PRODUCT MONOGRAPH

GAMIMUNE® N, 5%

IMMUNE GLOBULIN INTRAVENOUS (HUMAN), 5%
(IN 10% MALTOSE) pH 4.25
Solvent/Detergent Treated

10, 20, 50, 100, 250 and 500 mL

GAMIMUNE® N, 10%

IMMUNE GLOBULIN INTRAVENOUS (HUMAN), 10%
(IN 0.16-0.24 M GLYCINE) pH 4.25
Solvent/Detergent Treated

10, 25, 50, 100 and 200 mL

PASSIVE IMMUNIZING AGENT

Manufactured by:
Talecris Biotherapeutics, Inc.
8368 US 70 West
Clayton, NC 27250 U.S.A.

Distributed and imported by:
Bayer Inc.
77 Belfield Road
Toronto, Ontario
M9W 1G6 CANADA

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THERAPEUTIC CLASSIFICATION

PASSIVE IMMUNIZING AGENT

ACTION AND CLINICAL PHARMACOLOGY

Primary Humoral Immunodeficiency

Immune Globulin Intravenous (Human), 5% - GAMIMUNE® N, 5% and Immune Globulin Intravenous (Human), 10% - GAMIMUNE® N, 10%, treated with solvent/detergent, supply a broad spectrum of opsonic and neutralizing IgG antibodies for the prevention or attenuation of a wide variety of infectious diseases. Since GAMIMUNE® N, 5% and 10% are administered intravenously, essentially 100% of the infused IgG antibodies are immediately available in the recipient's

circulation.[1] Studies using a modified immunoglobulin at pH 6.8 have shown that approximately 30% of the infused IgG disappeared from the circulation in the first 24 hours due primarily to equilibration of IgG between the plasma and the extravascular space.[1-4] A further decline of about 40% of the peak level found immediately post-infusion is to be expected during the first week.[1-4] The in vivo half-life of Immune Globulin Intravenous (Human), 5% - GAMIMUNE® N, 5% equals or exceeds the three week half-life reported for IgG in the literature, but individual patient variation in half-life has been observed. [1] Thus, this variable as well as the amount of immune globulin administered per dose is important in determining the frequency of administration of the drug for each individual patient.

A comparative study of GAMIMUNE® N, 5% treated with solvent/detergent and GAMIMUNE® N, 5% in 16 subjects demonstrated bioequivalence. A comparative study of GAMIMUNE® N, 10% with GAMIMUNE® N, 5% (in 10% maltose) in 18 subjects demonstrated equivalent post-infusion recovery for the two preparations. A comparative study of GAMIMUNE® N, 10% treated with solvent/detergent and GAMIMUNE® N, 10% in 17 subjects demonstrated bioequivalence.

Idiopathic Thrombocytopenic Purpura

While GAMIMUNE® N, 5% and 10% have been shown to be effective in some cases of idiopathic thrombocytopenic purpura (ITP) (see INDICATIONS AND USAGE) the mechanism of action has not been fully elucidated.

Allogeneic Bone Marrow Transplantation

GAMIMUNE® N, 5% has been shown to be effective in allogeneic bone marrow transplant patients ≥20 years of age at increased risk for the following complications in the first 100 days post transplant: prevention of systemic and local infections, interstitial pneumonia of infectious and idiopathic etiologies and acute graft-versus-host disease (GVHD).[5] (See Indications and Usage).

Administration of GAMIMUNE® N, 5% to allogeneic bone marrow transplant patients significantly increased IgG and IgG subclass levels while those seen in the control group fell below predicted levels. The mechanism of action of GAMIMUNE® N, 5% in reducing the incidence of GVHD is presently unknown.

Pediatric HIV Infection

Children infected with human immunodeficiency virus (HIV) may display defects in both cellular and humoral immunity.[6-9] As a result, children with AIDS have a markedly increased rate of serious, potentially life-threatening bacterial infections.[10-12] The types of bacterial and viral infections observed in HIV-infected children are similar to those in children with primary hypogammaglobulinemia.[13] The replacement of opsonic and neutralizing IgG antibodies has been shown to reduce a wide variety of infectious diseases in HIV-infected children.[14,15]

General

The intravenous administration of solutions of maltose has been studied by several investigators.[16-20] Healthy subjects tolerated the infusions well, and no adverse effects were observed at a rate of 0.25 g maltose/kg body weight per hour.[17] In safety studies, infusions of 10% maltose administered at 0.27 - 0.62 g maltose/kg per hour [20] to normal subjects produced either mild side effects (e.g., headache) or no adverse reaction.[1] Following intravenous administrations of maltose, maltose was detected in the peripheral blood; there was a dose-dependent excretion of maltose and glucose in the urine and a mild diuretic effect. [1] These alterations were well tolerated without significant adverse effects.[1] The highest recommended infusion rate, 0.06 mL/kg body weight per minute (see Dosage And Administration), is equivalent to 0.36 g maltose/kg body weight per hour.

The buffer capacity of Immune Globulin Intravenous (Human), 5%, is 16.5 mEq/L (~0.3 mEq/g protein). A dose of 1000 mg/kg body weight therefore represents an acid load of 0.33 mEq/kg body weight. The total buffering capacity of whole blood

in a normal individual is 45-50 mEq/L of blood, or 3.6 mEq/kg body weight.[21] Thus, the acid load delivered with a dose of 1000 mg/kg of GAMIMUNE® N, 5% would be neutralized by the buffering capacity of whole blood alone, even if the dose were infused instantaneously. (An infusion usually lasts several hours.)

In Phase I human studies, no change in arterial blood pH measurements was detected following the intravenous administration of GAMIMUNE® N, 5% at a dose of 150 mg/kg body weight;[1] following a dose of 400 mg/kg body weight in 37 patients, there were no clinically important differences in mean venous pH or bicarbonate measurements in patients who received GAMIMUNE® N, 5% compared with those who received a chemically modified intravenous immunoglobulin preparation with a pH of 6.8.[1]

Glycine (aminoacetic acid) is a non-essential amino acid normally present in the body.[22] Glycine is a major ingredient in amino acid solutions employed in intravenous alimentation. [23] While toxic effects of glycine administration have been reported,[24] the doses and rates of administration were 3-4-fold greater than those for GAMIMUNE® N, 10%.

The buffer capacity of GAMIMUNE® N, 10% is 35.0 mEq/L (~ 0.35 mEq/g protein). A dose of 1000 mg/kg body weight therefore represents an acid load of 0.35 mEq/kg body weight. The total buffering capacity of whole blood in a normal individual is 45-50 mEq/L of blood, or 3.6 mEq/kg body weight.[21] Thus, the acid load delivered with a dose of 1000 mg/kg of GAMIMUNE® N, 10% would be neutralized by the buffering capacity of whole blood alone, even if the dose were infused instantaneously.

In Phase 1 human studies comparing GAMIMUNE® N, 10% with GAMIMUNE® N, 5% (in 10% maltose) venous blood measurements were taken following the intravenous administration of 400 mg/kg body weight in 18 patients. There were no

clinically important changes in mean venous pH, bicarbonate, or base excess measurements in these patients receiving either preparation.[1]

In a similar, earlier Phase 1 study GAMIMUNE® N, 5% (in 10% maltose) was compared with a chemically modified 5% intravenous immunoglobulin preparation with a pH of 6.8. No clinically important changes in mean venous pH and bicarbonate measurements were detected following infusions of either preparation at doses of 400 mg/kg body weight in 37 patients.

In patients with limited or compromised acid-base compensatory mechanisms and in patients in whom there is already an expanded fluid volume (e.g. during pregnancy), consideration should be given to the effect the additional acid and/or protein load GAMIMUNE® N, 5% and 10% might present.

INDICATIONS AND USAGE

Primary Humoral Immunodeficiency

Immune Globulin Intravenous (Human), 5% - GAMIMUNE® N, 5% and Immune Globulin Intravenous (Human), 10% - GAMIMUNE® N, 10% are efficacious in the treatment of primary immunodeficiency states in which severe impairment of antibody forming capacity has been shown, such as: congenital agammaglobulinemias, common variable immunodeficiency, Wiskott-Aldrich syndrome, x-linked immunodeficiency with hyper IgM, and severe combined immunodeficiencies.[4, 25-27] GAMIMUNE® N, 5% and 10% are especially useful when high levels or rapid elevation of circulating antibodies are desired or when intramuscular injections are contraindicated.

Idiopathic Thrombocytopenic Purpura (ITP)

In clinical situations in which a rapid rise in platelet count is needed to control bleeding or to allow a patient with ITP to undergo surgery, administration of

GAMIMUNE® N, 5% and 10% should be considered. Studies with Immune Globulin Intravenous (Human), 5% - GAMIMUNE® N, 5% demonstrate that in patients in whom a response was achieved, the rise of platelets was generally rapid (within 1-5 days), transient (most often lasting from several days to several weeks) and were not considered curative. It is presently not possible to predict which patients with ITP will respond to therapy, although the increase in platelet counts in children seems to be better than that of adults. Childhood ITP may, however, respond spontaneously without treatment.

GAMIMUNE® N, 10% has been studied in 31 adult and pediatric subjects with ITP using a dosage of 1000 mg/kg body weight on either one day or two consecutive days. Fourteen of sixteen children (87.5%) and 9 of 10 adults with platelet follow-up (90%) responded to treatment with clinically significant platelet increments of $\geq$30,000/mm^3. In the twelve children with acute ITP, there was an average increase in platelet count above baseline of 274,000/mm^3 (range 33,000 - 529,000/mm^3).

Two different dosing regimens of GAMIMUNE® N, 5% have been studied in clinical investigations: a regimen consisting of 400 mg/kg body weight daily for 5 consecutive days, and a high dose treatment regimen consisting of 1,000 mg/kg body weight administered on either 1 day or 2 consecutive days (these studies are summarized below).

In clinical studies of GAMIMUNE® N, 5% 5 of 6 (83.3%) children and 12 of 16 (75%) adults with acute or chronic ITP treated with 400 mg/kg body weight for five consecutive days demonstrated clinically significant platelet increments of $\geq$30,000/mm^3 over baseline. The mean platelet count in children with ITP rose from 27,800/mm^3 at baseline to 297,000/mm^3 (range 50,000 - 455,000/mm^3) and the mean platelet count in adults with ITP rose from 27,900/mm^3 at baseline to 124,900/mm^3 (range 11,000 - 341,000/mm^3). Two of three children with acute ITP rapidly went into complete remission.

Thirteen of 14 children (92.9%) and 26 of 29 adults (89.7%) with acute or chronic ITP treated with GAMIMUNE® N, 5% 1,000 mg/kg body weight administered on either one day or two consecutive days responded to treatment with clinically significant platelet increments of ≥ 30,000/mm^3 over baseline. This included three of three patients with ITP that were human immunodeficiency virus (HIV) antibody positive and two of two patients with ITP that were pregnant. The mean platelet count in children with ITP treated with GAMIMUNE® N, 5% 1,000 mg/kg body weight on 1 day or 2 consecutive days rose from 44,400/mm^3 at baseline to 285,600/mm^3 (range 89,000 - 473,000/mm^3) and the mean platelet count in adults with ITP treated with the regimen rose from 23,400/mm^3 at baseline to 173,100/mm^3 (range 28,000 - 709,000/mm^3). Two patients, one each with acute adult and chronic childhood ITP, entered complete remission with treatment.

Six of the 29 adult patients with ITP received GAMIMUNE® N, 5% 1,000 mg/kg on 1 day or 2 consecutive days to increase the platelet count prior to splenectomy. Mean platelet counts rose from 14,500/mm^3 at baseline to 129,300/mm^3 (range 51,000 - 242,000/mm^3) prior to surgery.

The duration of the platelet rise following treatment of ITP with either treatment regimen of GAMIMUNE® N, 5% was variable, ranging from several days to 12 months or more. Some ITP patients have demonstrated continuing responsiveness over many months to intermittent infusions of GAMIMUNE® N, 5% at doses of 400 - 1,000 mg/kg body weight, administered as a single maintenance dose, at intervals as indicated by the platelet count.

Allogeneic Bone Marrow Transplantation

GAMIMUNE® N, 5% and 10% could be considered for use in allogeneic bone marrow transplant (BMT) patients ≥20 years of age to decrease the risk of septicemia and other infections, interstitial pneumonia of infectious or idiopathic etiologies and acute graft-versus-host disease (GVHD) in the first 100 days post transplant.[5]

GAMIMUNE® N, 5% and 10% are not indicated in allogeneic bone marrow transplant patients below 20 years of age.

In a controlled study of 369 evaluable bone marrow transplant patients (185 untreated and 184 treated with GAMIMUNE® N, 5% in doses of 500 mg/kg body weight on days -7 and -2 pretransplant then weekly through day 90 posttransplant), posttransplant complications were evaluated. Analysis of the study group as a whole and of those <20 and ≥20 years of age showed significant reductions in posttransplant complications in the first 100 days. This was most evident in patients 20 years of age and over. For patients ≥20 years of age (128 patients in the control group and 119 patients in the treated group), there was a statistically significant reduction in interstitial pneumonia from 21% in the control group to 9% in the treated group (p=0.0032) during the first 100 days posttransplant. Also significantly reduced in this age group were: overall septicemia from 41% in the control group to 22% in the treated group (relative risk [RR] 2.36, p=0.0025); gram-negative septicemia from 19% in the control group to 7% in the treated group (RR 2.53, p=0.015); and Grade II to IV acute GVHD from 53% (58 of 110) in the control group to 35% in the treated group (38 of 108, p=0.0051).[5]

In patients below age 20, there appeared to be no benefit from treatment with GAMIMUNE® N, 5% and 10%, either in reducing the incidence of infections or the incidence of acute GVHD.

Pediatric HIV Infection

GAMIMUNE® N, 5%, 400mg/kg every 28 days, significantly decreases the frequency of serious and minor bacterial infections (laboratory-proven and clinically diagnosed) and the frequency of hospitalization, and increases the time free of serious infection in children with clinical or immunologic evidence of HIV disease with CD4+ counts of ≥ 200 mm^3. GAMIMUNE® N, 5% did not have any effect on

mortality or on the frequency of opportunistic infection. To achieve optimal efficacy the CD4+ counts should be determined prior to the onset of therapy.

	No. Of Serious Infections			
	None	1	2-5	≥5
GAMIMUNE® N, 5%	136	30	25	0
Placebo	107	45	40	1

In a randomized, double-blind, placebo-controlled, multicenter study, 383 HIV-infected, non-hemophilic children less than 13 years of age were randomized. Of the children randomized, 369 were included in the efficacy analysis and 376 in the safety analysis. The study population had 1) a mean age of 40 months (range 2.4 - 136.8 months), 2) acquired HIV primarily through vertical transmission (91%), 3) a majority (82%) of CDC Class P-2 (symptomatic), and 4) had a median CD4+ count of 937 cells/mm^3 (range 0 - 6660 cells/mm^3). At the time of study entry, 14% (52 of 369) were receiving *Pneumocystis carinii* pneumonia (PCP) prophylaxis. During the course of the study, 51% (189 of 369) received PCP prophylaxis and 44% (164 of 369) received zidovudine (ZDV). Children with HIV-1 infection were initially stratified into two groups based upon CD4+ count (< 200 cells/mm^3 versus ≥ 200 cells/mm^3) and CDC classification of pediatric HIV disease (history of opportunistic infections [P-2-D-1] and recurrent serious bacterial infections [P-2-D-2] versus others). Subjects received GAMIMUNE® N, 5% (400 mg/kg = 8 mL/kg) (n=185) or an equivalent volume of placebo (0.1% Albumin [Human]) (n=184) every 28 days. The mean follow-up for subjects receiving GAMIMUNE® N, 5% was 17.9 months and 17.6 months for patients on placebo.

The number of subjects who had at least one serious bacterial infection was 86 of 184 (47%) in the placebo group and 55 of 185 (30%) in the GAMIMUNE® N, 5%

group (p=0.0009). All p-values reported are two-sided. Treatment with GAMIMUNE® N, 5% compared to placebo was also associated with a significant reduction in both the number of subjects with at least one laboratory-proven infection (36 of 184 vs. 18 of 185, p = 0.0081), and the number of subjects with at least one clinically diagnosed infection (71 of 184 vs 45 of 185, p=0.0036). Efficacy in patients with CD4+ counts < 200/mm^3 was not established, possibly because of the small number of subjects in this category.

The 2-year treatment period defined in the protocol was truncated for some patients by the DSMB based on data from the interim analysis. Rates of serious bacterial infections per 100 patient-years were computed and analyzed to take into account both the unequal duration of treatment and follow-up, as well as recurrent infections in individual subjects.

Children treated with GAMIMUNE® N, 5% experienced a 50.0% lower frequency of laboratory-proven serious bacterial infection compared to the group treated with placebo (9.1 vs. 18.2 infections per 100 patient years, p = 0.031), a 36.0% lower frequency of clinically diagnosed serious infections (24.0 vs. 37.5 infections per 100 patient years, p = 0.003), a 40.6% reduction in total serious infections (laboratory proven and clinically diagnosed) (33.1 vs. 55.7 infections per 100 patient years, p = 0.009), a 60% lower frequency of primary bacteremia (5.8 vs. 14.5 infections per 100 patient years, p = 0.009), a 75.5% lower frequency of *Streptococcus pneumoniae* bacteremia (1.1 vs. 4.4 bacteremias per 100 patient years, p = 0.026), a 54.3% lower frequency of clinically diagnosed pneumonias (12.7 vs. 27.8 infections per 100 patient years, p = 0.001), and a 22.5% lower frequency of minor bacterial infections (including otitis media, skin and soft tissue infections, and upper respiratory tract infections) (123.6 vs. 159.5 infections per 100 patient years, p = 0.033).

In addition to a reduced frequency of infection, children treated with GAMIMUNE® N, 5% had a 36.8% lower number of hospitalizations per 100 patient years (72 vs.

114 per 100 patient years, p = 0.002) and a reduced average annual number of hospital days (6.9 vs. 10.5, p = 0.030) than patients treated with placebo. In addition, GAMIMUNE® N, 5% treated patients had a higher probability of remaining free of laboratory proven infections (p = 0.0093) and combined laboratory proven and clinically diagnosed infections (p = 0.0015) for 24 months than the group treated with placebo. At 24 months, the estimated probabilities of remaining infection-free for the Immune Globulin Intravenous (Human), and placebo arms were 87.8% vs. 76.0% respectively, for laboratory proven infections and 63.5% vs. 44.5% respectively, for combined laboratory proven and clinically diagnosed infections.

There was no effect of GAMIMUNE® N, 5% therapy on mortality, which was low in all study groups, or on frequency of opportunistic infection, regardless of treatment group.

This study was not designed to evaluate possible interactions between GAMIMUNE® N, 5% and trimethoprim/sulfamethoxazole (TMP-SMZ) but a study by Spector et al[28] did prospectively stratify patients receiving TMP-SMZ. However, the Bayer study stratified patients based on CD4+ counts < 200/mm^3 and/or HIV defining infection vs CD4+ counts > 200/mm^3 and no HIV defining infection . In actuality, these two different stratification schemes probably selected for nearly the same subgroups (namely less vs more ill). In both studies, the effect of GAMIMUNE® N, 5% was less apparent in the more ill group (i.e., CD4+ count < 200/mm^3 group in the Bayer study, TMP-SMZ group in the Spector study). When a statistical correction was applied to the Bayer database to assess the effect of TMP-SMZ on GAMIMUNE® N, 5%, there was no interaction specifically seen.

CONTRAINDICATIONS

Immune Globulin Intravenous (Human), 5% - GAMIMUNE® N, 5% and Immune Globulin Intravenous (Human), 10% - GAMIMUNE® N, 10% are contraindicated

in individuals who are known to have had an anaphylactic or severe systemic response to Immune Globulin (Human). Individuals with selective IgA deficiencies who have known antibody against IgA (anti-IgA antibody) should not receive GAMIMUNE® N, 5% and 10% since these patients may experience severe reactions to the IgA which may be present.[21]

WARNINGS

Immune Globulin Intravenous (Human) products have been reported to be associated with renal dysfunction, acute renal failure, osmotic nephrosis and death. Patients predisposed to acute renal failure include patients with any degree of pre-existing renal insufficiency, diabetes mellitus, age greater than 65, volume depletion, sepsis, paraproteinemia, or patients receiving known nephrotoxic drugs. Especially in such patients, IGIV products should be administered at the minimum concentration available and the minimum rate of infusion practicable. While these reports of renal dysfunction and acute renal failure have been associated with the use of many of the licensed IGIV products, those containing sucrose as a stabilizer accounted for a disproportionate share of the total number.

See PRECAUTIONS and DOSAGE and ADMINISTRATION sections for important information intended to reduce the risk of acute renal failure.

Immune Globulin Intravenous (Human) 5% - GAMIMUNE® N, 5% and Immune Globulin Intravenous (Human), 10% - GAMIMUNE® N, 10% are made from human plasma. Products made from human plasma may contain infectious agents, such as viruses, that can cause disease. The risk that such products will transmit an infectious agent has been reduced by screening plasma donors for prior exposure to certain viruses, by testing for the presence of certain current virus infections, and by inactivating and/or removing certain

viruses. Despite these measures, such products can still potentially transmit disease. There is also the possibility that unknown infectious agents may be present in such products. Individuals who receive infusions of blood or plasma products may develop signs and/or symptoms of some viral infections, particularly hepatitis C. ALL infections thought by a physician possibly to have been transmitted by this product should be reported by the physician or other healthcare provider to Bayer Inc. at 1-800-265-7382.

The physician should discuss the risks and benefits of this product with the patient, before prescribing or administering to the patient.

GAMIMUNE® N, 5% and GAMIMUNE® N, 10% should be administered only intravenously, as the intramuscular and subcutaneous routes have not been evaluated.

Immune Globulin Intravenous (Human), 5% - GAMIMUNE® N, 5% has, on rare occasions, caused a precipitous fall in blood pressure and a clinical picture of anaphylaxis, even when the patient is not known to be sensitive to immune globulin preparations. These reactions may be related to the rate of infusion. Accordingly, the infusion rate given under DOSAGE AND ADMINISTRATION for GAMIMUNE® N, 5% and 10% should be closely followed, at least until the physician has had sufficient experience with a given patient. The patient's vital signs should be monitored continuously and careful observation made for any symptoms throughout the entire infusion. Epinephrine should be available for the treatment of an acute anaphylactic reaction.

PRECAUTIONS

General

Any vial that has been entered should be used promptly. Partially used vials should be discarded. Do not use if turbid. Solution which has been frozen should not be used.

In patients with limited or compromised acid-base compensatory mechanisms and in patients in whom there is already an expanded fluid volume (e.g. during pregnancy), consideration should be given to the effect of the additional acid or protein load that Immune Globulin Intravenous (Human), 5% and 10% - GAMIMUNE® N, 5% and 10% may present.

An aseptic meningitis syndrome (AMS) has been reported to occur infrequently in association with Immune Globulin Intravenous (Human) (IGIV) treatment. The syndrome usually begins within several hours to two days following IGIV treatment. It is characterized by symptoms and signs including severe headache, nuchal rigidity, drowsiness, fever, photophobia, painful eye movements, and nausea and vomiting. Cerebrospinal fluid studies are frequently positive with pleocytosis up to several thousand cells per cu.mm., predominantly from the granulocytic series, and elevated protein levels up to several hundred mg/dL. Patients exhibiting such symptoms and signs should receive a thorough neurological examination, including CSF studies, to rule out other causes of meningitis. AMS may occur more frequently in association with high dose (2 g/kg) IGIV treatment. Discontinuation of IGIV treatment has resulted in remission of AMS within several days without sequelae. [29-32]

Isolated reports have appeared of transient and reversible renal insufficiency following administration of Immune Globulin Intravenous therapy. [34, 35] The mechanics involved are uncertain.

There is a possible association between thrombo-embolic events and administration of Immune Globulin Intravenous (Human) (IGIV) products. Caution should be

exercised in administration of IGIV in patients with coagulopathies, cardiovascular disease, thrombophilia, restricted mobility, and the elderly.

Drug Interactions

Antibodies in Immune Globulin Intravenous (Human), 5% - GAMIMUNE® N, 5% and Immune Globulin Intravenous (Human),10% - GAMIMUNE® N, 10% may interfere with the response to live viral vaccines such as measles, mumps and rubella. Therefore, use of such vaccines should be deferred until approximately six months after GAMIMUNE® N, 5% and 10% administration.

Please see **DOSAGE AND ADMINISTRATION** for other drug interactions.

Pregnancy

Animal reproduction studies have not been conducted with GAMIMUNE® N, 5% and 10%. It is not known whether GAMIMUNE® N, 5% and 10% can cause fetal harm when administered to a pregnant woman or can affect reproduction capacity. GAMIMUNE® N, 5% and 10% should be given to a pregnant woman only if benefits outweigh risks.

ADVERSE REACTIONS

In a study of 37 patients with immunodeficiency syndromes receiving Immune Globulin Intravenous (Human), 5% - GAMIMUNE® N, 5%, at a monthly dose of 400 mg/kg body weight, reactions were seen in 5.2% of the infusions. Symptoms reported included malaise, a feeling of faintness, fever, chills, headache, nausea, vomiting, chest tightness, dyspnea and chest, back or hip pain. Mild erythema following infiltration of GAMIMUNE® N, 5% at the infusion site was reported in some cases.[1] A safety study has been conducted in 16 adult and adolescent subjects with primary immunodeficiency syndrome, comparing the side effects and bioequivalency of GAMIMUNE® N, 5% with those of GAMIMUNE® N, 5% treated with solvent/detergent. The incidence, nature and severity of reactions with GAMIMUNE® N, 5% treated with solvent/detergent were not different from those observed with GAMIMUNE® N, 5%.

A safety study has been conducted in 20 adult and pediatric subjects with primary immunodeficiency syndrome comparing side effects of Immune Globulin Intravenous (Human), 5% - GAMIMUNE® N, 5% with those of Immune Globulin Intravenous (Human), 10% - GAMIMUNE® N, 10%. The incidence, nature, or severity of reactions with GAMIMUNE® N, 10% were not different from those observed with GAMIMUNE® N, 5%, and were consistent with those observed in previous studies with GAMIMUNE® N, 5%. Symptoms related to the infusion of GAMIMUNE® N, 10% were observed in 9 (3.5%) of 255 infusions. These symptoms were all mild to moderate in severity and included chills, fever, headache and emesis.

A safety study has been conducted in 17 adult and adolescent subjects with primary immunodeficiency syndrome, comparing side effects and bioequivalency of GAMIMUNE® N, 10% with those of GAMIMUNE® N, 10% treated with solvent/detergent. The incidence, nature and severity of reactions with

GAMIMUNE® N, 10% treated with solvent/detergent were not different from those observed with GAMIMUNE® N, 10%.

In studies of GAMIMUNE® N, 5% administered at a dose of 400 mg/kg body weight in the treatment of adult and pediatric patients with ITP, systemic reactions were noted in only 4 of 154 (2.6%) infusions, and all but one occurred at rates of infusion greater than 0.04 mL/kg body weight per minute.[1] The symptoms reported included chest tightness, a sense of tachycardia (pulse was 84 beats per minute), and a burning sensation in the head; these symptoms were all mild and transient.

In studies of GAMIMUNE® N, 5% administered at a dose of 1,000 mg/kg body weight either as a single dose or as two doses on consecutive days in the treatment of adult and paediatric patients with ITP, adverse reactions were noted in only 25 of 251 (10%) infusions. Symptoms reported included headache, nausea, fever, chills, back pain, chest tightness, and shortness of breath. In children, the high dose regimen has been well-tolerated at the highest rates of infusion. In adults, however, the frequency of adverse reactions tended to increase with infusion rates in excess of 0.06 mL/kg/minute. In general, reactions reported with infusion of GAMIMUNE® N, 5% in these studies were reported as mild or moderate.

An investigation of GAMIMUNE® N, 10% in 31 adult and pediatric subjects with ITP encountered side effects in 17 of 119 (14.3%) infusions. The dosage in these studies was 1,000 mg/kg body weight for 1 day or 2 consecutive days. However, in the adult study, an induction dosage of 500 mg/kg body weight for 1 day or 2 consecutive days was associated with 17 of these infusions. Of those 17 infusions, three had adverse events. Overall side effects included mild chest pain, mild and moderate emesis, moderate fever, mild or moderate headache (severe on one occasion) and a single incidence of hives, pruritus and rash. At least 17 of the

50 infusions in the pediatric study were given at rates of ≥0.1 mL/kg body weight per minute as part of a rate escalation investigation. Maximum infusion rates obtained were not limited by or interrupted due to adverse effects.

In studies of GAMIMUNE® N, 5% administered to 185 bone marrow transplant recipients at doses of 500 mg/kg (10 mL/kg) from day -7 and day -2 pretransplant then weekly through day 90 post transplant, adverse reactions were noted in 12 (6.5%) of the 185 treated patients and in 14 (0.6%) of 2,176 infusions. All reactions reported were rate-related and classified as mild. Chills were the most common symptom reported, occurring in 9 patients. The other symptoms reported included headache, flushing, fever, pruritis and slight back discomfort. All reactions resolved satisfactorily, usually without treatment or decreasing the infusion rate.

In a study with pediatric HIV infection patients, three hundred seventy-six (376) patients, 187 treated with GAMIMUNE® N, 5% 400 mg/kg, and 189 treated with placebo [0.1% Albumin (Human)], were evaluated for safety. Adverse reactions occurred during or within 24 hours of an infusion in 50 of 3,451 (1.4%) infusions of GAMIMUNE® N, 5% and 62 of 3,447 (1.8%) infusions of placebo. Fever was the most common symptom reported for both groups treated with placebo and GAMIMUNE® N, 5% with 30 of 105 (28.6%) reported symptoms and 19 of 78 (24.4%) reported symptoms, respectively. Irritability was the second most common symptom reported, with 10 (9.5%) reports for the placebo group and 9 (11.5%) for the group treated with GAMIMUNE® N, 5%. A large number of diverse symptoms accounted for the remaining symptoms in both groups. In general, the number of adverse events reported was comparable in both the placebo and GAMIMUNE® N, 5% treated groups. Three serious adverse reactions were reported. One patient experienced a hypersensitivity reaction and did not receive further GAMIMUNE® N, 5% treatment. A second patient developed tachycardia and was admitted to an intensive care unit, but later

continued treatment with GAMIMUNE® N, 5%. A third patient had skin infiltration during infusion and developed a full thickness skin slough over the dorsum of the hand that required skin grafting.

In the studies undertaken to date, other types of reactions have not been reported with GAMIMUNE® N, 5% or GAMIMUNE® N, 10%. It may be, however, that adverse effects will be similar to those previously reported with intravenous and intramuscular immunoglobulin administration. Potential reactions, therefore, may also include anxiety, flushing, wheezing, abdominal cramps, myalgias, arthralgia, and dizziness; rash has been reported only rarely. Very rarely have there been cases reported of severe injection site reactions. Reactions to intravenous immunoglobulin tend to be related to the rate of infusion.

True anaphylactic reactions to GAMIMUNE® N, 5% and 10% may occur in recipients with documented prior histories of severe allergic reactions to intramuscular immunoglobulin, but some patients may tolerate cautiously administered intravenous immunoglobulin without adverse effects. [1, 33] Very rarely an anaphylactoid reaction may occur in patients with no prior history of severe allergic reactions to either intramuscular or intravenous immunoglobulin. [1]

DOSAGE AND ADMINISTRATION

General

For intravenous use only. Dosages for specific indications are indicated below, but in general, it is recommended that Immune Globulin Intravenous (Human), 5% - GAMIMUNE® N, 5% and Immune Globulin Intravenous (Human), 10% - GAMIMUNE® N, 10% be infused by itself at an initial rate of 0.01 to 0.02 mL/kg body weight per minute for 30 minutes; if well-tolerated, the rate may be **gradually** increased to a maximum of 0.06 mL/kg body weight per minute. Investigations indicate that GAMIMUNE® N, 5% and 10% are well-tolerated and

less likely to produce side effects when infused at the recommended rate. If side effects occur, the rate may be reduced, or the infusion interrupted until symptoms subside. The infusion may then be resumed at the rate which is comfortable for the patient. Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit.

It is recommended that infusion of GAMIMUNE® N, 5% and 10% be given by a separate line, by itself, without mixing with other intravenous fluids or medications the patient might be receiving. GAMIMUNE® N, 5% and 10% should not be mixed with Immune Globulin Intravenous (Human), from another manufacturer. GAMIMUNE® N, 5% and 10% are not compatible with saline. If dilution is required, GAMIMUNE® N, 5% and 10% may be diluted with 5% dextrose in water (D5/W). No other drug interactions or compatibilities have been evaluated.

In patients with limited or compromised acid-base compensatory mechanisms and in patients in whom there is already an expanded fluid volume (eg. during pregnancy), consideration should be given to the effect of the additional acid or protein load that intravenous GAMIMUNE® N, 5% and 10% might present. Only 18 gauge needles should be used to penetrate the stopper for dispensing product from 10 mL vial sizes; 16 gauge needles should only be used with 20 mL vial sizes and larger. Needles should only be inserted within the stopper area dilineated by the raised ring. The stopper should be penetrated perpendicular to the plane of the stopper within the ring.

A number of factors beyond our control could reduce the efficacy of this product or even result in an ill effect following its use. These include improper storage and handling of the product after it leaves our hands, diagnosis, dosage, method of administration, and biological differences in individual patients. Because of

these factors, it is important that this product be stored properly and that the directions be followed carefully during use.

Primary Humoral Immunodeficiency

The usual dosage of GAMIMUNE® N, 5% and 10% for prophylaxis in primary immunodeficiency syndromes is 100-200 mg/kg of body weight administered approximately once a month by intravenous infusion. The dosage may be given more frequently or increased as high as 400 mg/kg body weight, if the clinical response is inadequate, or the level of IgG achieved in the circulation is felt to be insufficient. The minimum level of IgG required for protection has not been determined.

Idiopathic Thrombocytopenic Purpura (ITP)

Induction: An increase in platelet count has been observed in children and some adults with acute or chronic ITP receiving Immune Globulin Intravenous (Human) - GAMIMUNE® N, 5%, 400 mg/kg body weight daily for five days. Alternatively, studies in adults and children with GAMIMUNE® N, 5% and GAMIMUNE® N, 10% using a dose of 1,000 mg/kg body weight daily for 1 day or 2 consecutive days have also shown increases in platelet count. In the latter treatment regimen, if an adequate increase in the platelet count is observed at 24 hours, the second dose of 1,000 mg/kg body weight may be withheld. The high dose regimen (1,000 mg/kg x 1 - 2 days) is not recommended for individuals with expanded fluid volumes or where fluid volume may be a concern. With both treatment regimens, a response usually occurs within several days and is maintained for a variable period of time. In general, a response is seen less often in adults than in children.

Maintenance: In adults and children with ITP, if after induction therapy the platelet count falls to a level felt to be insufficient for the protection or normal function of the patient and/or the patient manifests clinically significant bleeding,

GAMIMUNE® N, 5% and 10%, 400 mg/kg body weight may be given as a single infusion. If an adequate response does not result, the dose can be increased to 800-1,000 mg/kg of body weight given as a single infusion. Maintenance infusions may be administered intermittently as clinically indicated to maintain an adequate platelet count.

Allogeneic Bone Marrow Transplantation

GAMIMUNE® N, 5% and 10% should be administered in doses of 500 mg/kg body weight beginning on days -7 and -2 pretransplant (or at the time conditioning therapy for transplantation is begun), then weekly through day 90 posttransplant. GAMIMUNE® N, 5% and 10% may be administered by itself through a Hickman line while it is in place, and thereafter through a peripheral vein.

Pediatric HIV Infection

A reduction in the incidence of infections has been observed in children infected with the HIV virus whose CD4+ counts are ≥ 200 mm^3. GAMIMUNE® N, 5% should be administered at a dose of 400 mg/kg (8 mL/kg) body weight every 28 days.

PHARMACEUTICAL INFORMATION

Immune Globulin Intravenous (Human), 5% - GAMIMUNE® N, 5% treated with solvent/detergent, is a sterile 4.5 - 5.5% solution of human protein in 9-11% maltose; it contains no preservative. Each millilitre (mL) contains approximately 50 mg of protein, not less than 98% of which has the electrophoretic mobility of gamma globulin and approximately 100 mg maltose. Not less than 90% of the immunoglobulin is monomer. Also present are traces of IgA and of IgM. The distribution of IgG subclasses is similar to that found in normal serum. GAMIMUNE® N, 5% has a buffer capacity of 16.5 mEq/L of solution (~0.3

mEq/g of protein). The calculated osmolality is 309 milliosmoles per kilogram of solvent (water) and the calculated osmolarity is 278 milliosmoles per litre of solution.

Immune Globulin Intravenous (Human), 10% - GAMIMUNE® N, 10% treated with solvent/detergent is a sterile solution of human protein containing no preservative. GAMIMUNE® N, 10% consists of 9 - 11% protein in 0.16 - 0.24 M glycine. Each millilitre (mL) contains approximately 100 mg of protein, not less than 98% of which has the electrophoretic mobility of gamma globulin, and approximately 12-18 mg glycine. Not less than 90% of the IgG is monomer. Also present are traces of IgA and of IgM. The distribution of IgG subclasses is similar to that found in normal serum. The measured buffer capacity is 35 mEq/L and the osmolality is 274 mOsmol/kg solvent.

The products are made by cold ethanol fractionation of large pools of human plasma. Part of the fractionation may be performed by another licensed manufacturer. The immunoglobulin is isolated from Cohn Effluent III by diafiltration and ultrafiltration. The solution is adjusted to 0.3 - 0.4% tri-n-butyl phosphate (TNBP) and 0.2 - 0.3% sodium cholate. After addition of the solvent (TNBP) and the detergent (sodium cholate), the solution is heated at 30° C and maintained at that temperature for not less than 6 hours. After the viral inactivation step the reactants are removed by precipitation, filtration and finally diafiltration and ultrafiltration. The protein has not been chemically modified other than in the adjustment of the pH of the solution to 4.0 - 4.5 [36] Isotonicity is achieved by the addition of maltose, for GAMIMUNE® N, 5%, or glycine for GAMIMUNE® N, 10%. GAMIMUNE® N, 5% and 10% treated with solvent/detergent are then incubated in the final container (at the low pH of 4.25), for a minimum of 21 days at 20° C. The products are intended for intravenous administration.

The removal and inactivation of spiked model enveloped and non-enveloped viruses during the manufacturing process for GAMIMUNE® N, 5% and 10% has been validated in laboratory studies.[1] Human Immunodeficiency Virus, Type 1 (HIV-1) was chosen as the relevant virus for blood products; Bovine Viral Diarrhea Virus (BVDV) was chosen to model for Hepatitis C Virus; Pseudorabies Virus (PRV) was chosen to model for Hepatitis B and Herpes viruses; and Reo Virus type 3 (Reo) was chosen to model non-enveloped viruses and for its resistance to physical and chemical inactivation. Significant removal of model enveloped and non-enveloped viruses is seen between the Fraction II + IIIW and the Effluent III steps and between the Effluent III and the Filtrate III steps. Significant reduction of enveloped viruses is achieved at the time of treatment of Filtrate III with TNBP/sodium cholate and also at the time of the low pH incubation in the final container.

Storage

Store at 2-8° C (36-46°F). Do not freeze. Do not use after expiration date.

AVAILABILITY OF DOSAGE FORMS

Immune Globulin Intravenous (Human), 5% - GAMIMUNE® N, 5% is supplied as single use vials in the following sizes:

Size	Protein (g)
10 mL	0.5
20 mL	1.0
50 mL	2.5
100 mL	5.0
250 mL	12.5
500 mL	25.0

Immune Globulin Intravenous (Human), 10% - GAMIMUNE® N, 10% is supplied as single use vials in the following sizes:

Size	**Protein (g)**
10 mL	1.0
25 mL	2.5
50 mL	5.0
100 mL	10.0
200 mL	20.0

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