DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

September 24, 1999

IMPORTANT DRUG WARNING

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) reported to be associated with the administration of Immune Globulin Intravenous (Human) (IGIV) products.

Since IGIVs were first introduced in 1981, the U.S. 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 reported rates of renal dysfunction for 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 15 of the IGIV-associated ARF cases. The findings were consistent in 7 of 15, suggesting an osmotic injury to the proximal renal tubules (acute tubular necrosis, vacuolar degeneration, and osmotic nephrosis). Approximately 55 percent of the reported cases of renal dysfunction involved patients being treated for idiopathic thrombocytopenic purpura (ITP) and fewer than five percent 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[e]
Alpha Therapeutic Corporation	Alpha Therapeutic Corporation	Venoglobulin-S® Venoglobulin-I®	0	None Reported
Baxter Healthcare Corporation	Baxter	Iveegam®	0	None Reported
		Gammagard S/D®[c]	0	3 (4%)
	American Red Cross	Polygam S/D®[c]		
Bayer Corporation	Bayer Corporation	Gamimune®-N, 5% Gamimune®-N, 10%	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]		

[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, the following precautions should be taken when considering administration of IGIV products:

1. Assure that patients are not volume depleted 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, which includes patients 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 for acute renal failure has been proposed in order to reduce the risk[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 for acute renal failure, FDA recommends that, for such patients, recommended doses should not be exceeded and the concentration and infusion rate selected should be the minimum levels practicable. For sucrose-containing IGIVs, a maximum infusion rate of 3 mg sucrose/kg/minute (2 mg Ig/kg/min for Sandoglobulin® and Panglobulin®; 1 mg Ig/kg/min for Gammar®-P I.V) should not be exceeded.

4. Periodic monitoring of renal function tests and urine output is particularly important in patients judged to have a potential increased risk for developing acute renal failure. Renal function, including measurement of blood urea nitrogen (BUN)/serum creatinine, should be assessed prior to the initial infusion and again at appropriate intervals thereafter. If renal function deteriorates, discontinuation of the product should be considered.

5. Patients should be instructed to immediately report symptoms of decreased urine output, sudden weight gain fluid retention/edema, and/or shortness of breath (which may suggest kidney damage) to their physicians.

A list of the FDA-approved indications for each of the IGIV products marketed in the U.S. is shown in Table 2. Please refer to the revised package inserts for these products for additional prescribing information. Revised package inserts are available on the websites listed in Table 2 and may also be obtained by directly contacting the manufacturer.

TABLE 2

Manufacturer/Distributor	Product	Approved Indications
Alpha Therapeutic Corporation 5555 Valley Boulevard Los Angeles, CA 90032 (800) 292-6118 www.alphather.com/products/ins_veno.htm www.alphather.com/products/ins_veno2.htm	Venoglobulin-S® Venoglobulin-I®	Primary Immune Deficiencies (PID) Immune Thrombocytopenic Purpura (ITP) Kawasaki Syndrome

Manufacturer/Distributor	Product	Approved Indications
The American Red Cross (Medical Affairs) 1616 North Fort Myer Drive Roslyn, VA 22209 (800) 293-5023 www.redcross.org/plasma/polygamsd/index.htm www.redcross.org/plasma/panglobulin/aba4.htm	Polygam S/D® Panglobulin®	Primary Immune Deficiencies (PID) Idiopathic Thrombocytopenic Purpura (ITP) Chronic B-Cell Lymphocytic Leukemia Kawasaki Syndrome Primary Immune Deficiencies (PID) Immune Thrombocytopenic Purpura (ITP)
Baxter Healthcare Corporation 550 North Brand Boulevard Glendale, CA 91203 (800) 423-2090 www.baxter.com/doctors/blood_therapies/hyland_immuno/index.html	Gammagard S/D® Iveegam®	Primary Immune Deficiencies (PID) Idiopathic Thrombocytopenic Purpura (ITP) Chronic B-Cell Lymphocytic Leukemia Kawasaki Syndrome Primary Immune Deficiencies (PID) Kawasaki Syndrome
Bayer Corporation 1884 Miles Avenue Elkhart, IN 46514 (800) 288-8371 http://www.univgraph.com/bayer/BioInserts.html	Gamimune®-N, 5% Gamimune®-N, 10%	Primary Humoral Immunodeficiency Idiopathic Thrombocytopenic Purpura (ITP) Bone Marrow Transplant Pediatric HIV Infection
Centeon L.L.C. 1020 First Avenue King of Prussia, PA 19406 (800) 504-5434 www.centeon.com/na/hq/hq_9a.htm	Gammar® P.I.V.	Primary Immune Deficiencies (PID)
Novartis Pharmaceuticals Corp 59 Route 10 East Hanover, NJ 07936 (888) 669-6682 www.pharma.us.novartis.com/product/pi/sandoglobulin.html	Sandoglobulin®	Primary Immune Deficiencies (PID) Immune Thrombocytopenic Purpura (ITP)

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 (800) FDA-1088, FAX (800) FDA-0178, or mail to MEDWATCH, HF-2, 5600 Fishers Lane, Rockville, MD 20852-9787.

Sincerely,

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References

1. Kessler DA, Introducing MEDWATCH: A new approach to reporting medication and device adverse effects and product problems. 1993; JAMA 269:2765-2768.

2. Barton J, Herrera G, Galla J, Bertoli L, Work J, Koopman W: Acute cryoglobulinemic renal failure after intravenous infusion of gamma globulin. 1987; Am J Med 82:624-629.

3. Cayco AV, Perazella MA, Hayslett JP: Renal insufficiency after intravenous immune globulin therapy: A Report of Two Cases and an Analysis of the Literature. 1997; J Amer Soc Nephrology 8: 1788-1793.

4. Rault R, Piraino B, Johnston J, Oral A: Pulmonary and renal toxicity of intravenous immunoglobulin. 1991; Clin Nephrol 36:83-86.

5. Michail S, Nakopoulou L, Stravrianopoulos I, Stamatiadis D, Avdikou K, Vaiopoulos G, Stathakis C: Acute renal failure associated with immunoglobulin administration. 1997; Nephrol Dial Transplant 12:1497-1499.

6. Decocq G, de Cagny B, Andrejak M, Desablens B: Acute kidney failure secondary to intravenous immunoglobulin administration: 4 cases and review of the literature. 1996; Therapie 51: 516-26.

7. Ahsan N, Wiegand LA, Abendroth CS, Manning EC: Acute renal failure following immunoglobulin therapy. 1996; Am J Nephrol 16: 532-536.

8. Hansen-Schmidt S, Silomon J, Keller F: Osmotic nephrosis due to high-dose immunoglobulin therapy containing sucrose (but not glycine) in a patient with immunoglobulin A nephritis. 1996; Am J Kidney Dis 28: 451-453.

9. Winward DB, Brophy MT: Acute renal failure after administration of intravenous immunoglobulin: review of the literature and case report. 1995; Pharmacotherapy 15: 765-772.

10. Arunabh S, Kumar G, Avila V: Acute renal failure induced by intravenous immune globulin [letter]. 1996; Am Fam Physician 53: 862-865.

11. Veber B, Mohammedi I, Gachot B, Bedos JP, Wolff M: High-dose intravenous IgG treatment and acute renal failure [letter]. 1995; Intensive Care Med 21: 288-289.

12. Poullin P, Moulin B, Ollier J, Benaicha M, Olmer M, Gabriel B: [Renal complications from intravenous immunoglobulins. Role of renal hemodynamic factors]. 1995; Presse Med 24:441-444.

13. Cantu TG, Hoehn-Saric EW, Burgess KM, Racusen L, Scheel PJ: Acute renal failure associated with immunoglobulin therapy. 1995; Am J Kidney Dis 25: 228-234.

14. Phillips AO: Renal failure and intravenous immunoglobulin [letter; comment]. 1992; Clin Nephrol 36: 83-86.

15. Kobosko J, Nicol P: Renal toxicity of intravenous immunoglobulin [letter; comment]. 1992; Clin Nephrol 37: 16-7.

16. Tan E, Hajinazarian M, Bay, et al. Acute renal failure resulting from intravenous immunoglobulin therapy. 1993; Arch Neurology 50:137-139.

17. Anderson W, Bethea W: Renal lesions following administration of hypertonic solutions of sucrose. 1940; JAMA 114:1983-1987.

18. Lindberg H, Wald A Renal changes following the administration of hypertonic solutions. 1939; Arch Intern Med 63:907-918.

19. Rigdon RH, Cardwell ES: Renal lesions following the intravenous injection of hypertonic solution of sucrose: A clinical and experimental study. 1942; Arch Intern Med 69:670-690.