

**Health Canada Endorsed Important Safety Information on
Gamunex[®] (Immune Globulin Intravenous [Human], 10%)**

October 19, 2005

To: Hospital Chief of Medical Staff

Please distribute to the Blood Bank, Hospital Pharmacy and to the relevant Departments of Transfusion Medicine, Immunology, Hematology, Oncology, Neurology, Rheumatology, Pediatrics, Nephrology, Infectious Diseases, Dermatology, Internal Medicine, Obstetrics, Gynecology and Family Medicine and other involved professional staff and POST THIS NOTICE IN YOUR INSTITUTION.

Subject: Association of Gamunex[®] (Immune Globulin Intravenous [Human], 10%) with Hemolytic Reactions

Talecris Biotherapeutics, Inc., in collaboration with Health Canada, is informing health care professionals of the receipt of spontaneous adverse event reports of suspected hemolytic anemia, hemolysis, or hemolytic reaction temporally associated with the use of Gamunex[®]. Gamunex[®] is indicated for the treatment of primary humoral immunodeficiency, idiopathic thrombocytopenic purpura, allogeneic bone marrow transplantation and pediatric Human Immunodeficiency Virus infection. Reactions have been reported when the product was used in approved indications and other medical conditions.

- Hemolytic anemia, hemolysis and hemolytic reaction, sometimes requiring blood transfusion, have been reported in association with the use of Gamunex[®].
- Hemolytic anemia has been reported in the medical literature in association with diverse Immune Globulin Intravenous (Human) (IGIV) products, particularly with high-dose therapy.
- Patients who receive IGIV products should be monitored for several days post-infusion for signs and symptoms of hemolysis. The diagnosis should be confirmed and the appropriate treatment should be initiated.

Hemolytic anemia has been reported in the medical literature in association with diverse Immune Globulin Intravenous (Human) (IGIV) products, particularly with high-dose therapy¹⁻⁵. IGIV products can contain blood group antibodies which may act as hemolysins and result in coating of red blood cells in vivo with immunoglobulin, causing a positive direct antiglobulin reaction and, rarely, hemolysis, from enhanced red blood cell (RBC) sequestration. In most reports from the literature, there is objective evidence for hemolytic anemia (demonstration of a hemoglobin drop ≥ 4 gm/dL, increase of bilirubin or LDH, decrease or negative haptoglobin within hours or days of receiving IGIV treatment), plus evidence of elutable blood group isoantibodies¹⁻¹². Since September 1, 2003, 26 cases of suspected hemolytic reactions in association with Gamunex[®] have been reported globally (20 in Canada), with a reporting rate of 0.04% in a total exposure of 58949 patient years. Analysis of suspected hemolytic anemia events, hemolysis, and hemolytic reactions reported in association with Gamunex[®] indicates that the etiology may include a combination of different factors. The reported cases reveal that some of these patients received doses exceeding recommended package instructions. The information from many of these reports identified the presence of other risk factors for hemolytic anemia, including use of antibiotic treatment, renal transplant rejection, multiple blood transfusions, history of idiopathic hemolytic anemia, hereditary spherocytosis, history of incompatible blood transfusion, and history of autoimmune disorder. For those cases in

which this information was reported, the time between Gamunex[®] infusion and reported hemolytic reactions was predominantly within 3 days of Gamunex[®] infusion. In all reports wherein Gamunex[®] lot numbers were provided, corresponding isoantibody titers were within specifications established in the European Pharmacopoeia for IGIV products.

In about half of all reported cases, there was no mention of the treatment of anemia. The remaining cases were treated by blood transfusion, corticosteroids, or plasmapheresis.

Patients with laboratory or clinical findings suggesting hemolytic anemia should be properly tested to confirm the diagnosis. Appropriate testing would include unconjugated serum bilirubin, serum haptoglobin, Direct Antiglobulin Test (DAT), and serum LDH. Twelve of 26 cases (46%) did not have data confirming a diagnosis of hemolytic anemia. Appropriate treatment should be determined according to the individual patient's clinical condition.

Reporting rates determined on the basis of spontaneously reported post-marketing adverse events are generally presumed to underestimate the risks associated with drug treatments.

Talecris and Health Canada depend on health care professionals to report any cases of hemolytic anemia and/or other serious and/or unexpected adverse reactions in patients receiving Gamunex[®] to Bayer Inc., Canadian distributor and importer of the product, or Health Canada at the following addresses:

Drug Safety and Medical Information
Bayer Inc.
77 Belfield Rd.
Toronto, ON M9W 1G6
Tel: 1-800-265-7382
Fax: 1-866-232-0565

Any suspected adverse reaction can also be reported to:

Canadian Adverse Drug Reaction Monitoring Program (CADRMP)
Marketed Health Products Directorate

HEALTH CANADA

Address Locator: 0701C

OTTAWA, Ontario, K1A 0K9

Tel: (613) 957-0337 or Fax: (613) 957-0335

To report an Adverse Reaction, consumers and health professionals may call toll free:

Tel: 866-234-2345

Fax: 866-678-6789

cadrmp@hc-sc.gc.ca

For other inquiries, please refer to contact information:

Marketed Health Products Directorate (MHPD)

MHPD_DPSC@hc-sc.gc.ca

Tel.: (613) 954-6522

Fax.: (613) 952-7738

The [AR Reporting Form](#) and the [AR Guidelines](#) can be found on the Health Canada web site or in *The Canadian Compendium of Pharmaceuticals and Specialties*.

http://www.hc-sc.gc.ca/dhp-mps/medeff/report-declaration/form/ar-ei_form_e.html

http://www.hc-sc.gc.ca/dhp-mps/medeff/report-declaration/guide/ar-ei_guide-ldir_e.html

Your professional commitment in this regard has an important role in protecting the well-being of your patients by contributing to early signal detection and informed use of drugs. Comprehensive information is important to our ability to evaluate the significance of the reported event in association with Gamunex[®].

Talecris, in consultation with Health Canada, has updated the Product Monograph for Gamunex[®]. The full copy of the Gamunex[®] Product Monograph will be posted at www.gamunex.ca.

If you require any further information on Gamunex[®], please contact Bayer Medical Information at 1-800-265-7382.

Sincerely,

TALECRIS BIOTHERAPEUTICS, INC.



Gerald L. Klein, MD
Vice President, Medical and Clinical Affairs

References

1. Comenzo RL, Malachowski ME, Meissner HC, Fulton DR, Berkman EM. Immune hemolysis, disseminated intravascular coagulation, and serum sickness after large doses of immune globulin given intravenously for Kawasaki disease. *J Pediatr* 1992;120(6):926-8.
2. Kluge A, Dopfer R, Pfeiffer-Wolf I, Roelcke D. Immunoglobulin high-dose therapy: RBC-alloantibodies in commercial preparations and haemolytic anaemia: a case report. *Beitr Infusionsther Transfusionsmed* 1994;32:474-5.
3. Nakamura S, Yoshida T, Ohtake S, Matsuda T. Hemolysis due to high-dose intravenous gammaglobulin treatment for patients with idiopathic thrombocytopenic purpura. *Acta Haematol* 1986;76(2-3):115-8.
4. Okubo S, Ishida T, Yasunaga K. Hemolysis after intravenous immune globulin therapy: relation to IgG subclasses of red cell antibody. *Transfusion* 1990;30(5):436-8.
5. Salama A, Mueller-Eckhardt C, Kiefel V. Effect of intravenous immunoglobulin in immune thrombocytopenia. *Lancet* 1983;2(8343):193-5.
6. Brox AG, Cournoyer D, Sternbach M, Spurll G. Hemolytic anemia following intravenous gamma globulin administration. *Am J Med* 1987;82(3 Spec No):633-5.
7. Copelan EA, Strohm PL, Kennedy MS, Tutschka PJ. Hemolysis following intravenous immune globulin therapy. *Transfusion* 1986;26(5):410-2.
8. Nakagawa M, Watanabe N, Okuno M, Kondo M, Okagawa H, Taga T. Severe hemolytic anemia following high-dose intravenous immunoglobulin administration in a patient with Kawasaki disease. *Am J Hematol* 2000;63(3):160-1.
9. Nicholls MD, Cummins JC, Davies VJ, Greenwood JK. Haemolysis induced by intravenously-administered immunoglobulin. *Med J Aust* 1989;150(7):404-6.
10. Robertson VM, Dickson LG, Romond EH, Ash RC. Positive antiglobulin tests due to intravenous immunoglobulin in patients who received bone marrow transplant. *Transfusion* 1987;27(1):28-31.
11. Strobel E, Wullenweber J, Peters J. [Detection and side effects of isoantibodies in intravenously administered immunoglobulin preparations]. *Infusionsther Transfusionsmed* 1995;22(1):31-5.
12. Wilson JR, Bhoopalam H, Fisher M. Hemolytic anemia associated with intravenous immunoglobulin. *Muscle Nerve* 1997;20(9):1142-5.

