DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

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

IMPORTANT DRUG WARNING

November 13, 1998

Dear Doctor:

This letter is intended to alert physicians to safety precautions that should be taken to reduce the potential risk of ACUTE RENAL FAILURE (ARF) associated with the administration of Immune Globulin Intravenous (Human) (IGIV) products.

Since IGIVs were first introduced in 1981, the Food and Drug Administration (FDA) has received over 114 worldwide (approximately 83 U.S.) adverse event reports[a] of renal dysfunction and/or acute renal failure associated with the administration of these products[1-16]. Although acute renal failure was successfully managed in the majority of cases, deaths were reported in 17 patients worldwide. Many of the patients who died had serious underlying conditions.

Preliminary evidence suggests that IGIV products containing sucrose may present a greater risk for this complication. Hyperosmolality of certain reconstituted products, as well as differences in stabilizer sugar choice and content between IGIVs, may be among the factors that have contributed to different reporting rates for renal dysfunction among the various IGIV products. A disproportionate share of the cases (approximately 88% of U.S. reports) have been associated with the sucrose-containing products. The sucrose containing products are (A) the product manufactured by the Central Laboratory Blood Transfusion Service, Swiss Red Cross (SRC), (Sandoglobulin®, distributed by Novartis, and Panglobulin®, distributed by the American Red Cross), and (B) the IGIV products manufactured by Centeon L.L.C. (Gammar®-P I.V./Gammar®-I.V.[b]).

Renal histopathologic examination was performed in 8 of the IGIV-associated ARF cases. The findings were consistent in 7 of 8, suggesting an osmotic injury to the proximal renal tubules (acute tubular necrosis, vacuolar degeneration, and osmotic nephrosis). Approximately fifty-five percent of the reported cases of renal dysfunction involved patients being treated for idiopathic thrombocytopenic purpura (ITP) and fewer than 5% involved patients with primary immune deficiency (PID). This may relate to the fact that higher and consecutive doses are used for ITP, in contrast to the dosing regimens used for PID. It is not known whether age and baseline glomerular filtration rate (GFR) differences could also be factors explaining the greater proportion of case reports of renal dysfunction following the administration of IGIV for ITP.

Table 1

Manufacturer	Distributor	Product	g sucrose/ g Ig	No. (%) of U.S. cases of Renal Adverse Events
Alpha Therapeutic Corporation	Alpha Therapeutic Corporation	Venoglobulin-S® Venoglobulin-I®	0	None Reported
Baxter Healthcare Corporation	Baxter	Gammagard S/D®[c]	0	3 (4%)
	American Red Cross	Polygam S/D®[c]		
Bayer Corporation	Bayer Corporation	Gamimune-N®[c]	0	4 (5%)
Centeon L.L.C.	Centeon L.L.C.	Gammar®-P I.V. Gammar® I.V.[b]	1.0	18 (22%)
Central Laboratory, Blood Transfusion Service, Swiss Red Cross	Novartis Pharmaceuticals	Sandoglobulin®[d]	1.67	56 (69%)
	American Red Cross	Panglobulin®[d]		
Oesterreichisches Institut fuer Haemoderivative Ges.m.b.H. (O.I.H.)	Immuno U.S., Inc.	Iveegam®	0	None Reported

[a] Additional literature reports were under review at time of printing.

[b] Gammar® I.V. was withdrawn from the market after the introduction of Gammar®-P I.V.

[c] Same formulation

[d] Same formulation

[e] Three Renal Adverse Event Reports were associated with unspecified IGIV products.

In an effort to reduce the risk of acute renal failure and based on the data which currently are available, FDA recommends that the following precautions be taken when considering administration of IGIV products:

1. Assure that patients are adequately hydrated prior to the initiation of the infusion of IGIV.
2. Exercise particular caution in the administration of IGIV products in patients at increased risk for developing acute renal failure. Such patients include, but are not limited to, those with:
   - any degree of pre-existing renal insufficiency
   - diabetes mellitus
   - age greater than 65
   - volume depletion
   - sepsis, paraproteinemia
   - concomitant nephrotoxic drugs.

   For patients at increased risk, physicians should carefully weigh the potential benefits of administering sucrose-containing IGIV products against the risks of causing renal damage.
3. Do not exceed the recommended dose. Reduction in dose, concentration, and/or rate of administration in patients at risk of acute renal failure has been proposed in order to reduce the risk of acute renal failure[16]. Because no prospective data are presently available to identify a maximal safe dose, concentration, or rate of infusion for IGIV products for patients at risk of acute renal failure, FDA recommends that, for such patients, prescribers reconstitute/dilute the product in such a manner as to produce both the minimum concentration and rate of infusion practicable. For sucrose-containing IGIVs, a maximum infusion rate of 3 mg sucrose/kg/minute (2 mg Ig/kg/min for Sandoglobulin and Panglobulin; 3 mg Ig/kg/min for Gammar-P I.V) should not be exceeded.
4. Renal function, including urine output and blood urea nitrogen (BUN)/serum creatinine, should be assessed prior to infusion of IGIV, particularly in patients judged to have a potential increased risk for developing acute renal failure, and again at appropriate intervals. If renal function deteriorates, discontinuation of the product should be considered.

IGIV manufacturers are working with FDA to revise their prescribing information to reflect these reports of acute renal dysfunction/acute renal failure and to advise physicians of the above recommendations. FDA intends to work with the IGIV product manufacturers to monitor the implementation and impact of these interim recommendations on the risk of IGIV-associated ARF. The Agency is prepared to take further measures in the future as may be appropriate to ensure product safety. Until additional information further clarifies the safety concerns outlined above, physicians and other health care professionals should follow the recommendations contained in this letter when administering IGIV products and they should use the least amount of product that is judged to be effective. A list of the FDA-approved indications for each of the IGIV products marketed in the U.S. is shown in Table 2. Revised package inserts for these products will include a boxed warning concerning the risk of ARF, new precautions, and new dosage and administration recommendations. All IGIV manufacturers will provide you with revised package inserts by letter in the near future.

As with all medical products, healthcare professionals are strongly encouraged to report any serious adverse events that are associated with the use of IGIVs, including cases of acute renal failure, to the manufacturer or distributor. (See Table 2). Alternatively, adverse events may be reported to FDA's **MEDWATCH** program by **phone (1-800-FDA-1088), FAX (1-800-FDA-0178),** or **mail to MEDWATCH, HF-2, 5600 Fishers Lane, Rockville, MD 20852-9787.** The following is a list of FDA-approved indications for each of the IGIV products currently licensed in the USA, together with the address and telephone number for reporting adverse events:

Table 2

Manufacturer/Distributor	**Product**	**Approved Indications**
Alpha Therapeutic Corp 5555 Valley Blvd. Los Angeles, CA 90032 1-800-421-0008	Venoglobulin-S® Venoglobulin-I®	Primary Immune Deficiencies (PID) Immune-mediated Thrombocytopenia Kawasaki Syndrome
The American Red Cross 1-800-293-5023 (Professional Affairs) 1-800-312-8736 (Medical Affairs)	Panglobulin® Polygam S/D®	Primary Immune Deficiencies (PID) Immune Thrombocytopenic Purpura (ITP)
Baxter Healthcare Corp 550 North Brand Blvd. Glendale, CA 91203 1-800-423-2090	Gammagard S/D® Polygam S/D® (manufactured by Baxter for American Red Cross.)	Primary Immunodeficiency Diseases (PID) Idiopathic Thrombocytopenic Purpura (ITP) Chronic B-cell Lymphocytic Leukemia
Bayer Corp 800 Dwight Way Berkeley, CA 94701 1-800-288-8371	Gamimune-N® Gamimune-N S/D®	Primary Humoral Immunodeficiency Idiopathic Thrombocytopenic Purpura (ITP) Bone Marrow Transplant Pediatric HIV-1 Infect.
Centeon L.L.C. 1020 First Avenue King of Prussia, PA 19406-1310 1-800-504-5434	Gammar®-P I.V.	Primary Immune Deficiencies (PID)
Immuno U.S., Inc.	Iveegam®	Primary Immune

Manufacturer/Distributor	Product	Approved Indications
1200 Parkdale Road Rochester, MI 48307 1-800-423-2090		Deficiencies (PID) Kawasaki Syndrome
Novartis Pharmaceuticals Corp East Hanover, NJ 07936 FAX 1-888-299-4565	Sandoglobulin®	Primary Immune Deficiencies (PID) Immune Thrombocytopenic Purpura (ITP)

Sincerely,

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