Managing Care During Immune Globulin Product Shortages

Understanding the reasons behind the shortages and what to do during these periods can help patients gain access to their lifesaving treatment.

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RECENT SHORTAGES of immune globulin (IG) products are impacting the care and treatment of patients across the U.S. and worldwide. It is likely some patients are currently affected by the limited availability of a specific product. What are some of the factors that contribute to limited product availability, and how can patients navigate the bumpy roads of product shortages?

What Causes Shortages?

IG products are derived from human plasma, which is the clear liquid part of blood that contains proteins like immunoglobulin, albumin, clotting factors and many others. Manufacturing of plasma proteins is complicated and very expensive, taking between nine and 12 months from the time plasma is collected to the finished product. This process involves a series of intricate steps designed to produce a highly purified product that is safe and effective. Interruptions in the manufacturing process, the plasma collection process or any issues with the final product can result in a disruption of supply. Also, brief delays in new product approvals by the U.S. Food and Drug Administration (FDA) or temporary product (or specific lot) withdrawals from the market can negatively impact supply and, therefore, patient access to this lifesaving therapy.

The manufacture of plasma products is completely dependent on human donors for its raw material. Plasma donors in the U.S. go through a rigorous screening process to ensure they are healthy and meet all the strict selection requirements. At the present time, there is an acute need for more plasma donations to increase the supply of this valuable raw material.

The need for IG products is expected to continue to grow each year. New indications, increased off-label usage and earlier diagnoses are a few of the factors driving this growth. Indeed, the Plasma Protein Therapeutics Association reports there was a 66 percent increase in IG use between 2012 and 2018 across North America and Europe.[1] More than 88 million grams of IG were administered to more than 200,000 patients receiving therapy.[2] This expansion of demand also contributes to IG supply problems.

In August 2019, FDA released a statement addressing the issues of product shortages along with a list of the products with limited availability.[3] FDA cited increased demand for IG products with a supply that is not able to keep pace as the reason for the shortages. Its recommendations for healthcare providers are to develop a system to determine which patients should receive priority treatment and to consider adding additional products to their formularies to use during times of shortages.

During these periods of shortages, it is extremely important for patients to understand their options. With this knowledge, patients can be their own advocates to help navigate the bumpy roads of limited product availability.

Managing Therapy Through Shortages

It can be a stressful time when patients learn they may not receive their scheduled treatment. Feeling they have somehow lost control over their healthcare can be frightening. However, patients can take back that control by advocating for themselves and by working closely with their healthcare team and insurance providers. Also, having knowledge of the other available product alternatives may help in making decisions regarding a change in IG brand or route of administration, should either become necessary.

As each IG product is unique, there are no generics. And, while all IG products are considered effective for treating various disease states, patients should be knowledgeable about the specific product attributes that may have an effect on personal, patient-specific side effects. Organizations like the Immunoglobulin National Society (www.ig-ns.org) and patient foundations provide free resources (Table) that increase knowledge and awareness about currently available products.

Because each product is unique and every patient is different, patients can experience different side effects from product to product. Sodium, sugar and other additives can also increase the incidence of serious adverse events such as kidney issues, stroke or heart attack. In the event of an IG shortage, working closely with a nurse, pharmacist and physician to determine which product is the best fit can make the transition to a new product safer.

A change in the route of administration is another option to consider during product shortages. Transitioning from intravenous IG (IVIG) to subcutaneous IG (SCIG) therapy, or vice versa, can help bridge the gap until the preferred product becomes available again.

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Changing to SCIG requires careful planning and preparation to ensure a successful transition. SCIG is self-administered by the patient or caregiver. This type of therapy is traditionally administered once per week; however, depending on the dose, it may need to be administered more often. SCIG requires willingness on the part of patients to self-administer on a consistent basis to maintain therapeutic levels of immunoglobulins in their bodies. Keeping a regular self-administration schedule without missing doses is a critical part of successful SCIG therapy. In addition, self-administration of SCIG requires the ability to work with equipment and administration sets. Patients who cannot operate the equipment, have a fear of needles or vision issues, or those who do not have anyone to assist them if any difficulties take place, should avoid SCIG.

The differences in IG products make it necessary to take extra care during the first several infusions when a new product is started. A nurse will carefully observe each patient, and the infusion rate will need to be slower than usual until it is known how the patient feels on the new product. A healthcare

Table. U.S. Food and Drug Administration-Approved Immune Globulin Products

Product	Manufacturer	Route	FDA-approved Indication(s)	IgA Content (mcg/mL)	pH	Sodium Content (mEq/L)	Stabilizer	Osmolality/ Osmolarity (mOsm/kg)
Asceniv 10%	ADMA Biologics	IV	PI in adults and adolescents (12 years-17 years)	≤200	4.0-4.6	100-140 (0.10-0.14 M)	Glycine, Polysorbate 80	Not listed
Bivigam 10%	ADMA Biologics	IV	PI in adults	≤200	4.0-4.6	100-140 (0.10-0.14 M)	Glycine, Polysorbate 80	Not listed
Cutaquig 16.5%	Octapharma	SC	PI in adults	≤600	5.0-5.5	≤30	Maltose	310-380
Cuvitru 20%	Takeda	SC	PI in adults and pediatric patients 2 years and older	80	4.6-5.1	No added sodium	Glycine	280-292
Flebogamma 5% DIF	Grifols	IV	PI in adults and pediatric patients 2 years and older	Typically <50	5-6	Trace amounts	Sorbitol	240-370
Flebogamma 10% DIF	Grifols	IV	PI Chronic ITP in patients 2 years and older	Typically <100	5-6	Trace amounts	Sorbitol	240-370
Gammagard Liquid 10%	Takeda	IV, SC	(IV) PI in adults and pediatric patients 2 years and older (IV) Maintenance therapy in MMN in adults (SC) PI in adults and pediatric patients 2 years and older	37	4.6-5.1	No added sodium	Glycine	240-300
Gammagard S/D (5% or 10% when reconstituted)	Takeda	IV	PI in adults and pediatric patients over 2 years and older CLL ITP KD	"<1 (5%) <2 (10%)"	6.8±0.4	146 [5% (8.5mg/ml)] 292 [10%) (~17mg/ml)]	Glucose, Glycine	636 (5%) From Monograph ~1250 (10%) From Monograph
Gammaked 10%	Kedrion	IV, SC	(IV) PI in adults and pediatric patients 2 years and older (IV) ITP in adults and children (IV) CIDP in adults (SC) PI in adults and pediatric patients 2 years and older	46	4.0-4.5	Not listed	Glycine	258
Gammaplex 5%	BPL	IV	PI in adults and pediatric patients 2 years and older Chronic ITP in adults	<10	4.8-5.1	Not listed	Sorbitol, Glycine, and Polysorbate 80	Not < 240 (Typically 420-500)
Gammaplex 10%	BPL	IV	PI in adults and pediatric patients 2 years and older Chronic ITP in adults	<20	4.9-5.2	<30	Glycine and Polysorbate 80	Not < 240 (Typically 280)
Gamunex-C 10%	Grifols	IV, SC	(IV) PI in adults and pediatric patients 2 years and older (IV) ITP in adults and children (IV) CIDP in adults (SC) PI in adults and pediatric patients 2 years and older	46	4.0-4.5	Not listed	Glycine	258
Hizentra 20%	CSL Behring	SC	PI in adults and pediatric patients 2 years and older CIDP in adults (Maintenance therapy)	≤50	4.6-5.2	Trace amounts	L-proline	Not listed
HyQvia 10%	Takeda	SC	PI in adults	37	4.6-5.1	No sodium added	Glycine	240-300
Octagam 5%	Octapharma	IV	PI	≤200	5.1-6.0	≤30	Maltose	310-380
Octagam 10%	Octapharma	IV	Chronic ITP in adults	106	4.5-5.0	≤30	Maltose	310-380
Panzyga 10%	Octapharma	IV	PI in adults and pediatric patients 2 years and older Chronic ITP in adults	100	4.5-5.0	Trace amounts	Glycine	240-310
Privigen 10%	CSL Behring	IV	PI in adults and pediatric patients 3 years and older Chronic ITP in patients 15 years and older CIDP in adults	≤25	4.6-5.0	Trace amounts	L-proline	240-440
Xembify 20%	Grifols	SC	PI in patients 2 years and older	Not listed	4.1-4.8	Not listed	Glycine, Polysorbate 80	280-404

PI = Primary Immunodeficiency ITP = Immune Thrombocytopenia CIDP = Chronic Inflammatory Demyelinating Polyneuropathy CLL = Chronic Lymphocytic Leukemia KD = Kawasaki Disease MMN = Multifocal Motor Neuropathy

provider should provide education about possible reactions, how to lessen their severity and when and how to report any reaction that may occur hours or days after the infusion.

Site-of-Care Considerations

During shortages, facilities or providers may have different access to IG therapies, and not all may be experiencing supply interruptions. Patients should know their options and be able to switch where and how they receive IG during product shortages. Understanding site-of-care options may allow patients to continue to receive IG therapy without interruption. For example, patients receiving IG therapy in the home may be able to continue service uninterrupted at a local infusion center. And, some patients receiving treatment at an infusion center may be able to continue therapy in the home.

Insurance Considerations

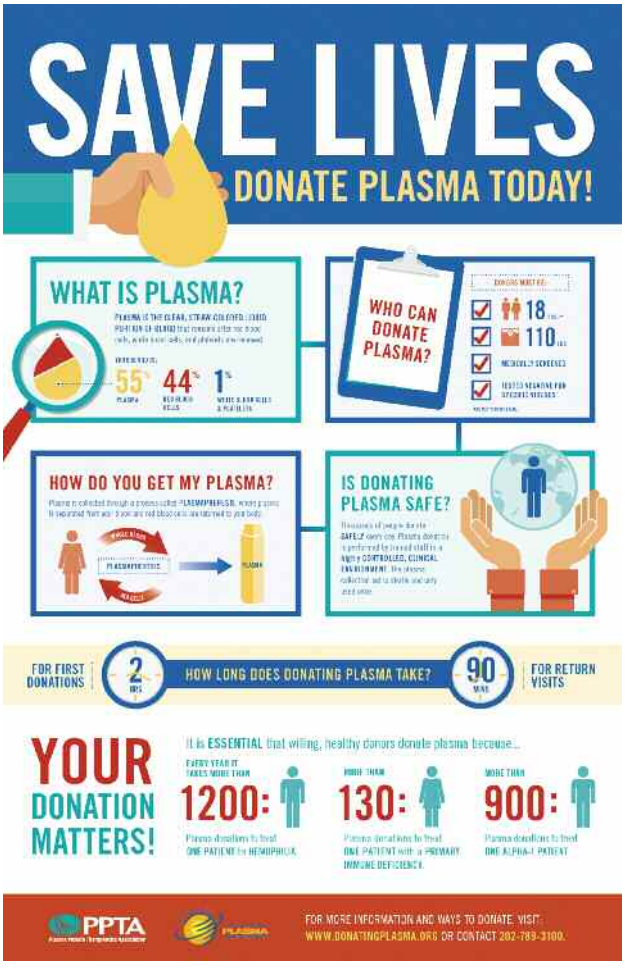
Changes in product or site of care will likely require prior authorization from patients' insurance. To facilitate any changes, patients' healthcare providers should work with them to minimize the interruption of therapy as much as possible. Payers often have preferred brands and contracts that limit patient access to certain brands of products. Requests for changes are occasionally denied and then must go through an appeal process. Establishing open communication with a representative from the insurance company may help provide it with additional insight for how best to meet patients' needs.

The Importance of Plasma

Plasma is a finite resource, and there is no substitute for this precious liquid. As the use of IG and other plasma proteins increases, it is vital the supply continues to grow as well. Plasma donors are compensated for their time in the U.S., which has allowed our country to supply many more patients than in other countries. Plasma donors must meet specific criteria and may donate up to three times per week with a 24-hour break between donations (Figure).

Plasma donation is a commitment for individuals who choose to give their time in this way. Without regular donations from qualified donors, the supply of plasma products would cease to exist. As the primary and only source of supplying hundreds of thousands of patients in the U.S alone with the therapies they need to survive, these invisible heroes are saving lives with every single donation. If patients know someone who is a plasma donor, they should thank them. If they have friends and family who can donate, they should ask them. For more information about the plasma donation process, visit www.donatingplasma.org. ■

Figure. Donating Plasma



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Resources

1. Plasma Protein Therapeutics Association: www.pptaglobal.org.
2. Research and Markets. U.S. Intravenous Immunoglobulin (IVIG) Market Size, Share and Trends Analysis Report by Application (CIDP, Congenital AIDS), by Route of Administration (IV, Subcutaneous), by Distribution Channel, and Segment Forecasts. 2018-2025. Accessed at www.researchandmarkets.com/reports/4621728/u-s-intravenous-immunoglobulin-ivig-market.
3. U.S. Food and Drug Administration. Information About Immune Globulin (Human) Product Shortage, Aug. 16, 2019. Accessed at www.fda.gov/vaccines-blood-biologics/safety-availability-biologics/information-about-immune-globulin-human-product-shortage.

Editor's note: The original table contains dosing information for the IG products. To obtain a copy of the original table, contact the Immunoglobulin National Society at (888) 855-4443 or info@Ig-NS.org.