Immune Globulin Intravenous [Human], 10%, Caprylate/Chromatography Purified

GAMUNEX®

DESCRIPTION

Immune Globulin Intravenous (Human), 10% Caprylate/Chromatography Purified (GAMUNEX®) is a ready-to-use sterile solution of human immune globulin protein for intravenous administration. GAMUNEX® consists of 9%–11% protein in 0.16–0.24 M glycine. Not less than 98% of the protein has the electrophoretic mobility of gamma globulin. GAMUNEX® contains trace levels of fragments and IgA (average 0.046 mg/mL). IgM levels were at or below the limit of quantitation (0.002 g/L). 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 258 mOsmol/kg solvent, which is close to physiological osmolality (285-295 mOsmol/kg). The pH of GAMUNEX® is 4.0 – 4.5. GAMUNEX® contains no preservative.

GAMUNEX® is made from large pools of human plasma by a combination of cold ethanol fractionation, caprylate precipitation and filtration, and anion-exchange chromatography. Two of the four ethanol fractionation steps of the Cohn-Oncley process have been replaced by tandem anion-exchange chromatography. The IgG proteins are not subjected to heating or chemical or enzymatic modification steps. Fc and Fab functions of the IgG molecule are retained, but do not activate complement or pre-Kallikrein activity in an unspecific manner. The protein is stabilized during the process by adjusting the pH of the solution to 4.0-4.5. Isotonicity is achieved by the addition of glycine. GAMUNEX® is incubated in the final container (at the low pH of 4.0 – 4.3), for a minimum of 21 days at 23° to 27°C. The product is intended for intravenous administration.

The capacity of the manufacturing process to remove and/or inactivate enveloped and non-enveloped viruses has been validated by laboratory spiking studies on a scaled down process model, using the following enveloped and non-enveloped viruses: human immunodeficiency virus, type I (HIV-1) as the relevant virus for HIV-1 and HIV–2; bovine viral diarrhea virus (BVDV) as a model for hepatitis C virus; pseudorabies virus (PRV) as a model for large DNA viruses (e.g. herpes viruses); Reo virus type 3 (Reo) as a model for non-enveloped viruses and for its resistance to physical and chemical inactivation; hepatitis A virus (HAV) as relevant non-enveloped virus, and porcine parvovirus (PPV) as a model for human parvovirus B19.

The following process steps contribute to virus inactivation and/or removal: caprylate precipitation/cloth filtration, caprylate incubation, column chromatography and final container low pH incubation. Caprylate is the basis of two mechanistically distinct virus clearance steps, the caprylate precipitation/cloth filtration step and the caprylate incubation step. During the caprylate precipitation/cloth filtration step, protein impurities and potential

enveloped or non-enveloped viral contaminants are precipitated by caprylate and the precipitate is removed from the product stream by filtration through a cloth filter. In a subsequent step, enveloped viruses are inactivated during incubation with caprylate. The table below presents the contribution of each process step to virus reduction and the overall process reduction. Virus removal steps were evaluated independently and in combination to identify those steps, which were mechanistically distinct. Overall virus reduction was calculated only from steps that were mechanistically independent from each other and truly additive. In addition, each step was verified to provide robust virus reduction across the production range for key operating parameters.

Log_{10} Virus Reduction

Process Step	Log_{10} Virus Reduction					
	Enveloped Viruses			Non-enveloped Viruses		
	HIV	PRV	BVDV	Reo	HAV	PPV
Caprylate Precipitation / Cloth Filtration	C/I[a]	C/I	2.4 ± 0.3	2.1 ± 0.4	2.6 ± 0.2	2.2 ± 0.1
Caprylate Incubation	≥ 4.5	≥ 4.6	≥ 4.5	NA[b]	NA	NA
Depth Filtration[d]	CAP[c]	CAP	CAP	≥4.3	≥2.0	3.3 ± 0.3
Column Chromatography	≥3.0	≥3.3	4.0 ± 0.3	≥4.0	≥1.4	4.2 ± 0.2
Low pH Incubation (21 days)	≥6.5	≥4.3	3.5 ± 0.4	NA	NA	NA
Global Reduction	[3] **14.0**	[3] **12.2**	[3] **14.4**	[3] **6.1**	[3] **4.0**	**6.4**

[a] C/I - Interference by caprylate precluded determination of virus reduction for this step. Although removal of viruses is likely to occur at the caprylate precipitation/ cloth filtration step, BVDV is the only enveloped virus for which reduction is claimed. The presence of caprylate prevents detection of other, less resistant enveloped viruses and therefore their removal cannot be assessed.

[b] Not Applicable – This step has no effect on non-enveloped viruses .

[c] CAP - The presence of caprylate in the process at this step prevents detection of enveloped viruses, and their removal cannot be assessed.

[d] Some mechanistic overlap occurs between depth filtration and other steps. Therefore, Bayer has chosen to exclude this step from the global virus reduction calculations.

CLINICAL PHARMACOLOGY

Primary Humoral Immunodeficiency (PI)

In a double-blind, randomized, parallel group clinical trial with 172 subjects with primary humoral immunodeficiencies (study 100175) GAMUNEX® (Immune Globulin Intravenous (Human), 10% Caprylate/Chromatography Purified) was demonstrated to be at least as efficacious as GAMIMUNE® N in the prevention of any infection, i.e. validated plus clinically defined, non-validated infections of any organ system, during a nine month treatment period. Twenty six subjects were excluded from the Per Protocol analysis (2 due to non-compliance and 24 due to protocol violations). The primary efficacy endpoint was the proportion of subjects with at least one of the following validated infections: pneumonia, acute sinusitis and acute exacerbations of chronic sinusitis.

Primary Endpoint Per Protocol Analysis (Study 100175)

	GAMUNEX® (n=73) No. of subjects with at least one infection	GAMIMUNE® N (n=73) No. of subjects with at least one infection	Mean Difference (90% confidence interval)	p-Value
Validated Infections	9 (12%)	17 (23%)	-0.117 (-0.220, -0.015)	0.06
Acute Sinusitis	4 (5%)	10 (14%)		
Exacerbation of Chronic Sinusitis	5 (7%)	6 (8%)		
Pneumonia	0 (0%)	2 (3%)		
Any Infection (Validated plus Clinically defined non-validated Infections)	56 (77%)	57(78%)	-0.020 (-0.135, 0.096)	0.78

The annual rate of validated infections (Number of Infection/year/subject) was 0.18 in the group treated with GAMUNEX® and 0.43 in the group treated with GAMIMUNE® N, 10% (p=0.023). The annual rates for any infection (validated plus clinically-defined, non-validated infections of any organ system) were 2.88 and 3.38, respectively (p=0.300). [1, 2]

A post hoc analysis of serious infection events during the trial showed five (5) cases of clinically defined pneumonia occurred in 4 GAMUNEX® treated subjects and 11 cases of validated or clinically defined pneumonia occurred in 9 GAMIMUNE® N 10% treated subjects and 1 case of sepsis occurred in GAMIMUNE® N 10%. The annual infection rate and 98% confidence interval for serious infections are:

Post Hoc Analysis of Serious Infections*(Study 100175)

	GAMUNEX® (n=73) Annual Infection Rate (Infections/year/subject); 98% Confidence Interval	GAMIMUNE® N (n=73) Annual Infection Rate (Infections/year/subject) 98% Confidence Interval
Serious Infections (Validated and clinically defined Pneumonia, Sepsis)	0.07 (0[1] - 0.16)	0.18 (0.06 - 0.32)

*****The definition of Serious Infections was any of the following: validated plus clinically-defined, non-validated pneumonia, bacteremia/sepsis, osteomyelitis/septic arthritis, visceral abscess, bacterial and/or viral meningitis; however, only pneumonia and sepsis were observed.

[1]The actual lower limit was less than 0, but this is not a plausible value

As a secondary endpoint, consequences of infections were recorded and are displayed in the table below:

Secondary Endpoint Clinical Outcomes (Study 100175)

	GAMUNEX® No. of patient days on study: 21479	GAMIMUNE® N No. of patient days on study: 21388
Days on prophylactic antibiotics	3078 (14.4%)	4305 (20.1%)
Days on therapeutic antibiotics	2157 (10.0%)	2494 (11.7%)
Days off school/work	240 (1.1%)	230 (1.1%)

Days with visits of physician's office or emergency room	148 (0.7%)	174 (0.8%)
Hospitalization days	38 (0.2%)	71 (0.3%)

Two randomized pharmacokinetic crossover trials were carried out with GAMUNEX® in 38 subjects with Primary Humoral Immunodeficiencies given 3 infusions 3 or 4 weeks apart of test product at a dose of 100-600 mg/kg body weight per infusion. One trial compared the pharmacokinetic characteristics of GAMUNEX® to GAMIMUNE® N 10% (Immune Globulin Intravenous (Human), 10%) (study 100152) and the other trial compared the pharmacokinetics of GAMUNEX® (10% strength) with a 5% concentration of this product (study 100174). The ratio of the geometric least square means for dose-normalized IgG peak levels of GAMUNEX® and GAMIMUNE® N was 0.996. The corresponding value for the dose-normalized area under the curve (AUC) of IgG levels was 0.990. The results of both PK parameters were within the pre-established limits of 0.080 and 1.25. Similar results were obtained in the comparison of GAMUNEX®10% to a 5% concentration of GAMUNEX®. [3, 4]
The main pharmacokinetic parameters of GAMUNEX®, measured as total IgG in study 100152 are displayed below:

PK Parameters of GAMUNEX® and GAMIMUNE® N 10% (Study 100152)

	GAMUNEX®				GAMIMUNE® N 10%			
	N	Mean	SD	Median	N	Mean	SD	Median
Cmax (mg/mL)	17	19.04	3.06	19.71	17	19.31	4.17	19.30
Cmax-norm (kg/mL)	17	0.047	0.007	0.046	17	0.047	0.008	0.047
AUC(0-tn)[a] (mg*hr/mL)	17	6746.48	1348.13	6949.47	17	6854.17	1425.08	7119.86
AUC(0-tn)norm[a] (kg*hr/mL)	17	16.51	1.83	16.95	17	16.69	2.04	16.99
$T_{1/2}$[b] (days)	16	35.74	8.69	33.09	16	34.27	9.28	31.88

[a]Partial AUC: defined as pre-dose concentration to the last concentration common across both treatment periods in the same patient.
[b]only 15 subjects were valid for the analysis of $T_{1/2}$

The two pharmacokinetic trials with GAMUNEX® show the IgG concentration/time curve follows a biphasic slope with a distribution phase of about 5 days characterized by a fall in serum IgG levels to about 65-75% of the peak levels achieved immediately post-infusion. This phase is followed by the elimination phase with a half-life of approximately 35 days [3, 4]. IgG trough levels were measured over nine months in the therapeutic equivalence trial (100175). Mean trough levels were 7.8 +/- 1.9 mg/mL for the GAMUNEX® treatment group and 8.2 +/- 2.0 mg/mL for the GAMIMUNE® N, 10% control group [1].

Idiopathic Thrombocytopenic Purpura (ITP)

The mechanism of action of high doses of immunoglobulins in the treatment of Idiopathic Thrombocytopenic Purpura (ITP) has not been fully elucidated.

Several lines of evidence suggest that Fc-receptor blockade of phagocytes as well as down regulation of auto-reactive B-cells by antiidiotypic antibodies provided by IGIV may constitute the main mechanisms of action [5-10].
A double-blind, randomized, parallel group clinical trial with 97 ITP subjects was carried out to prove the hypothesis that GAMUNEX® was at least as effective as GAMIMUNE® N, 10% in raising platelet counts from less than or equal to 20 $x10^9$/L to more than 50 $x10^9$/L within 7 days after treatment with 2 g/kg IGIV (study 100176). Twenty-four percent of the subjects were less than or equal to 16 years of age.

GAMUNEX® was demonstrated to be at least as effective as GAMIMUNE® N, 10% in the treatment of adults and children with acute or chronic ITP.[11]

Platelet Response of Per Protocol Analysis (Study 100176)

	GAMUNEX® (n=39)	GAMIMUNE® N (n=42)	Mean Difference (90% confidence interval)
By Day 7	35 (90%)	35 (83%)	0.075 (-0.037, 0.186)
By Day 23	35 (90%)	36 (86%)	0.051 (-0.058, 0.160)
Sustained for 7 days	29 (74%)	25 (60%)	0.164 (0.003, 0.330)

A trial was conducted to evaluate the clinical response to rapid infusion of GAMUNEX® in patients with ITP. The study involved 28 chronic ITP subjects, wherein the subjects received 1 g/kg GAMUNEX® on three occasions for treatment of relapses. The infusion rate was randomly assigned to 0.08, 0.11, or 0.14 mL/kg/min (8, 11 or 14 mg/kg/min). Pre-medication with corticosteroids to alleviate infusion-related intolerability was not permitted. Pre-treatment with antihistamines, anti-pyretics and analgesics was permitted. The average dose was approximately 1 g/kg body weight at all three prescribed rates of infusion (0.08, 0.11 and 0.14 mL/kg/min). All patients were administered each of the three planned infusions except seven subjects. Based on 21 patients per treatment group, the a posteriori power to detect twice as many drug-related adverse events between groups was 23%. Of the seven subjects that did not complete the study, five did not require additional treatment, one withdrew because he refused to participate without concomitant medication (prednisone) and one experienced an adverse event (hives); however, this was at the lowest dose rate level (0.08 mL/kg/min).

General

GAMUNEX® supplies a broad spectrum of opsonic and neutralizing IgG antibodies against bacteria or their toxins, which were demonstrated to be effective in the prevention or attenuation of lethal infections in animal models. GAMUNEX® proved to be effective in preventing severe infections in patients with Primary Humoral Immunodeficiency (PI).

Glycine (aminoacetic acid) is a nonessential amino acid normally present in the body. Glycine is a major ingredient in amino acid solutions employed in intravenous alimentation [12]. While toxic effects of glycine administration have been reported [13], the doses and rates of administration were 3 – 4 fold greater than those for GAMUNEX®. In another study it was demonstrated that intravenous bolus doses of 0.44 g/kg glycine were not associated with serious adverse effects [14]. GAMUNEX® doses of 1 g/kg correspond to a glycine dose of 0.15 g/kg. 0.2M Glycine stabilizer has been used safely in GAMIMUNE® N since 1992.

Caprylate is a saturated medium-chain (C8) fatty acid of plant origin, which is subjected to rapid beta-oxidation. Medium chain fatty acids are considered to be essentially non-toxic. Human subjects receiving medium chain fatty acids parenterally have tolerated doses of 3.0 to 9.0 g/kg/day for periods of several months without adverse effects [15]. Residual Caprylate concentrations in the final container are no more than 0.216 g/L (1.3 mmol/L).

The buffering capacity of GAMUNEX® 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 [16]. Thus, the acid load delivered with a dose of 1000 mg/kg of GAMUNEX® would be neutralized by the buffering capacity of whole blood alone, even if the dose was infused instantaneously.

INDICATIONS AND USAGE

Primary Humoral Immunodeficiency (PI)

GAMUNEX® (Immune Globulin Intravenous (Human), 10% Caprylate/Chromatography Purified) is indicated as replacement therapy of primary immunodeficiency states in which severe impairment of antibody forming capacity has been shown, such as congenital agammaglobulinemia, common variable immunodeficiency, X-linked immunodeficiency with hyper IgM, Wiskott-Aldrich syndrome, and severe combined immunodeficiencies [17-24].

Idiopathic Thrombocytopenic Purpura (ITP)

GAMUNEX® is indicated in Idiopathic Thrombocytopenic Purpura to rapidly raise platelet counts to prevent bleeding or to allow a patient with ITP to undergo surgery [5-10].

CONTRAINDICATIONS

GAMUNEX® (Immune Globulin Intravenous (Human), 10% Caprylate/Chromatography Purified) is contraindicated in individuals with known anaphylactic or severe systemic response to Immune Globulin (Human). Individuals with severe, selective IgA deficiencies (serum IgA <0.05 g/L) who have known antibody against IgA (anti-IgA antibody) should only receive

GAMUNEX® with utmost cautionary measures, due to the risk of severe immediate hypersensitivity reactions including anaphylaxis. No experience is available on tolerability of GAMUNEX® in subjects with selective IgA deficiency since they were excluded from participation in the clinical trials with GAMUNEX®.

WARNINGS

Immune Globulin Intravenous (Human) products have been reported to be associated with renal dysfunction, acute renal failure, osmotic nephrosis and death. [25] 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. GAMUNEX® does not contain sucrose. Glycine, a natural amino acid, is used as a stabilizer.

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

Because this product is made from human blood, it may carry a risk of transmitting infectious agents, e.g. 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.

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 Corporation [1-888-765-3203]. The physician should discuss the risks and benefits of this product with the patient, before prescribing or administering it to the patient.

GAMUNEX® (Immune Globulin Intravenous (Human), 10% Caprylate/Chromatography Purified) should be administered only intravenously. On rare occasions, treatment with an immune globulin preparation may cause 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.

Epinephrine and other appropriate supportive care 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. Visually inspect each bottle before use. Do not use if turbid. Solution that has been frozen should not be used.

An aseptic meningitis syndrome (AMS) has been reported to occur infrequently in association with Immune Globulin Intravenous (Human) treatment. The syndrome usually begins within several hours to two days following Immune Globulin Intravenous (Human) treatment. It is characterized by symptoms and signs including severe headache, nuchal rigidity, drowsiness, fever, photophobia, painful eye movements, nausea and vomiting.

AMS may occur more frequently in association with high dose (2 g/kg) and or rapid infusion of Immune Globulin Intravenous (Human) treatment. Discontinuation of Immune Globulin Intravenous (Human) treatment has resulted in remission of AMS within several days without sequelae [26-28].

Assure that patients are not volume depleted prior to the initiation of the infusion of IGIV. Periodic monitoring of renal function 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 of GAMUNEX® (Immune Globulin Intravenous (Human), 10% Caprylate/Chromatography Purified) and again at appropriate intervals thereafter. If renal function deteriorates, discontinuation of the product should be considered. For patients judged to be at risk for developing renal dysfunction, it may be prudent to reduce the amount of product infused per unit time by infusing GAMUNEX® at a rate less than 8 mg IG/kg/min (0.08 mL/kg/min).

Information for Patients

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.

Drug Interactions

Antibodies in GAMUNEX® 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 6 months after GAMUNEX® administration.
Please see DOSAGE AND ADMINISTRATION for other drug interactions.

Pregnancy Category C

Animal reproduction studies have not been conducted with GAMUNEX®. It is not known whether GAMUNEX® can cause fetal harm when administered to a

pregnant woman or can affect reproduction capacity. GAMUNEX® should be given to a pregnant woman only if clearly needed.

ADVERSE REACTIONS

General

Increases in creatinine and blood urea nitrogen (BUN) have been observed as soon as one to two days following infusion with Immune Globulin Intravenous [Human] products, predominantly with products containing sucrose as stabilizer. Progression to oliguria and anuria requiring dialysis has been observed, although some patients have improved spontaneously following cessation of treatment [29]. GAMUNEX® (Immune Globulin Intravenous (Human), 10% Caprylate/Chromatography Purified) does not contain sucrose. Glycine, a natural amino acid, is used as a stabilizer. In the studies undertaken to date with GAMUNEX®, no increase in creatinine and blood urea nitrogen was observed.

Although not necessarily observed for GAMUNEX®, adverse effects similar to those previously reported with administration of intravenous and intramuscular immunoglobulin products may occur. Potential reactions, therefore, may include pyrexia, rigors, dyspnea, cyanosis, hypoxemia, bronchospasm, hepatic dysfunction, leukopenia, pancytopenia, tremor, erythema multiforme, epidermolysis, back pain, abdominal pain, pulmonary edema, seizures, hypotension, thrombosis, transfusion related acute lung injury (TRALI).

True anaphylactic reactions to GAMUNEX® may occur in recipients with documented prior histories of severe allergic reactions to intramuscular immunoglobulin, but some subjects may tolerate cautiously administered intravenous immunoglobulin without adverse effects [30, 31]. Very rarely an anaphylactoid reaction may occur in subjects with no prior history of severe allergic reactions to either intramuscular or intravenous immunoglobulin. [31]

Laboratory Abnormalities

During the course of the clinical program, ALT and AST elevations, similar to those reported for other IGIV products [32, 33], were identified in some subjects. For ALT, in the primary humoral immunodeficiency (PI) study (100175) treatment emergent elevations above the upper limit of normal were transient and observed among 14/80 (18%) of subjects in the GAMUNEX® group versus 5/88 (6%) of subjects in the GAMIMUNE® N group ($p = 0.026$). In the ITP study which employed a higher dose per infusion, but a maximum of only two infusions, the reverse finding was observed among 3/44 (7%) of subjects in the GAMUNEX® group versus 8/43 (19%) of subjects in the GAMIMUNE® N group ($p = 0.118$). Elevations of ALT and AST were generally mild (<3 times upper limit of normal), transient, and were not associated with obvious symptoms of liver dysfunction.

GAMUNEX® may contain low levels of anti-Blood Group A and B antibodies primarily of the IgG_4 class. Direct antiglobin tests (DAT or direct Coombs tests), which are carried out in some centers as a safety check prior to red blood cell

transfusions, may become positive temporarily. GAMUNEX® does not contain irregular antibodies to Rhesus antigens or other non-ABO RBC antigens. Hemolytic events were not detected in association with positive DAT findings in clinical trials.[1, 3, 4, 11, 34]

Primary Humoral Immunodeficiencies (PI)

In three randomized clinical trials, 119 subjects with primary humoral immunodeficiencies were exposed to 939 infusions with GAMUNEX®. The rates of discontinuation from controlled clinical trials of GAMUNEX® due to adverse events were comparable to those of the GAMIMUNE® N treatment group. For the Primary Humoral Immunodeficiency studies, 2 subjects (1.4%) treated with GAMUNEX® discontinued due to adverse events (Coombs negative hypochromic anemia, autoimmune pure red cell aplasia). Both events were considered unrelated to study drug as per the investigator.

Two pharmacokinetic trials were carried out in 18-20 subjects each with primary humoral immunodeficiencies, who received 100-600 mg/kg GAMUNEX® or GAMIMUNE® N, 10% for three infusions on a 3 or 4 week infusion interval and then crossed over to three infusions of the alternate product (studies 100152, 100174). In a third trial investigating therapeutic equivalence, 172 subjects were randomized to GAMUNEX® or GAMIMUNE® N for a nine-month double-blinded treatment with either of the two products at a dose between 200 and 600 mg/kg on a 3 or 4 week infusion interval (study 100175). In this trial, only 9 subjects in each treatment group were pretreated with non-steroidal medication prior to infusion. Generally, diphenhydramine and acetaminophen were used. Any adverse events in trial 100175, irrespective of the causality assessment, reported by at least 15% of subjects during the 9-month treatment are given in the table below.

Subjects with At Least One Adverse Event *Irrespective of Causality* (Study 100175)

Adverse Event	GAMUNEX® No. of subjects: 87 No of subjects with AE (percentage of all subjects)	GAMIMUNE® N No. of subjects: 85 No of subjects with AE (percentage of all subjects)
Cough increased	47 (54%)	46 (54%)
Rhinitis	44 (51%)	45 (53%)
Pharyngitis	36 (41%)	39 (46%)
Headache	22 (25%)	28 (33%)
Fever	24 (28%)	27 (32%)
Diarrhea	24 (28%)	27 (32%)
Asthma	25 (29%)	17 (20%)
Nausea	17 (20%)	22 (26%)
Ear Pain	16 (18%)	12 (14%)
Asthenia	9 (10%)	13 (15%)

The severity of the adverse events across the treatment groups is displayed below.

Severity of Adverse Events *Irrespective of Causality* (Study 100175)

	GAMUNEX®	GAMIMUNE® N

	No. events with severity statement: 968	No. events with severity statement: 1083
Mild	558 (58%)	751 (69%)
Moderate	329 (34%)	259 (24%)
Severe	81 (8%)	73 (7%)

The subset of drug related adverse events in trial 100175 reported by at least 3% of subjects during the 9-month treatment are given in the table below.

Subjects with At Least One *Drug Related* Adverse Event (Study 100175)

Drug Related Adverse Event	GAMUNEX® No. of subjects: 87 No. of subjects with drug related AE (percentage of all subjects)	GAMIMUNE® N No. of subjects: 85 No. of subjects with drug related AE (percentage of all subjects)
Headache	7 (8%)	8 (9%)
Cough increased	6 (7%)	4 (5%)
Injection site reaction	4 (5%)	7 (8%)
Nausea	4 (5%)	4 (5%)
Pharyngitis	4 (5%)	3 (4%)
Urticaria	4 (5%)	1 (1%)
Asthma	3 (3%)	0 (0%)
Asthenia	3 (3%)	2 (2%)
Fever	1 (1%)	6 (7%)

Adverse events, which were reported by at least 5% of subjects, were also analyzed by frequency and in relation to infusions administered. The analysis is displayed below.

Adverse Event Frequency (Study 100175)

Adverse Event	GAMUNEX® No. of infusions: 825 Number of AE (percentage of all infusions)	GAMIMUNE® N No. of infusions: 865 Number of AE (percentage of all infusions)
Cough increased		
All	154 (18.7%)	148 (17.1%)
Drug related	*14 (1.7%)*	*11 (1.3%)*
Pharyngitis		
All	96 (11.6%)	99 (11.4)
Drug related	*7 (0.8%)*	*9 (1.0%)*
Headache		
All	57 (6.9%)	69 (8.0%)
Drug related	*7 (0.8%)*	*11 (1.3%)*
Fever		
All	41 (5.0%)	65 (7.5%)
Drug related	*1 (0.1%)*	*9 (1.0%)*
Nausea		
All	31 (3.8%)	43 (5.0%)
Drug related	*4 (0.5%)*	*4 (0.5%)*
Urticaria		
All	5 (0.6%)	8 (0.9%)
Drug related	*4 (0.5%)*	*5 (0.6%)*

The mean number of adverse events per infusion that occurred during or on the same day as an infusion was 0.21 in both the GAMUNEX® and GAMIMUNE® N treatment groups.

In all three trials in primary humoral immundeficiencies, the maximum infusion rate was 0.08 mL/kg/min (8 mg/kg/min). The actual infusion rate was reduced for 11 of 222 exposed subjects (7 GAMUNEX®, 4 GAMIMUNE® N) at 17 occasions. In most instances, mild to moderate hives/urticaria, itching, pain or reaction at infusion site, anxiety or headache was the main reason. There was one case of severe chills. There were no anaphylactic or anaphylactoid reactions to GAMUNEX® or GAMIMUNE® N.

In trial 100175, serum samples were drawn to monitor the viral safety at baseline and one week after the first infusion (for parvovirus B19), eight weeks after first and fifth infusion, and 16 weeks after the first and fifth infusion of IGIV (for hepatitis C) and at any time of premature discontinuation of the study. Viral markers of hepatitis C, hepatitis B, HIV-1, and parvovirus B19 were monitored by nucleic acid testing (NAT, Polymerase Chain Reaction (PCR)), and serological testing. There were no treatment emergent findings of viral transmission for either GAMUNEX®, or GAMIMUNE® N.[1, 3, 4]

Idiopathic Thrombocytopenic Purpura (ITP)

Two randomized clinical trials in acute or chronic ITP were conducted with GAMUNEX®. Seventy-six subjects with acute or chronic ITP were exposed to 170 infusions with GAMUNEX® (study 100176 and 100213). The rates of discontinuation from controlled clinical trials of GAMUNEX® due to adverse events were comparable to those of the GAMIMUNE® N treatment group. Altogether, 2 subjects (3%) treated with GAMUNEX® discontinued due to adverse events (headache, fever, vomiting, hives).

Study 100176 was a randomized double-blind therapeutic equivalence study, where 97 ITP subjects with acute or chronic ITP were randomized to a single dose of 2 g/kg of GAMUNEX® or GAMIMUNE® N. The total dose was divided into two 1 g/kg doses given on two consecutive days at a maximum infusion rate of 0.08 mL/kg/min. 48 subjects were exposed to 95 infusions with GAMUNEX®. One subject, a 10-year-old boy, died suddenly from myocarditis 50 days after his second infusion of GAMUNEX®. The death was unrelated to GAMUNEX®
As expected, the adverse event rate of IGIV in this ITP trial was higher than observed in the replacement therapy for Primary Humoral Immunodeficiencies (PI), but was within the range reported earlier for IGIV [35]. It should be noted that the dose per infusion is 2-2.5 fold higher than in Primary Humoral Immunodeficiency and that the total dose was given on two consecutive days. Administration of other IGIV product(s) at 1g/kg/day for 2 consecutive days has been associated with a higher adverse event rate than when the same total dose of product(s) was administered over a 5 day period [5]. Finally, no pre-medication with corticosteroids was permitted by the protocol. Only 12 subjects treated in each treatment group were pretreated with medication prior to infusion. Generally, diphenhydramine and/or acetaminophen were used. More than 90% of the observed drug related adverse events were of mild to moderate severity and of transient nature.

Any adverse events in trial 100176, irrespective of the causality assessment, reported by at least 15% of subjects during the 3-month trial are given in the table below.

Subjects with At Least One Adverse Event *Irrespective of Causality* (Study 100176)

Adverse Event	GAMUNEX® No. of subjects: 48 No of subjects with AE (percentage of all subjects)	GAMIMUNE® N No. of subjects: 49 No of subjects with AE (percentage of all subjects)
Headache	28 (58%)	30 (61%)
Ecchymosis, Purpura	19 (40%)	25 (51%)
Hemorrhage (All systems)	14 (29%)	16 (33%)
Epistaxis	11 (23%)	12 (24%)
Petechiae	10 (21%)	15 (31%)
Fever	10 (21%)	7 (14%)
Vomiting	10 (21%)	10 (20%)
Nausea	10 (21%)	7 (14%)
Thrombocytopenia	7 (15%)	8 (16%)
Accidental injury	6 (13%)	8 (16%)

The severity of the adverse events across the treatment groups is displayed below:

Severity of Adverse Events *Irrespective of Causality* (Study 100176)

	GAMUNEX® No. events with severity statement: 418	GAMIMUNE® N No. events with severity statement: 444
Mild	307 (73%)	326 (73%)
Moderate	97 (23%)	96 (22%)
Severe	14 (3%)	22 (5%)

The subset of drug related adverse events in trial 100176 reported by at least 3% of subjects during the 3-month trial are given in the table below.

Subjects with At Least One *Drug Related* Adverse Event (Study 100176)

Drug Related Adverse Event	GAMUNEX® No. of subjects: 48 No. of subjects with drug related AE (percentage of all subjects)	GAMIMUNE® N No. of subjects: 49 No. of subjects with drug related AE (percentage of all subjects)
Headache	24 (50%)	24 (49%)
Vomiting	6 (13%)	8 (16%)
Fever	5 (10%)	5 (10%)
Nausea	5 (10%)	4 (8%)
Back Pain	3 (6%)	2 (4%)
Rash	3 (6%)	0 (0%)
Asthenia	2 (4%)	3 (6%)
Abdominal Pain	2 (4%)	2 (4%)
Pruritus	2 (4%)	0 (0%)
Arthralgia	2 (4%)	0 (0%)
Dizziness	1 (2%)	3 (6%)
Neck Pain	0 (0%)	2 (4%)

The actual infusion rate was reduced for only 4 of the 97 exposed subjects (1 GAMUNEX®, 3 GAMIMUNE® N) on 4 occasions. Mild to moderate headache, nausea, and fever were the reported reasons. There were no anaphylactic or anaphylactoid reactions to GAMUNEX® or GAMIMUNE® N.

At baseline, nine days after the first infusion (for parvovirus B19), and 3 months after the first infusion of IGIV and at any time of premature discontinuation of the study, serum samples were drawn to monitor the viral safety of the ITP subjects. Viral markers of hepatitis C, hepatitis B, HIV-1, and parvovirus B19 were monitored by nucleic acid testing (NAT, PCR), and serological testing. There were no treatment related emergent findings of viral transmission for either GAMUNEX®, or GAMIMUNE® N [11].

Although the incidences of abnormal hematocrit, hemoglobin, RBC and glucose were twice as high in the GAMUNEX® group, the actual mean changes from baseline in these parameters were not different between study drugs and the magnitudes of these mean changes were small and clinically insignificant. These changes were attributed to pre-existing differences at baseline for the hematology parameters, which continued through the study with no incremental effect carried forward. For glucose, confounding variables such as non-fasting samples further suggest the finding to be by random chance.

DOSAGE AND ADMINISTRATION

Dosage

General

For patients judged to be at increased risk for developing renal dysfunction, it may be prudent to reduce the amount of product infused per unit time by infusing GAMUNEX® (Immune Globulin Intravenous (Human), 10% Caprylate/Chromatography Purified) at a rate less than 8 mg/kg/min (0.08 mL/kg/min). No prospective data are presently available to identify a maximum safe dose, concentration, and rate of infusion in patients determined to be at increased risk of acute renal failure. In the absence of prospective data, recommended doses should not be exceeded and the concentration and infusion rate should be the minimum level practicable. Reduction in dose, concentration, and/or rate of administration in patients at risk of acute renal failure has been proposed in the literature in order to reduce the risk of acute renal failure [36].

Primary Humoral Immunodeficiency (PI)

GAMUNEX® doses between 300 and 600 mg/kg (3 and 6 mL/kg), which represented the dose range for 92% of the subjects in the therapeutic equivalence trial (100175), may be used for infection prophylaxis. The dose should be individualized taking into account dosing intervals (e.g. 3 or 4 weeks) and GAMUNEX® dose (between 300 and 600 mg/kg). A target serum IgG trough level (i.e. prior to the next infusion) of at least 5 g/L has been proposed in the literature [22, 37], however no randomized controlled trial data are available to

validate this recommendation. In a clinical trial with 73 subjects with Primary Immune Deficiencies, treated for nine months with GAMUNEX®, the relationship of validated infections and serum IgG levels at trough are shown in the table below:

Average Serum IgG levels [g/L] Before Next GAMUNEX® Infusion (at Trough)[1]

Average serum IgG levels [g/L]	Number of subjects with validated infections	Number of subjects with any infection (validated plus clinically defined non-validated infections of any organ system)
	GAMUNEX®	GAMUNEX®
≤7	3/22 (14%)	19/22 (86%)
>7 and ≤9	5/33 (15%)	24/33 (73%)
>9	1/18 (6%)	13/18 (72%)
Cochran-Armitage Trend Test	P=0.46 (NS)	P=0.27 (NS)

NS = Non-significant

Idiopathic Thrombocytopenic Purpura (ITP)

GAMUNEX® may be administered at a total dose of 2 g/kg, divided in two doses of 1 g/kg (10 mL/kg) given on two consecutive days or into five doses of 0.4 g/kg (4 mL/kg) given on five consecutive days. If after administration of the first of two daily 1 g/kg (10 mL/kg) doses, an adequate increase in the platelet count is observed at 24 hours, the second dose of 1g/kg body weight may be withheld. Forty-eight ITP subjects were treated with 2 g/kg GAMUNEX®, divided in two 1 g/kg doses (10 mL/kg) given on two successive days. With this dose regimen 35/39 subjects (90%) responded with a platelet count from less than or equal to 20 $x10^9$/L to more than or equal to 50 $x10^9$/L within 7 days after treatment. [11] The high dose regimen (1 g/kg × 1-2 days) is not recommended for individuals with expanded fluid volumes or where fluid volume may be a concern.

Administration

GAMUNEX® is not compatible with saline. If dilution is required, GAMUNEX® may be diluted with 5% dextrose in water (D5/W). No other drug interactions or compatibilities have been evaluated.

It is recommended that GAMUNEX® should initially be infused at a rate of 0.01 mL/kg per minute (1 mg/kg per minute) for the first 30 minutes. If well-tolerated, the rate may be gradually increased to a maximum of 0.08 mL/kg per minute (8 mg/kg per minute). 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.

Only 18 gauge needles should be used to penetrate the stopper for dispensing product from 10mL vial sizes; 16 gauge needles or dispensing pins should only be used with 25 mL vial sizes and larger. Needles or dispensing pins should only be inserted within the stopper area delineated by the raised ring. The stopper should be penetrated perpendicular to the plane of the stopper within the ring.

GAMUNEX® vial size	Gauge of needle to penetrate stopper
10 mL	18 gauge
25, 50, 100, 200 mL	16 gauge

Content of vials may be pooled under aseptic conditions into sterile infusion bags and infused within 8 hours after pooling.

It is recommended to infuse GAMUNEX® using a separate line by itself, without mixing with other intravenous fluids or medications the subject might be receiving.

A number of factors 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, diagnosis, dosage, method of administration, and biological differences in individual subjects. Because of these factors, it is important that this product be stored properly and that the directions be followed carefully during use.

HOW SUPPLIED

GAMUNEX® (Immune Globulin Intravenous (Human), 10% Caprylate/Chromatography Purified) is supplied in the following sizes:

NDC Number	Size	Grams Protein
0026-0645-12	10 mL	1.0
0026-0645-15	25 mL	2.5
0026-0645-20	50 mL	5.0
0026-0645-71	100 mL	10.0
0026-0645-24	200 mL	20.0

STORAGE

GAMUNEX® (Immune Globulin Intravenous (Human), 10% Caprylate/Chromatography Purified) may be stored for 36 months at 2 - 8°C (36 - 46°F), AND product may be stored at temperatures not to exceed 25°C (77°F) for up to 5 months during the first 18 months from date of manufacture, after which the product must be immediately used or discarded. Do not freeze. Do not use after expiration date.

Rx only

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