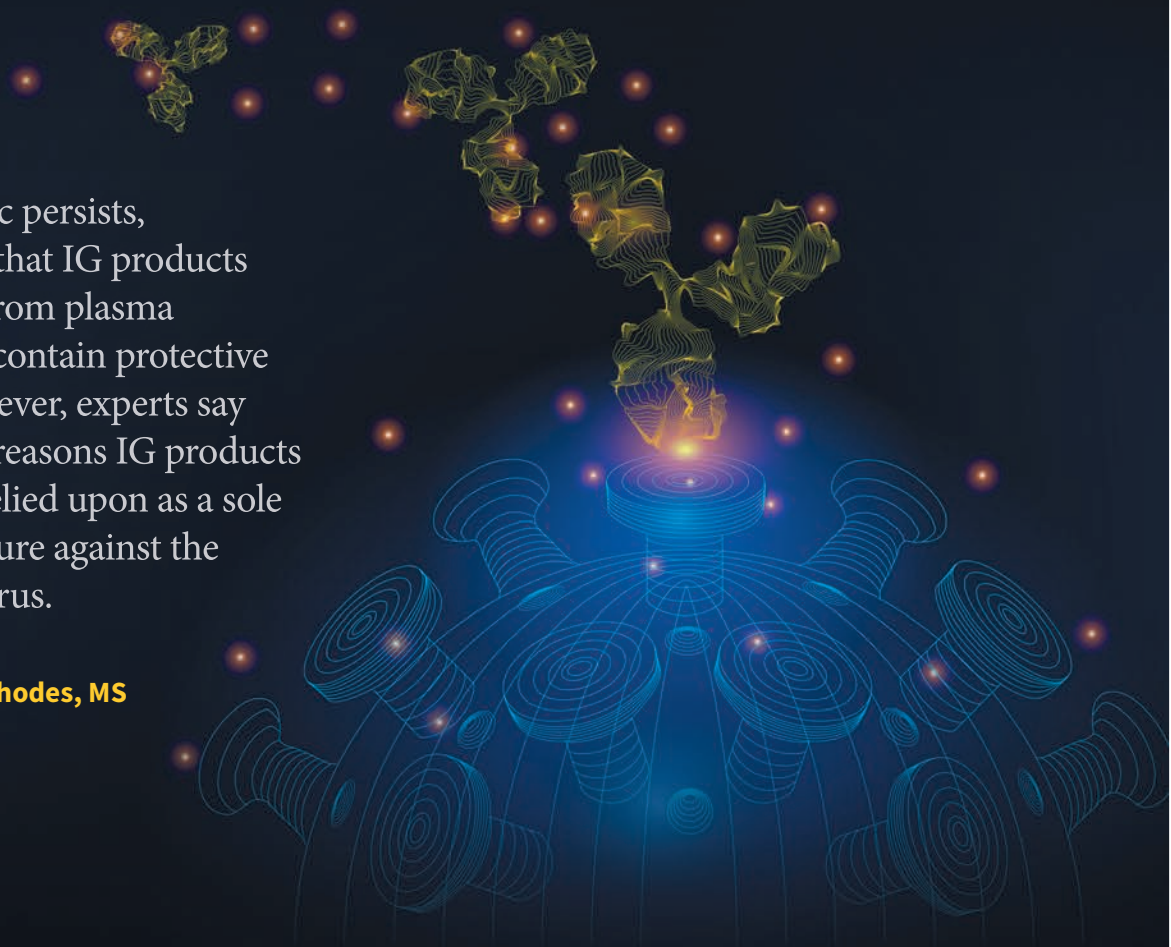
IG Products and COVID-19 Antibodies:
What We Now Know



As the pandemic persists, research shows that IG products manufactured from plasma donations now contain protective antibodies; however, experts say there are many reasons IG products should not be relied upon as a sole protective measure against the SARS-CoV-2 virus.

By Ronale Tucker Rhodes, MS

MANY PATIENTS treated with immune globulin (IG) products have been questioning whether IG products contain protective SARS-CoV-2 (the virus that causes COVID-19) antibodies. It's now been two-and-a-half years since the start of this pandemic, and while it was known IG products could not have contained protective antibodies early on due to the time it takes to manufacture IG, that is no longer the case. Research now shows that antibodies to SARS-CoV-2, either through natural infection or vaccination, exist in current plasma donations used to manufacture IG products, and these antibodies are increasing rapidly. And, while it is not known how much neutralizing COVID-19 antibodies are in any given IG lot, the rapidly rising levels of SARS-CoV-2 antibodies in collected plasma may already be close to similar levels of protection against the virus as found in current monoclonal antibody therapies (treatments preventing progression to severe COVID-19 infection in high-risk individuals and reducing hospitalizations).

That being said, neutralizing antibodies to SARS-CoV-2 in IG products will always be behind the latest variants since it takes nine months to 12 months from the time plasma is collected until it is manufactured and distributed. Even so, according to an Immune Deficiency Foundation (IDF) report, "it is likely there will still be some protection, despite 'being behind' the latest variants." In addition, says the IDF report, "it is currently not known exactly what level of protection is needed, and it is not known how this may vary from individual to individual and from strain to strain.

[But,] the good news is that the current vaccines seem to offer protection against the latest variants and even most of those who are immunocompromised seem to mount a decent, protective T-cell response."[1]

Immunodeficient Patients' Susceptibility to COVID

Without question, primary immunodeficiency (PI) patients who rely on IG treatment have an increased susceptibility to vaccine-preventable infections. Therefore, since the start of the pandemic, it was feared PI patients, as well as other immunodeficient patients, would experience an increased risk of severe disease if infected with the COVID-19 virus. However, not all research shows that these patients do experience severe illness.

In a study conducted in Israel, clinical and laboratory data was collected on PI patients who tested positive for the SARS-CoV-2 virus from mid-February 2020 to the end of September 2020. During that time, Israel experienced two waves of COVID-19 diseases — the first from mid-February to mid-May and the second from mid-June to the end of data collection. A total of 20 PI patients, aged 4 months to 60 years, tested positive for SARS-CoV-2, and all but one were detected during the second wave. Fourteen of the patients were on routine monthly intravenous IG (IVIG) replacement therapy at the time of virus detection. However, none of the patients displayed severe illness, and none required hospitalization; moreover, seven of the 20 patients were completely asymptomatic. According to the researchers, possible explanations for the minimal clinical impact of the COVID-19 pandemic observed in the patients include a high level of awareness, extra precautions and even self-isolation. It is also possible, they surmise, that only specific immune pathways (e.g., type I interferon signaling) may increase the risk for a more severe course of disease, and these are not affected in many PI patients. Furthermore, in some cases, lack of an immune response actually may be a protective measure against the development of COVID-19 sequelae.[2]

However, a smaller case series conducted earlier described seven PI patients with COVID-19 (two with agammaglobulinemia and five with common variable immune deficiency [CVID]), the latter of whom had a more severe course (three requiring intensive care unit admission and one death) than those with agammaglobulinemia (who both had mild disease). The authors postulated this may be related to a role of B cells in the pathologic inflammatory response to SARS-CoV-2 since patients with agammaglobulinemia lack B cells. An additional case report describes a case of severe COVID-19 in a patient with CVID who required mechanical ventilation but fully recovered.[3]

This same study also looked at clinical features and outcomes of COVID-19 among immunosuppressed patients, ranging from patients with cancer and solid-organ transplant (SOT) recipients to patients with HIV and those receiving immunomodulatory therapy for autoimmune disease, who are at presumed risk of more severe disease but who may also have decreased detrimental inflammatory responses. These findings showed: "First, immunocompromised patients seem to have typical clinical manifestations of COVID-19. Second, patients with cancer and SOT recipients may be at higher risk of more severe COVID-19 disease. Third, patients taking biologics may not be at higher risk of severe disease based on current data; whether they are actually at lower risk of severe COVID-19 is not yet clear. Fourth, the current data in people with HIV are inconclusive regarding whether HIV imparts a higher risk of severe disease."[3]

Since the start of the pandemic, it was feared PI patients, as well as other immunodeficient patients, would experience an increased risk of severe disease if infected with the COVID-19 virus.

Most recently, in a study conducted from March 2021 through February 2022, data were taken from 10 states (California, Colorado, Connecticut, Georgia, Michigan, Minnesota, New Mexico, New York, Oregon and Tennessee) in the COVID-19-Associated Hospitalization Surveillance Network (COVID-NET). Of the 22,345 adults admitted to the hospital for COVID-19 during this time period, 2,209 were immunocompromised (12.2 percent, despite accounting

for only about 3 percent of the U.S. population, 354 of whom were vaccinated and 1,855 of whom were unvaccinated). Vaccination status was defined as having completed both doses of a two-dose series, or one dose of a single-dose vaccine, with or without additional or booster doses either 14 days or later before a positive test result, per state immunization information system records. Results showed that once hospitalized, there was no difference in the risk for death between vaccinated and unvaccinated immunocompromised patients. However, among vaccinated adults, those who were immunocompromised had higher odds of intensive care unit (ICU) admission and in-hospital death compared with non-immunocompromised patients. And, immunocompromised patients who were not vaccinated also had higher odds of both ICU admission and in-hospital death compared with unvaccinated non-immunocompromised patients.[4]

"The decision to vaccinate a patient must include a risk and benefit assessment to ensure maximum protection and avoid adverse events."

According to Kathleen Sullivan, MD, PhD, chief of the division of allergy and immunology at Children's Hospital of Philadelphia, and Maria Jimena Gutierrez, MD, assistant professor of pediatrics and an allergist/immunologist/pediatric rheumatologist at Johns Hopkins Children's Center, who presented a forum on Oct. 5, 2021, PI patients do not appear to be at any higher risk of mortality from COVID than those without PI. "Overall, I'm going to say that the risks are not dramatically elevated in people with the classic PI … but I don't want to minimize that there's been a lot of pain in the PI community," said Dr. Sullivan. "For example, if you have CVID and are older than 65 and have chronic lung disease, you have a higher mortality rate if you get COVID (10 percent) — but it's the same mortality rate as a person who is over 65 and has a chronic lung condition and doesn't have a PI who gets COVID." However, she added, there are some exceptions. If you have a PI that compromises your ability to make interferon, then your risks of severe disease are elevated beyond the average person who doesn't have a PI. Interferon is a hormone that stimulates cells to block viruses. Those with a PI that affects their interferon do not have recurrent infections and were only identified with a PI upon a COVID-19 diagnosis. "In the folks who recover, there's a lot more interferon-stimulated genes than in the ones who go on to get severe disease," explained Dr. Sullivan. "The people with PI who have antibodies to interferon have more severe disease. Antibodies can be protective, but they can also get in the way. Also, people with interferon pathway mutations have more severe disease."[5]

Are COVID-19 Vaccines Effective for Immunodeficient Patients?

According to the Committee of Experts on Primary Immunodeficiency of the International Union of Immunological Societies, "the type and severity of the immunodeficiency determines the efficacy of vaccines, with varying levels of impairment, ranging from normal as in immunocompetent individuals, to incomplete or even absent. The degree of immunodeficiency and the specific defect in antibody production are variable … and each patient should be studied as unique in terms of cellular and humoral responses. The decision to vaccinate a patient must include a risk and benefit assessment to ensure maximum protection and avoid adverse events. In addition, other factors, including the type of vaccine, the interval between administrations and the time between [immune] globulin administration and vaccination, must also be taken into account in defining an immunization strategy."[6]

Still, Drs. Sullivan and Gutierrez recommend the best way for PI patients to protect themselves against severe disease is to receive a COVID-19 vaccine. In addition, although studies are still underway to determine how well those with a PI respond to a vaccine, they said that some will need a booster, starting a month after their last dose. But, they recommend each patient consult with his or her immunologist about the specific recommendations and best timing for a booster.[5]

One large study does show that COVID-19 mRNA vaccines are beneficial. In a meta-analysis that looked at the effectiveness of COVID-19 vaccines in immunocompromised individuals versus those with healthy immune systems, the

researchers found the Pfizer-BioNTech and Moderna mRNA COVID-19 vaccines help keep people with weakened immune systems out of the hospital if they are infected, but don't offer as much protection as they do in people with fully functioning immune systems.

Specifically, the researchers looked at information on adults hospitalized for COVID-like illness from 187 hospitals in nine states from Jan. 17, 2021, to Sept. 5, 2021, including 20,101 immunocompromised adults (53 percent had received two doses of either the Pfizer or Moderna vaccines) and 69,116 adults with fully functioning immune systems (43 percent had received two doses of either the Pfizer or Moderna vaccines). Among the immunocompromised people, half were older than 70 and half were younger; 41 percent had received the Moderna vaccine; 59 percent had received the Pfizer vaccine; 44 percent had a solid-tumor cancer, which means the cancer has no cysts or liquid areas; 14 percent had blood cancer; 25 percent had a rheumatologic or inflammatory disorder such as rheumatoid arthritis, psoriatic arthritis or lupus; 7 percent had received organ or stem cell transplants; and 32 percent had some other type of immune condition or immunodeficiency. Among the people with fully functioning immune systems, half were older than 68 and half were younger, 42 percent had received the Moderna vaccine and 58 percent had received the Pfizer vaccine.

Overall, the results showed the vaccines were 77 percent effective at keeping immunocompromised people from being hospitalized with COVID-19 and 90 percent effective at keeping people with fully functioning immune systems from being hospitalized with COVID-19. This difference was the same no matter the vaccine brand, person's age or COVID-19 variant. Specifically in immunocompromised people, the Moderna vaccine was 81 percent effective and the Pfizer vaccine was 71 percent effective. The effectiveness of the vaccines did vary depending on why a person was immunocompromised. Vaccine effectiveness was 59 percent for people who had organ or stem cells transplants, 79 percent for people with a solid-tumor cancer, 74 percent for people with blood cancer and 81 percent for people with rheumatologic and inflammatory conditions.

"Immunocompromised persons benefit from and should receive COVID-19 vaccines," the researchers wrote. "Given that [vaccine effectiveness] is lower compared to immunocompetent patients, immunocompromised persons receiving mRNA vaccines should receive three doses and a booster six months after the third dose, consistent with CDC recommendations. In addition to vaccination, immunocompromised persons should implement nonpharmaceutical prevention strategies such as masking to help prevent SARS-CoV-2 infection, and if infected with SARS-CoV-2, be monitored closely and considered early for proven therapies that might prevent progression to severe illness."[7]

"I would remind everyone that patients with CVID — 80 percent make antibodies after the vaccine. If you don't respond to other vaccines, there's still a good chance that you will respond to these vaccines. These are very powerful vaccines," said Dr. Sullivan. "It's a relatively small slice of pie where we don't expect people to make antibody response to vaccine. From the data we have so far, that would be largely men with XLA [X-linked agammaglobulinemia] and a small subset of people with CVID. If you have no B cells at all in your body, I would not keep getting more and more doses."[5]

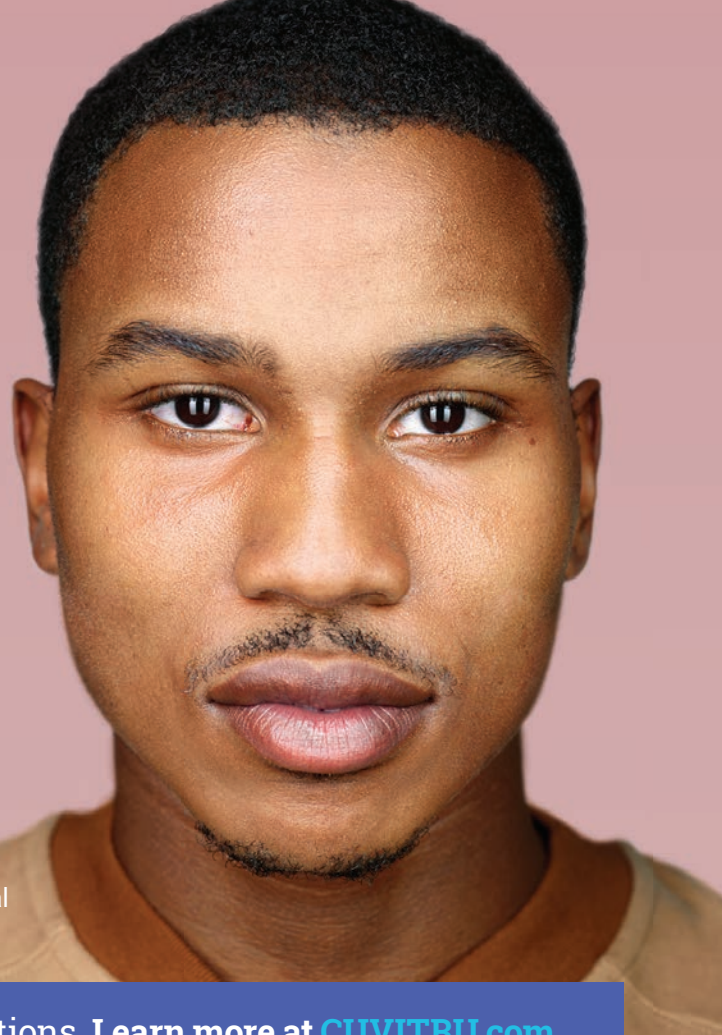
IG and COVID-19 Antibodies

Since the COVID-19 mRNA vaccines don't offer *as* robust protection for immunodeficient patients, the question many are asking is: Do IG products provide protection against the COVID-19 virus? Indeed, for some time now, the assumption has been that given the time frame of the start of the pandemic, most IG products probably have some level of COVID-19 antibodies by now, but how much is unknown. However, the nationwide blood donor seroprevalence survey estimates the percentage of the U.S. population ages 16 and older that have developed antibodies against SARS-CoV-2 from vaccination or infection is 94.7 percent as of Dec. 31, 2021,[8] which means most donated plasma today contains COVID-19 antibodies. In addition, two studies confirm that today's IG products contain protective antibodies.

Octapharma conducted a study that tested its IVIG and subcutaneous IG (SCIG) products between the end of 2020 through June 2021 from plasma collected by plasmapheresis (source plasma) in the U.S. and found its IG products do contain antibodies to SARS-CoV-2, and they have the ability to neutralize the virus. The company also found that concentrations of these antibodies increased over the time of the study, probably as a result of increasing numbers of donors who had been infected or vaccinated before donating

Cuvitru
[Immune Globulin Subcutaneous (Human)] 20%

Protection from infection.



CUVITRU [Immune Globulin Subcutaneous (Human)] 20% is a primary immunodeficiency treatment that offers consistent Ig levels in between infusions, protection from infection,* and a flexible treatment schedule.[1,2]

Your healthcare team will teach you how to administer CUVITRU, step by step, so you can infuse at home.[1]

*The goal of the clinical study was to look at the rate of acute serious bacterial infections (ASBIs) in patients receiving treatment. Patients on CUVITRU experienced 0.012 ASBIs per patient per year, which is significantly less than the FDA's standard of 1 ASBI per patient per year for determining if the treatment works. Only one ASBI occurred in CUVITRU's clinical study; it was a case of pneumonia in a 78-year-old patient.

Your doctor is your best resource for questions. **Learn more at CUVITRU.com.**

What is CUVITRU?

CUVITRU is a ready-to-use liquid medicine that is given under the skin (subcutaneously) to treat primary immunodeficiency (PI) in people 2 years and older.

IMPORTANT SAFETY INFORMATION

What is the most important information I need to know about CUVITRU?

CUVITRU can cause the following serious reactions:

- Severe allergic reactions causing difficulty in breathing or skin rashes
- Decreased kidney function or kidney failure
- Blood clots in the heart, brain, lungs, or elsewhere in the body
- Severe headache, drowsiness, fever, painful eye movements, or nausea and vomiting
- Dark colored urine, swelling, fatigue, or difficulty breathing

Who should not use CUVITRU?

Do not use CUVITRU if you:

- Have had a severe allergic reaction to immune globulin or other blood products.
- Have a condition called selective (or severe) immunoglobulin A (IgA) deficiency.

What should I avoid while taking CUVITRU?

- CUVITRU can make vaccines (like measles/mumps/rubella or chickenpox vaccines) not work as well for you. Before you get any vaccines, tell your healthcare provider (HCP) that you take CUVITRU.
- Tell your HCP if you are pregnant, or plan to become pregnant, or if you are nursing.

What are the possible or reasonably likely side effects of CUVITRU?

CUVITRU can cause serious side effects. If any of the following problems occur after starting CUVITRU, stop the infusion immediately and contact your HCP or call emergency services.

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Treatment on my terms.

You and your doctor can create a treatment plan based on your preference—faster infusions or fewer needlesticks, but with a flexible schedule.

Faster infusions[1]

In the study,* once-weekly infusions took just under an hour.†

Fewer needlesticks[1]

In the study, most (84.9%) used 1 to 2 needlesticks.*

Flexible schedule[1]

CUVITRU can be infused at the fastest rates of any subQ (up to 60mL/hr/site as tolerated).†† With the fastest rates of any subcutaneous Ig, CUVITRU can make treatment every 1 to 2 weeks a reality, even for patients with the highest volumes.

*CUVITRU was studied in 77 people with primary immunodeficiency (PI) ≥ 2 years of age, with the main goal of measuring how many acute serious bacterial infections (ASBIs) were experienced over the course of 1 year. ASBIs are short-term but serious infections that require immediate medical care.

†The average infusion time was 0.95 hrs (range 0.2-6.4 hrs).

††You'll infuse your first 2 infusions at 10 to 20 mL/hr/site. After that, you'll be able to increase your rate, as tolerated. Infuse at up to 4 sites simultaneously.

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IMPORTANT SAFETY INFORMATION, CONTINUED

- Hives, swelling in the mouth or throat, itching, trouble breathing, wheezing, fainting or dizziness. These could be signs of a serious allergic reaction.
- Bad headache with nausea, vomiting, stiff neck, fever, and sensitivity to light. These could be signs of irritation and swelling of the lining around your brain.
- Reduced urination, sudden weight gain, or swelling in your legs. These could be signs of a kidney problem.
- Pain, swelling, warmth, redness, or a lump in your legs or arms. These could be signs of a blood clot.
- Brown or red urine, fast heart rate, yellow skin or eyes. These could be signs of a liver or blood problem.
- Chest pain or trouble breathing, or blue lips or extremities. These could be signs of a serious heart or lung problem.
- Fever over 100°F. This could be sign of an infection.

The following one or more possible side effects may occur at the site of infusion. These generally go away within a few hours, and are less likely after the first few infusions.

- Mild or moderate pain
- Redness
- Itching

The most common side effects that may occur are:

- Headache
- Nausea
- Fatigue
- Diarrhea
- Vomiting

These are not all the possible side effects. Talk to your HCP about any side effect that bothers you or that does not go away.

Please see Important Facts about CUVITRU on the following page.

You are encouraged to report negative side effects of prescription drugs to the FDA. Visit www.fda.gov/medwatch, or call 1-800-FDA-1088.

Takeda

IMPORTANT FACTS about CUVITRU (CUE-vih-troo) [Immune Globulin Subcutaneous (Human)] 20% Solution

What is the most important information I need to know about CUVITRU?

CUVITRU can cause the following serious reactions:

- Severe allergic reactions causing difficulty in breathing or skin rashes
- Decreased kidney function or kidney failure
- Blood clots in the heart, brain, lungs, or elsewhere in the body
- Severe headache, drowsiness, fever, painful eye movements, or nausea and vomiting
- Dark colored urine, swelling, fatigue, or difficulty breathing

What is CUVITRU?

CUVITRU is a ready-to-use liquid medicine that contains immunoglobulin G (IgG) antibodies, which protect the body against infection. CUVITRU is used to treat patients with primary immunodeficiency diseases (PI).

There are many forms of PI. The most common types of PI result in an inability to make a very important type of protein called antibodies, which help the body fight off infections from bacteria or viruses. CUVITRU is made from human plasma that is donated by healthy people. CUVITRU contains antibodies collected from these healthy people that replace the missing antibodies in PI patients.

Who should not use CUVITRU?

Do not use CUVITRU if you have a known history of a severe allergic reaction to immune globulin or other blood products. If you have such a history, discuss this with your healthcare provider (HCP) to determine if CUVITRU can be given to you. Tell your HCP if you have a condition called selective (or severe) immunoglobulin A (IgA) deficiency.

How should I use CUVITRU?

CUVITRU is given under the skin (subcutaneously). Most of the time, infusions under the skin are given at home by self-infusion or by caregivers. Instructions for giving CUVITRU under the skin (subcutaneously) are provided in the FDA-approved patient labeling (Information for Patients and Instructions for Use). Only use CUVITRU by yourself after you have been instructed by your HCP.

What should I avoid while taking CUVITRU?

CUVITRU can make vaccines (like measles/mumps/rubella or chickenpox vaccines) not work as well for you. Before you get any vaccines, tell your HCP that you take CUVITRU.

Tell your HCP if you are pregnant, or plan to become pregnant, or if you are nursing.

What are the possible or reasonably likely side effects of CUVITRU?

The following are one or more possible reactions that may occur at the site of infusion. These generally go away within a few hours, and are less likely after the first few infusions.

- Mild or moderate pain
- Redness
- Itching

The most common side effects of CUVITRU are headache, nausea, fatigue, diarrhea, and vomiting.

If any of the following problems occur after starting treatment with CUVITRU, stop the infusion immediately and contact your HCP or call emergency services. These could be signs of a serious problem.

- Hives, swelling in the mouth or throat, itching, trouble breathing, wheezing, fainting or dizziness. These could be signs of a serious allergic reaction.
- Bad headache with nausea, vomiting, stiff neck, fever, and sensitivity to light. These could be signs of irritation of the lining around your brain.
- Reduced urination, sudden weight gain, or swelling in your legs. These could be signs of a kidney problem.
- Pain, swelling, warmth, redness, or a lump in your legs or arms. These could be signs of a blood clot.
- Brown or red urine, fast heart rate, yellow skin or eyes. These could be signs of a liver or blood problem.
- Chest pain or trouble breathing, or blue lips or extremities. These could be signs of a serious heart or lung problem.
- Fever over 100°F. This could be a sign of an infection.

These are not all the possible side effects. You can ask your HCP for a physician's information leaflet. Tell your HCP about any side effect that bothers you or that does not go away.

Whenever giving yourself treatments at home, you should have another responsible person present to help treat side effects or get help if you have a serious adverse reaction occur. Ask your HCP whether you should have rescue medications, such as antihistamines or epinephrine.

How do I store CUVITRU?

Store CUVITRU refrigerated or at room temperature.

- You can store CUVITRU in the refrigerator (36°F to 46°F [2°C to 8°C]) for up to 36 months or
- You can store CUVITRU at room temperature (up to 77°F [25°C]) for up to 24 months.
- Do not return CUVITRU to the refrigerator if you take it out to room temperature.
- Do not freeze.
- Do not shake.
- Check the expiration date on the carton and vial label. Do not use CUVITRU after the expiration date.
- Protect from light. You can use the original CUVITRU containers to protect it from light.

How do I get more information about CUVITRU?

The risk information provided here is not comprehensive. To learn more, talk about CUVITRU with your HCP or pharmacist. The FDA-approved Full Prescribing Information, including Information for Patients, can be found at www.CUVITRU.com or by calling 1-877-TAKEDA7 (1-877-825-3327).

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their plasma. According to the company spokesperson, "The increasing levels of SARS-CoV-2 antibodies in Octapharma IVIG and SCIG products indicate that a certain level of protection could be possible against COVID-19 in patients … who are receiving standard IG therapy."[9]

Another study conducted by Takeda evaluated SARS-CoV-2 antibodies in its product, Gammagard Liquid, and found similar results. In this study, a total of 176 Gammagard Liquid lots released between March 2020 and January 2021 from plasma collected by plasmapheresis in the U.S. were analyzed. For a subset of 12 of these IVIG lots, information about the dates of plasma collection was obtained. The study found that SARS-CoV-2 neutralizing antibodies were undetectable for Gammagard Liquid lots released to the market between March and August 2020. However, for lots released in September 2020, 12 of 26 lots (46 percent) were seropositive with a mean SARS-CoV-2 neutralizing antibody concentration of 1.8 IU/ml. And, from there onward, the proportion of SARS-CoV-2 neutralizing antibody-positive lots steadily increased, with mean neutralizing antibody concentrations of 3.0 (54 percent) in October 2020, 4.8 (67 percent) in November 2020, 12.1 (94 percent) in December 2020 and 36.7 (93 percent) in January 2021.[10]

As such, researchers from both studies expect COVID-19 antibodies to continue to increase in the plasma supply as more donors are exposed to or vaccinated against the SARS-CoV-2 virus. In fact, since there is a nine- to 12-month lead time from plasma collection to release of an IG product, they predicted IG patients could expect a similar level of antibodies as that found in convalescent plasma (plasma donated by individuals who have recently recovered from COVID-19) by summer 2021.

A follow-up study provides even stronger evidence that anti-SARS-CoV-2 antibodies in pooled plasma and IG products mirror exposure in the general population. In this study, subsequent data show anti-SARS-CoV-2 antibodies dramatically increased (10 to 50 times) in all plasma pools and IG products regardless of geographic origin. The highest titers and the greatest increases in titers of anti-SARS-CoV-2 antibodies were seen in regions where antibodies first appeared (Spain and the U.S.). The titers of anti-SARS-CoV-2 antibodies in the final products showed similar changes over time as those seen in pooled plasma up to September 2021, as well as neutralizing activity of these antibodies against wild-type virus and variants of concern.[11]

Despite these study's findings, the researchers stress that it is impossible to know at what levels SARS-CoV-2 antibodies may be present in any given dose of IG. It is also unclear exactly how high plasma antibody levels would need to be to provide COVID-19 protection to PI or other immunodeficient patients through IG therapy. Therefore, IG therapy should not be considered a source of protection against COVID-19 infection. According to CDC, vaccination against SARS-CoV-2 is still the best way to avoid severe disease and hospitalization.[9]

With Mutations Prevailing, All Precautions Are Necessary

While research shows that immunocompromised individuals are not necessarily in greater danger of severe disease from the SARS-CoV-2 virus, it does appear to come down to specific factors on a case-by-case basis. Research also shows that IG products contain neutralizing antibodies against COVID-19, but how much protection they provide is still in question. Since mutations to the virus continue to evade immune protection, the best advice for PI and other immunodeficient patients is to get vaccinated, including a booster vaccine; take precautions such as masking, social distancing, handwashing and disinfecting high-touch areas; and seek early treatment with monoclonal antibodies for early infections or prophylaxis.

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