DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
1401 Rockville Pike
Rockville, MD 20852-1448

January 28, 1998

Dear Doctor:

In recent weeks, the Food and Drug Administration (FDA) has received numerous calls from physicians, pharmacists, and pharmaceutical distributors about difficulties in obtaining sufficient amounts of Immune Globulin Intravenous (human) (IGIV). These difficulties may have resulted from a number of factors, including decreases in production, product recalls, and a progressive increase in usage. Supply disruptions may also have occurred due to stockpiling or other market phenomena. To address supply issues, the FDA is working closely with manufacturers to expedite lot release and to facilitate increased production and distribution, without compromising the safety or efficacy of the products. FDA also has asked the manufacturers to establish reserves for emergency use.

Some of the major manufacturers have established toll-free telephone numbers for use by prescribing physicians to assist them in obtaining products for patients with an urgent need for IGIV. These telephone numbers are as follows:

Alpha Therapeutic Corporation (Contact Person = Chris Chow, PharmD.)	l-800-42l-0008
Baxter Healthcare Corporation (Contact Person = Kyle Bush)	l-847-940-5955
Bayer Corporation	l-800-288-8370
Centeon, L.L.C. (Contact Person = Arlene Santhouse, R. Ph.)	l-800-504-5434
Novartis Pharmaceuticals Corporation	
1. IGIV Hotline	l-973-503-7500
2. Customer Service number	l-800-526-0175

Manufacturer	Product	Distributor
Alpha Therapeutic Corporation	Venoglobulin-S Venoglobulin-I	The product is mailed directly to a pharmacy or to the local physician on a priority basis.
Baxter Healthcare Corporation	Gammagard S/D Gammagard Polygam S/D	The product is mailed directly to a pharmacy or to the local physician on a priority basis. Note: American Red Cross (l-800-446-8883-Ext 8763) is the distributor for Polygam S/D.
Bayer Corporation	Gamimune-N5% Gamimune-NS%S/D Gamimune-N 10% Gamimune-N 10%S/D	The product is mailed directly to a pharmacy or to the local physician on a priority basis.
Centeon, L.L.C.	Gammar-P-IV	The product is mailed directly to a pharmacy or to the local physician on a priority basis.
Central Lab. Blood Transfusion Service Swiss Red Cross	Sandoglobulin	Novartis Pharmaceutical Corp.
Oesterreichisches Institut fuer Haemoderivate G.m.b.H. (O.I.H.)	Iveegam	Baxter Healthcare Corp.

In addition, supply information may be available from the Immune Deficiency Foundation, telephone: l-800-296-4433. Physicians who have contacted the above sources to acquire IGIV for the licensed indication but who have been unable to do so may then contact the Product Shortage Officer for FDA's Center for Biologics Evaluation and Research (CBER), Mr. Boyd Fogle, at the CBER Office of Compliance, telephone: 301-827-6220, for assistance.

We encourage all physicians to consider whether other appropriate treatment options may be available. Medical centers which treat many patients with IGIV are encouraged to develop and implement a prioritization system for the use of these products to assist practicing physicians in making these important decisions.

The following is a list of FDA-approved indications for each of the IGIV products currently licensed in the USA:

- Primary Immunodeficiency (PID): Gammagard (Baxter), Gammagard S/D (Baxter), Polygam S/D (Baxter), Gamimune-N 5% (Bayer), Gamimune-N 5% S/D (Bayer), Gamimune-N 10% (Bayer), Gamimune-N 10% S/D (Bayer), Sandoglobulin (CLB-Swiss Red Cross), Iveegam (O.I.H.), Venoglobulin-I (Alpha), Venoglobulin-S (Alpha), Gammar-P-IV (Centeon, L.L.C.).

. Immune-mediated Thrombocytopenia (ITP): Gammagard (Baxter), Gammagard S/D (Baxter), Polygam S/D (Baxter), Gamimune-N 5%(Bayer), Gamimune-N 5% S/D (Bayer), Gamimune-N 10% (Bayer), Gamimune-N 10% S/D (Bayer), Sandoglobulin (CLB-Swiss Red Cross), Venoglobulin-I (Alpha), Venoglobulin-S (Alpha).

- Kawasaki syndrome: Iveegam (O.I.H.), Venoglobulin-I (Alpha), Venoglobulin-S (Alpha).

- Bone Marrow Transplantation: Gamimune-N 5% (Bayer), Gamimune-N 5% S/D (Bayer), Gamimune-N 10% (Bayer), Gamimune-N 10% S/D (Bayer)

. Chronic B-cell Lymphocytic Leukemia: Gammagard (Baxter), Gammagard S/D (Baxter), Polygam S/D (Baxter)

- Pediatric HIV-l Infection: Gamimune-N 5% (Bayer), Gamimune-N 5% S/D (Bayer), Gamimune-N 10% (Bayer), Gamimune-N 10% S/D (Bayer)

The following brief summary describes the potential impact of an inability to provide IGIV to patients with illnesses which are serious or life-threatening:

- Primary Immunodeficiency: IGIV is the main form of treatment for primary immunodeficiency, and it reduces the frequency of infection, and hospitalization, and reduces morbidity. Infections can be life threatening to these patients.

- Kawasaki syndrome: In this primarily pediatric syndrome, life-threatening coronary artery aneurysms can occur. The use of IGIV within 10 days of Kawasaki syndrome onset significantly reduces the risk of coronary artery abnormalities.

. Idiopathic Thrombocytopenic Purpura (ITP): Steroids and splenectomy may be alternative forms of treatment for ITP. IGIV is often effective in refractory cases, and its use results in rapid increases in platelet counts. Bleeding, especially intracerebral episodes, can be life-threatening.

- Bone Marrow Transplantation: Some experts recommend administering IGIV to prevent

bacterial infections in severely hypogammaglobulinemic allogeneic bone marrow transplant recipients, e.g., those with serum IgG < 400 mg/dl. In these patients IGIV is given from the time of engraftment to 100 days post-transplant.
The use of IGIV in other bone marrow transplant settings is currently the subject of scientific debate.

Chronic B-cell Lymphocytic Leukemia: Subjects with B-cell CLL often have a variable clinical course, and the prognosis depends directly on the stage of the tumor. Frequently, subjects develop anemia, cytopenias, splenomegaly, and lymphadenopathy, along with recurrent life-threatening infections. IGIV is effective in prophylaxis against these recurrent infections and may allow the use of treatments including one or more of the following: an alkylating agent such as Chlorambucil, 2-chlorodeoxyadenosine, deoxycoformycin, fludarabine monophosphate, with or without glucocorticoids, as indicated.

Pediatric HIV-l Infection: B-cell defects, natural killer cell dysfunction, and a lack of memory B cells are factors which result in a high rate of serious bacterial infections in HIV-infected children compared with adults. IGIV therapy in HIV-infected pediatric patients is based on evidence of impaired antibody production in these patients. A recent double-blind, placebo-controlled study showed that IGIV 400 mg/kg every 28 days can decrease the morbidity associated with serious bacterial infections in HIV-infected children with CD4 cell counts of > 200 cells/cu mm. Another study (involving HIV-infected children receiving concurrent zidovudine) demonstrated that IGIV helped to prevent serious bacterial infections in children who were not concurrently receiving trimethoprim-sulfamethoxazole, but not in those who were receiving trimethoprim-sulfamethoxazole. IGIV has not been shown to alter mortality in HIV-infected children, but IGIV therapy in this population may decrease the morbidity associated with serious bacterial infections.

Sincerely,

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REFERENCES

The following references are provided without endorsement to help physicians review current publications discussing therapeutic uses of IGIV:

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Fasano, M.B. Risks and Benefits of Intravenous Immunoglobulin treatment in children. Curr Opin Pediatr, 1995. Dec, 7:6; 688-694.

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Newberger, J.W., Takahashi, M., Beiser, A.S., et al. A single intravenous infusion of gamma globulin as compared with four infusions in the treatment of acute Kawasaki Syndrome. N Engl J Med, 1991. 324:23;1633-1639.

Anonymous. NIH Consensus Conference on Intravenous Immune Globulin: Prevention and Treatment of disease. JAMA, 1990. Dec 26, 264:24; 3 189-3 193.