



PRODUCT PROFILER

Immune Globulin Intravenous (Human), 5% Liquid

Gammaplex[®]

FDA-approved indication

For replacement therapy of primary humoral immunodeficiency. This includes, but is not limited to, the humoral immune defect in common variable immunodeficiency, X-linked agammaglobulinemia, congenital agammaglobulinemia, Wiskott-Aldrich syndrome, and severe combined immunodeficiencies.

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THE PRODUCT PROFILER

The Product Profiler provides P&T committee members with current, detailed information about a specific therapeutic agent to help them manage their formularies and establish medication-related policies. The Profiler provides information about pharmacology, clinical studies and FDA-approved indications, safety, efficacy, acquisition costs, and other pharmacoeconomic variables, along with additional P&T committee considerations, in a convenient package. Articles are written by experts in the field.

ABOUT THE AUTHOR

Carole Alison Chrvala, PhD, was trained as an epidemiologist at the University of Colorado. Dr. Chrvala is a seasoned researcher and medical writer with 22 years experience in chronic disease screening, diagnosis, treatment, and evaluation. Highlighting a career that spanned the public and private health sectors, Dr. Chrvala was director of Cancer Prevention and Control for the Colorado Department of Public Health and Environment (CDPHE). During her tenure at CDPHE, she was a principal investigator or co-principal investigator on more than 10 grants, contracts, and cooperative agreements. Dr. Chrvala also served as invited reviewer for several National Institutes of Health (NIH) grant review panels, and has had the honor of participating on a variety of advisory boards and steering committees on cancer, diabetes, cardiovascular disease, HIV/AIDS, and women's health.

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DISCLOSURES

Carole Alison Chrvala, PhD, and Alan Caspi, PhD, PharmD, MBA, both report that they have no financial arrangements or affiliations that might constitute a conflict of interest with respect to this publication. Bio Products Laboratory provided funding for this publication.



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Gammaplex[®]

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Immune Globulin Intravenous (Human), 5% Liquid Gammalex®

For Replacement Therapy of Primary Humoral Immunodeficiency

INTRODUCTION

This Product Profiler introduces health care professionals to Gammalex®, an FDA-approved immune globulin intravenous (IV) (human) for replacement therapy in primary humoral immunodeficiency (PI).

Numerous trials have established the clinical efficacy of immunoglobulin replacement therapy in patients with PI (Wood 2007). Based on the results of these studies, standard treatment for patients with PI consists of immunoglobulin replacement every 3 to 4 weeks using human immunoglobulin derived from donated plasma (National Institute of Child Health & Human Development 2008). Long-term adherence to this regimen allows patients to maintain serum levels of immunoglobulin that approximate physiologic concentrations in healthy individuals (Ochs 2006).

The following text presents an overview of PI, current treatment options for this disorder, a review of the evidence supporting the FDA-approved indication for Gammalex® in patients with PI, and considerations for P&T committee decisions concerning this product.

DISEASE BACKGROUND

Etiology and Pathology

Innate and adaptive immunity are the cooperative mechanisms by which the body recognizes microbial pathogens (Chaplin 2006). Innate immunity is an ancient immune-recognition system, evolved over millions of years, that uses a variety of cells, including natural killer-cell lymphocytes and dendritic cells, to recognize and eliminate pathogens (Chaplin 2006, Haynes 2008). The adaptive

immune system, on the other hand, consists of immune responses mediated by T and B lymphocytes (Chaplin 2006). In adaptive immunity, gene rearrangements create antigen receptors on the surfaces of T and B cells, allowing these cells to recognize the antigens of countless infectious agents. The surface antigen receptors on B cells consist of immunoglobulin molecules (Haynes 2008).

The innate and adaptive immune systems usually work together, with innate responses representing the body's first line of defense (Chaplin 2006). Adaptive immunity "kicks in" several days later as antigen-specific T and B lymphocytes become activated (Chaplin 2006).

Adaptive immunity comprises cellular and humoral immune functions. T lymphocytes play the primary role in cellular immunity, and B lymphocytes are the essential components of humoral immunity (Haynes 2008). In cellular immunity, cytotoxic T lymphocytes recognize and destroy virus-infected or foreign cells (Chaplin 2006, Haynes 2008). In humoral immunity, the primary function of B cells is to produce antibodies in response to specific antigens (Haynes 2008). Surface immunoglobulins play a key role in this process; these molecules "recognize" antigens and signal the B cell to make targeted antibodies (Chaplin 2006, Haynes 2008, WHO 1995).

PI comprises a heterogeneous group of disorders characterized by the body's inability to mount an effective antibody response to pathogens (Wood 2007). PI disorders may be congenital or they may develop later in life in response to environmental triggers or iatrogenic factors (Cooper 2008, Herriot 2008, Wood 2007). Most cases of immunodeficiency are believed to result from genetic

TABLE 1
Major PI disorders

Disorder	B Lymphocytes	Immunoglobulins	Mechanism
X-linked agammaglobulinemia	Absent/low	Low IgG, IgA, and IgM	Failure of B-lymphocyte differentiation
Common variable immunodeficiency (CVID)	≥1%	Low IgG and IgA with normal or elevated IgM	Failure of B-lymphocyte function
Hyper IgM syndromes	Normal	Increased IgM with low IgG and IgA	Failure of T-lymphocyte cooperation
Selective IgG subclass deficiency with or without IgA deficiency	Normal	Normal	Unknown
Specific antibody deficiencies	Normal	Normal	Unknown

Source: Wood 2007.

defects that disrupt either the development or differentiation of B or T lymphocytes, the essential components of the body's adaptive immune system (Cooper 2008, Haynes 2008, Wood 2007). The majority of PI disorders (50% to 60%) are caused by B-lymphocyte dysfunction, resulting in immunoglobulin and antibody deficiencies (Merck Manual 2010). T-cell disorders account for less than 10% of PI syndromes (Merck Manual 2010).

More than 200 PI disorders have been identified (Merck Manual 2010). Some of the major types of disorders are listed in Table 1.

Incidence and Prevalence

PI syndromes affect an estimated 500,000 Americans, and 50,000 new cases are diagnosed each year (Cooper 2003). The prevalence of clinically significant PI is estimated at 1 in 25,000 to 1 in 110,000 persons in the general population (Wood 2009).

At least half of all PI syndromes are believed to be due to genetically based (primary) antibody deficiency (Herriot 2008, Wood 2007). Isolated IgA deficiency, the most common PI disorder, affects approximately 1 in 600 individuals in the general populations of Europe and North America (Cooper 2008). Common variable immunodeficiency (CVID), the second most common PI disorder, affects approximately 1 in 25,000 individuals (Herriot 2008). PI disorders usually manifest during infancy or childhood as abnormally recurrent or unusual infections. The majority of patients with PI syndromes (approximately 70%) are younger than 20 years of age at onset. Because genetic transmission of the disease is often X-linked, 60% of affected individuals are male (Merck Manual 2010).

Clinical Presentation and Evaluation

PI disorders are primarily characterized by susceptibility to bacterial infections of the upper and lower respiratory tracts (eg, sinusitis, bronchitis, and pneumonia) in the absence of other contributing factors, such as smoking (Herriot 2008, Paul 2002, Wood 2007). The gastrointestinal (GI) tract, skin, eyes, skeleton, and central nervous system may also be affected by persistent or recurrent infections (Herriot 2008). Nonspecific features of PI syndromes include arthropathy and tissue abnormalities, such as lymphadenopathy, hepatosplenomegaly, and nodular lymphoid hyperplasia (Herriot 2008, Wood 2007). Among children, symptoms of antibody deficiency may include failure to thrive, recurrent pyrexia of unknown origin, and recurrent respiratory and GI tract infections (Wood 2007).

Early diagnosis, treatment, and referral of patients with suspected PI disorders may prevent or reduce the severity of infections and decrease the risk of serious systemic complications (Wood 2009). A definitive diagnosis of PI begins with a thorough medical history and physical examination to identify significant antibody deficiency and to

TABLE 2
Warning signs of PI disorders

1. Four or more new ear infections within 1 year
2. Two or more serious sinus infections within 1 year
3. Two or more months on antibiotics with little effect
4. Two or more episodes of pneumonia within 1 year
5. Failure of an infant to gain weight or to grow normally
6. Recurrent deep-organ or skin abscesses
7. Persistent oral thrush or cutaneous fungal infection
8. Need for intravenous antibiotics to resolve infections
9. Two or more deep-seated infections, including septicemia
10. A family history of PI disorders

Source: Modell 2009.

distinguish primary and secondary diseases (de Vries 2006, Wood 2009). The Jeffrey Modell Foundation (2009) has published a list of clinical warning signs to help physicians diagnose PI disorders more accurately. These signs are described in Table 2.

Initial laboratory evaluations include a complete blood cell count with manual differential to screen for defects in B and T lymphocytes (Cooper 2003, Paul 2002). Since most humoral immune deficiencies result in decreased immunoglobulin concentrations (Merck Manual 2010), serum IgG, IgM, and IgA levels are also assessed in patients with suspected PI disorders (Cooper 2003, Wood 2009).

Figure 1 presents an algorithm for the diagnosis of antibody production defects.

Health-related Quality of Life and Economic Burden

Patients with PI disorders are at risk of developing secondary complications, such as structural tissue damage at sites of recurrent infection (Herriot 2008). Early diagnosis is critical in preventing tissue damage from infection and inflammation (Ballou 2002). Damage to the respiratory tract can lead to secondary lung disorders, including bronchiectasis (estimated to affect up to 76% of patients), pulmonary fibrosis, and pulmonary hypertension (Herriot 2008, Wood 2009, Wood 2007). The risk of developing a malignancy is increased up to 13-fold in patients with PI disorders, especially those with CVID (Herriot 2008, Wood 2009). The most common malignancies are lymphomas of B-cell origin (Herriot 2008).

Study results have shown that individuals with untreated PI disorders have a poorer self-reported functional status compared with healthy persons. PI was associated with restrictions in several areas of daily life, including ambulation, physical mobility, emotional behavior, home management, and the ability to do work (Gardulf 1993). In patients with PI disorders, the purpose of lifelong immunoglobulin replacement therapy is to reduce the frequency and severity of infections. Successful immunoglobulin treatment may be expected, therefore, to provide patients with a sense of increased resistance to infections, which in turn may promote a greater willingness to participate in social and family activities (Gardulf 2004).

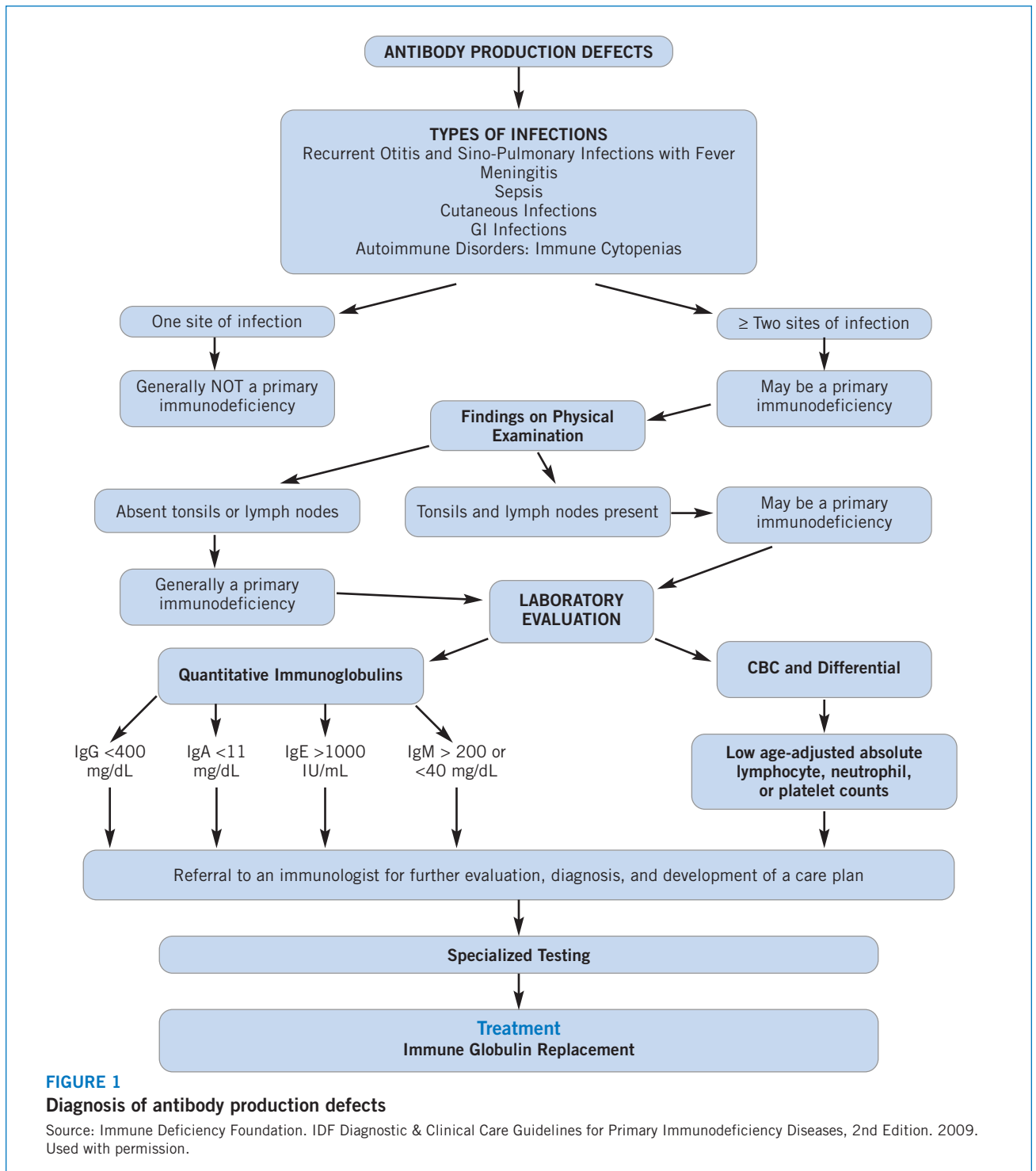


FIGURE 1
Diagnosis of antibody production defects

Source: Immune Deficiency Foundation. IDF Diagnostic & Clinical Care Guidelines for Primary Immunodeficiency Diseases, 2nd Edition. 2009. Used with permission.

In an economic impact study (Modell 2007), the average annual health care cost for an undiagnosed patient with an underlying PI disorder was \$102,736, compared with \$22,696 for a diagnosed patient. These estimates took into account the costs of treating infections, includ-

ing bacterial pneumonia; physician, hospital, and emergency room visits; hospitalizations; and school or work days missed. The study concluded that the economic impact of undiagnosed PI disorders on the US health care system totals more than \$40 billion annually.

Current Treatment Options

IMMUNOGLOBULIN REPLACEMENT

Ever since Bruton first introduced immunoglobulin injections to treat a patient with agammaglobulinemia in 1952, immunoglobulin replacement therapy has been the standard of treatment for PI disorders (Cooper 2003, Gelfand 2003, Herriot 2008, Ochs 2006). Immunoglobulin was first administered via intramuscular injection, generally at a dose of 100 mg per kilogram (kg) of body weight. These injections were painful, however, and limited the amount of immunoglobulin that could be given (Gelfand 2003). Immune Globulin Intravenous (IGIV) therapy was introduced in the early 1980s (Ballow 2002). This approach allowed larger doses (400 to 600 mg/kg body weight) to be administered over a relatively short time, reduced the amount of pain associated with intramuscular injection, and was fast-acting (Gelfand 2003, National Institute of Child Health & Human Development 2008). Today, most patients receive immunoglobulin replacement therapy via the IV route, with few indications for intramuscular injection (Gelfand 2003). Subcutaneous infusion is another option, but this approach is more popular in Europe than in the United States (Ochs 2006). IGIV infusions take 2 to 4 hours and are given every 3 to 4 weeks, either in an outpatient clinic or at home (National Institute of Child Health & Human Development 2008). Dosing is more frequent (every 7 to 14 days) for subcutaneously administered immunoglobulin (Buckley 2009).

Typical total monthly doses of IGIV range from 400 to 800 mg/kg of body weight (Buckley 2009). Clinical studies have indicated that infections and the need for hospitalization may be reduced if trough levels of immunoglobulin (4 weeks after infusion) are maintained above 500 mg/dL (Buckley 2009, Gelfand 2003). In a double-blind, randomized study, doubling the standard dosage of IGIV (from 300 mg/kg to 600 mg/kg of body weight every 4 weeks in adults, and from 400 mg/kg to 800 mg/kg of body weight every 4 weeks in children) significantly reduced the mean number (2.5 vs 3.5 per patient; $P=.004$) and median duration (21 vs 33 days; $P=.015$) of infections compared with standard dosing. IgG trough levels increased significantly during high-dose therapy (from 6.3 to 9.4 g/L; $P<.001$). Importantly, the incidence and type of side effects did not differ significantly between the two dosages (Eijkhout 2001). These findings underscore the potential benefit of tailoring IGIV regimens to the requirements of the individual patient rather than relying on a fixed-dose approach (Gelfand 2003).

IgG levels peak immediately after the infusion of IGIV and then slowly decline over the following days (Octagam PI 2007). The mean IgG half-lives of representative IGIV drug products have ranged from 34 to 42 days

(Flebogamma PI 2010, Gammaplex PI 2010, Gamunex PI 2010, Octagam PI 2007); the half-life of IgG can show considerable variation among individual patients (Flebogamma PI 2010, Octagam PI 2007). IGIV products differ in terms of donor pools, manufacturing processes, and final formulation, and these differences may affect the infusion rate, efficacy, tolerability, and risk of adverse events (Gelfand 2003). Tolerability and adverse events, in particular, may be influenced by the differing osmolality, pH, and sugar and sodium contents of IGIV products (Gelfand 2003, Immune Deficiency Foundation 2003). For example, some products contain sucrose, which has been associated with kidney problems in certain patients (Immune Deficiency Foundation 2003).

PRODUCTION OF INTRAVENOUS IMMUNOGLOBULIN PREPARATIONS

In 1982, the World Health Organization (WHO) published minimal requirements for IGIV preparations. These guidelines stipulated that IGIV should be obtained from a pool of at least 1,000 donors. The preparations should contain at least 90% intact IgG without immunoglobulin fragments, and the IgG should be biochemically modified as little as possible to maintain opsonic, complement-binding, and other biologic activities. All IgG subclasses should be present in proportions similar to those found in normal pooled plasma. The immunoglobulins should be free from prekallikrein activator, kinins, plasmin, and preservatives or other potentially harmful contaminants (Cunningham-Rundles 1982).

Today, IGIV products are prepared from plasma pooled from 3,000 to 10,000 healthy blood donors (Gelfand 2003, Shah 2005). In most production processes, IgG is isolated from other plasma proteins by sequential precipitation and fractionation with ethanol. The IgG concentrates then undergo additional processing to produce material suitable for IV administration. Because manufacturers use different purification techniques, IGIV products vary in terms of their levels of IgG monomer, dimer, and polymers, immunoglobulin fragments, and excipient proteins, such as albumin (Gelfand 2003).

The varying product characteristics have important clinical implications. For example, liquid preparations may be preferred over freeze-dried products in that the former are generally considered to be more convenient and easier to use, and may cause fewer adverse events. Moreover, liquid preparations in ready-to-use form shorten preparation time and delays for patients (Gelfand 2003).

Viral inactivation is another important consideration in the manufacturing process (Shah 2005). The process of manufacturing IGIV includes an array of precipitation,

centrifugation, filtration, and other stages designed to eliminate clinically relevant pathogenic viruses, and each manufacturing step can be monitored for its potential to inactivate specific viruses (Rütter 1994). In the manufacture of Gammaplex®, for example, three processing steps have been specifically designed to remove or inactivate viruses. First, solvent/detergent treatment is targeted to enveloped viruses. Next, a virus filtration step removes small viruses, including nonenveloped viruses, on a size-exclusion basis. Finally, a low-pH incubation step contributes to the overall viral clearance capacity for enveloped and nonenveloped viruses (Gammaplex PI 2010). All of these steps have been validated for viral clearance and/or inactivation by regulatory agencies.

TOLERABILITY AND SAFETY CONSIDERATIONS

In patients with PI disorders, the overall incidence of adverse events associated with IGIV therapy ranges from <5% to 16% (Gelfand 2003). Differences in the production, composition, and characteristics of the various IGIV preparations may influence their tolerability and adverse-event profiles (Shah 2005). The most common adverse reactions to IGIV products include low-grade fever, headache,

myalgia, chills, malaise, nausea, and vomiting (Gelfand 2003, Hamrock 2006). Low-grade fever often occurs during the infusion and may be prevented by premedicating the patient with acetaminophen. Other minor side effects, such as headache and nausea, rarely occur during infusion but usually develop 1 to 3 days after administration (Hamrock 2006).

Serious (but rare) side effects associated with IGIV therapy include acute renal failure, stroke, myocardial infarction, deep venous thrombosis, and aseptic meningitis. Many of these serious adverse reactions have occurred in patients with significant risk factors or underlying disease states (Hamrock 2006). Reports indicate that 90% of patients who developed renal dysfunction during IGIV therapy received a product that contained sucrose as a stabilizer. IV sucrose is known to be damaging to the kidneys (Hamrock 2006). Gammaplex® does not contain sucrose (Gammaplex PI 2010).

Based on postmarketing reports, the FDA requires all manufacturers of IGIV products to include a boxed warning regarding the risk of renal dysfunction, acute renal failure, osmotic nephropathy, and death associated with the use of these products (see Boxed Warning in full Prescribing Information beginning on page 17).

Gammalex® Chemistry and Pharmacokinetics

PHYSICAL AND CHEMICAL PROPERTIES

Gammalex® is a ready-to-use sterile solution of polyclonal human IgG for IV administration that contains sorbitol, glycine, and polysorbate 80 as stabilizers. Specifically, Gammalex® contains approximately 5 g normal human immunoglobulin and 5 g D-sorbitol in 100 mL of buffer solution containing 0.6 g glycine, 0.2 g sodium acetate, 0.3 g sodium chloride, and approximately 5 mg polysorbate 80. IgG purity is 95% (typically 100%); the pH is in the range of 4.8 to 5.1; and osmolality is not less than 240 mOsmol/kg (typically 420 to 500 mOsmol/kg). The distribution of the four IgG subclasses is approximately 64% IgG₁, 30% IgG₂, 5% IgG₃, and 1% IgG₄. The content of IgA is lower than 10 µg/mL. The anti-D and anti-A/anti-B hemagglutinin content of the product is strictly controlled to specification. Gammalex® contains no reducing carbohydrate stabilizers (eg, sucrose, maltose) and no preservative (Gammalex PI 2010).

Cleavage of an immunoglobulin molecule with proteolytic enzymes produces two Fab fragments and one Fc fragment. The Fab fragments contain the antigen-binding sites, and the Fc fragment is essential for a number of biologic functions, including binding to effector cells and complement (Gammalex Product Monograph 2011). In the manufacture of Gammalex®, Fab functions tested include antigen binding activity, and Fc functions tested include complement activation and rubella antibody-mediated hemolysis (Gammalex PI 2010).

Gammalex® is manufactured from plasma obtained from healthy US donors who have passed viral screening tests. All donors are subjected to medical examinations, laboratory tests, and a review of their medical history before being allowed to donate blood or plasma. Several stages within the Gammalex® manufacturing process contribute to viral reduction, including management of donors, screening of donations, and specific virus-removal steps during manufacturing (Gammalex PI 2010).

All plasma donations are screened for antibody to human immunodeficiency virus (HIV)-1/2 and hepatitis C virus (HCV), and hepatitis B surface antigen (HBsAg). Further, plasma minipools (512 donations per pool) undergo nucleic acid amplification testing (NAT) for HIV, HCV, hepatitis B virus, hepatitis A virus, and Parvovirus B19. Further testing is carried out on the manufacturing pools for HBsAg and antibody to HIV-1/2; HCV and Parvovirus B19 are also tested by NAT, with the limit for Parvovirus B19 set to not exceed 10⁴ IU B19 DNA per mL plasma (Gammalex PI 2010).

PHARMACOLOGY AND MECHANISM OF ACTION

Gammalex® is a replacement therapy for PI. It acts through a broad spectrum of opsonic and neutralizing IgG antibodies against pathogens and their toxins involving antigen binding and effector functions. However, the mechanism of action in PI has not been fully elucidated (Gammalex PI 2010).

DRUG METABOLISM AND PHARMACOKINETICS

In a US-based clinical study that assessed the safety and efficacy of Gammalex® in 24 subjects with PI, the pharmacokinetics of Gammalex® were evaluated for 28 days after administration on 21- or 28-day infusion cycles. Blood samples for pharmacokinetic (PK) analysis were obtained after Infusion 9 for subjects on a 21-day schedule (9 subjects) and after Infusion 7 for subjects on a 28-day schedule (15 subjects), ie, during the sixth month after initiation of Gammalex® treatment (Gammalex PI 2010).

The mean dose for subjects on the 21-day schedule was 476 mg/kg (range: 330–721 mg/kg), and the corresponding mean dose for those on the 28-day schedule was 468 mg/kg (range: 324–799 mg/kg). Table 3 summarizes the PK parameters of Gammalex®, measured as serum concentrations of total IgG (Gammalex PI 2010).

Assessment of the clinical relevance of half-life measurements in this study should be viewed with caution. Although half-life estimates are provided for total IgG and the specific antibodies, drug elimination half-lives

TABLE 3

Pharmacokinetic parameters of Gammalex® in subjects with PI

Parameter (unit)	21-day Dosing Interval (n = 9) Mean ± SD (range)	28-day Dosing Interval (n = 15) Mean ± SD (range)
C _{max} (mg/mL)	21.6 ± 3.8 (16.3–27.3)	21.4 ± 4.3 (15.9–31.0)
T _{max} (h)	5.4 ± 7.2 (2.1–24.5)	6.1 ± 11.6 (2.4–48.1)
AUC _{0-tau}	289 ± 41 (214–365)	346 ± 52* (262–455)
Half-life (days)	42 ± 26 (22–108)	41 ± 14* (22–70)
Clearance (mL/d/kg)	0.59 ± 0.24 (0.19–1.02)	0.58 ± 0.27* (0.24–1.28)

AUC=area under the curve; C_{max}=maximum plasma concentration; T_{max}=time to maximum plasma concentration; tau=dosing interval.
*n=14 for these calculations.

Source: Gammalex PI 2010.

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should be measured over a minimum period of at least 3 half-lives. However, the short dosing intervals relative to

the long half-life of IgG in this clinical trial do not permit an accurate assessment of half-life (Gammalex PI 2010).

Gammalex® Clinical Trials

PIVOTAL PHASE 3 CLINICAL STUDY

A US-based Phase 3 multicenter, open-label study of Gammalex® was conducted on 50 subjects with PI diseases who had received regular IGIV replacement therapy for at least 3 months prior to participation. The subjects were treated with Gammalex® for 12 months at 21-day (22 subjects) or 28-day (28 subjects) dosing intervals. Twenty-six of the subjects (52%) were men, and 46 (92%) were Caucasian. The subjects' mean age was 44 years (range: 9–78 years) (Gammalex PI 2010, Moy 2010).

The doses of Gammalex® ranged from 279 mg/kg to 799 mg/kg. The mean dose per infusion for the 21-day interval was 465 mg/kg (range: 330–693 mg/kg), and the mean dose for the 28-day interval was 458 mg/kg (range: 326–790 mg/kg). Subjects received a total of 703 infusions of Gammalex®. The maximum infusion rate allowed during this study was 0.08 mL/kg/min (240 mg/kg/h) (Gammalex PI 2010, Moy 2010).

The study's primary objective was to determine whether Gammalex® was efficacious with respect to the incidence of acute, serious bacterial infections (aSBIs), defined as bacterial pneumonia, bacteremia or sepsis, osteomyelitis/septic arthritis, visceral abscess, or bacterial meningitis in individuals with PI diseases. Secondary efficacy endpoints included the annual rate of nonserious infections, antibiotic use, days off work/school/day care or unable to perform normal activities due to illness, and

days of acute care visits or hospitalization (Gammalex PI 2010, Moy 2010).

Study Results

During the 12-month study period, no aSBIs occurred in any subject with an onset date between the first infusion of Gammalex® and the first follow-up visit, inclusive. Thus, the mean event rate of aSBIs per year was zero (with an upper 1-sided 99% confidence interval of 0.101) (Gammalex PI 2010, Moy 2010). During the 6 months prior to entering the study, 12% of the patients reportedly developed an aSBI while receiving another IGIV product (Moy 2010).

Forty subjects (80%) reported at least 1 non-serious infection during the study. These presumed infections involved primarily the upper respiratory tract (eg, sinusitis). The mean number of presumed infectious episodes per subject per year was 3.28 (Moy 2010).

During the study, more than half (54%) of all patients experienced no absences from school/work/day care (or inability to perform normal activities) because of an infection or other medical problem; the majority (88%) missed fewer than 14 days per year (Moy 2010). Moreover, the vast majority of subjects (92%) did not require hospitalization (Gammalex PI 2010).

Table 4 summarizes the key efficacy results from this study.

Number of subjects:	50
Total number of subject days:	16,715
Infections	
Annual rate of confirmed aSBIs*	0/subject year [†]
Annual rate of other infections (median)	3.07 infections/subject year
Antibiotic use (therapeutic)	
Number of subjects (%)	40 (80%)
Annual rate	47.2 days/subject year
Out of work/school/day care or unable to perform normal activities due to illness	
Number of subjects (%)	23 (46%)
Number of days (%)	394 (2.36%)
Annual rate	8.73 days/subject year
Hospitalization	
Number of subjects (%)	4 (8%)
Number of days (%)	29 (0.17%)
Annual rate	0.75 days/subject year
*aSBIs=acute, serious bacterial infections (defined as pneumonia, bacterial meningitis, bacteremia/septicemia, osteomyelitis/septic arthritis, and visceral abscesses).	
[†] Upper 1-sided 99% confidence interval: 0.101.	
Source: Gammalex PI 2010.	

The infusions of Gammalex® were generally well tolerated: only 5 of the 50 subjects discontinued the study prematurely, with three subjects withdrawing because of an adverse event (possibly related to Gammalex® in two cases). One subject was hospitalized because of adverse events (thrombosis and chest pain) possibly related to Gammalex® (Moy 2010).

The most common adverse reactions observed in this clinical trial were headache (18 subjects, 36.0%), fatigue (6 subjects, 12.0%), nausea (6 subjects, 12.0%), pyrexia (6 subjects, 12.0%), hypertension (3 subjects, 6.0%), myalgia (3 subjects, 6.0%), pain (3 subjects, 6.0%), and vomiting (3 subjects, 6.0%) (Gammalex PI 2010).

Gammaplex® Indications, Dosage, and Administration

INDICATION

Gammaplex® is indicated for replacement therapy of PI. This includes, but is not limited to, the humoral immune defect in common variable immunodeficiency, X-linked agammaglobulinemia, congenital agammaglobulinemia, Wiskott-Aldrich syndrome, and severe combined immunodeficiencies (Gammaplex PI 2010).

RECOMMENDED DOSAGE

Because there are significant differences in the half-life of IgG among patients with PI, the frequency and amount of immunoglobulin therapy may vary from patient to patient. The proper amount can be determined by monitoring clinical response (Gammaplex PI 2010).

The recommended dosage of Gammaplex® for patients with PI is 300 to 800 mg/kg (6 to 16 mL/kg) administered every 3 to 4 weeks. The dosage should be adjusted over time to achieve the desired serum trough levels and clinical responses. If a patient misses a dose, the missed dose should be administered as soon as possible, and then scheduled treatments should be resumed every 3 or 4 weeks, as applicable (Gammaplex PI 2010).

ADMINISTRATION

Gammaplex® is approved for IV use only (Gammaplex PI 2010).

Gammaplex® should be administered in the following steps: 1) hydrate the patient adequately prior to the initiation of infusion; 2) because of the absence of antimicrobial preservatives, promptly administer Gammaplex® after piercing the cap; and 3) infuse Gammaplex® intravenously using an IV infusion set preferably fitted with an in-line 15- to 20-micron filter (Gammaplex PI 2010).

Recommended infusion rates are listed in Table 5. Gammaplex® offers the potential for a short infusion time (<2.5 hours at recommended escalation rates for a 70-kg adult patient at a prescribed dose of 400 mg/kg) (Gammaplex PI 2010, Gammaplex Product Monograph 2011). The short infusion time of Gammaplex® is convenient for both health care providers and patients.

PREPARATION AND ADMINISTRATION INSTRUCTIONS

When stored between 2°C (35.6°F) and 25°C (77°F), Gammaplex® has a shelf life of 24 months (Gammaplex PI 2010).

The Gammaplex® bottle is for single use only. Because of the absence of antimicrobial preservatives, Gammaplex® should be administered promptly after piercing the cap. Partially used or unused product should be disposed of in accordance with local requirements (Gammaplex PI 2010).

Gammaplex® should not be mixed with other IV medications (including normal saline) or other IGIV products. If large doses of Gammaplex® are to be administered, several bottles may be pooled using aseptic technique. The infusion should begin within 2 hours after pooling (Gammaplex PI 2010).

Before Gammaplex® is administered, it should be inspected visually for particulate matter and discoloration. If the solution is cloudy or turbid, or if it contains particulate matter, it should not be used. The solution should not be shaken, and it should not be used if it has been frozen (Gammaplex PI 2010).

TABLE 5
Recommended infusion rates for Gammaplex®

Initial infusion rate for first 15 minutes	Maximum infusion rate (if tolerated)
0.5 mg/kg/min (0.01 mL/kg/min)	Increase gradually every 15 minutes to 4 mg/kg/min (0.08 mL/kg/min)

Source: Gammaplex PI 2010.

P&T Committee Considerations

A product's acquisition cost can be a major determining factor when P&T committees consider drugs for inclusion in the formulary. Selection or rejection of a drug based on acquisition cost alone, however, may be more costly in the long run if biologic function or efficacy is compromised or if adverse events are higher and need to be managed (Gelfand 2003). In addition to a product's cost, other important factors to be considered include drug safety, efficacy, the clinical need for the agent, potential misuse, and side effects. This section reviews P&T committee considerations that may apply to Gammalex®.

CLINICAL NEED

The efficacy of IGIV in reducing the number of infections in patients with antibody deficiency syndromes is well established (Herriot 2008, Ochs 2006, Wood 2007). IGIV products are the fastest-growing group of blood products in the world (Gammalex Product Monograph 2011). Gammalex®, a liquid IGIV preparation, is manufactured using well-established purification methods of cold ethanol fractionation integrated with ion-exchange chromatography, coupled with rigorous virus-reduction techniques. Gammalex® offers several clinical benefits for patients with PI and their caregivers (Gammalex PI 2010):

- Proven protection against infections in PI patients
- Low incidence of infusion-associated adverse events (most common: headache [7.5% of infusions], pyrexia [1.4%], fatigue [1.3%], sinusitis [1.3%] and nausea [1.0%])
- Mean half-life: 41 to 42 days
- Trace amounts of IgA (<10 mcg/mL)
- A broad spectrum of IgG antibodies against endemic pathogens
- The complete range of IgG subclasses
- Optimal pH (4.8–5.1) for stability and virus safety
- Three dedicated virus inactivation/removal steps incorporated into the manufacturing process
- 24-month shelf life with storage at room temperature (up to 25°C [77°F]); full storage range: 2–25°C (36–77°F)

PRODUCT PROFILE

The proportion of the four IgG subclasses in Gammalex® is clinically relevant and compares well with normal plasma and other IGIV products (Table 6) (Gammalex PI 2010, Gammalex Product Monograph 2011).

TABLE 6
IgG subclasses in Gammalex®

IGIV	Process	IgG Subclass (% Ratio)			
		IgG ₁	IgG ₂	IgG ₃	IgG ₄
Gammalex®	Ion exchange + SD + VF	64	30	5	1
Plasma		60–70	20–30	5–8	1–4

SD=solvent/detergent; VF=virus filtration (20 nm).
Source: Gammalex Product Monograph 2011.

Patients with various forms of immunodeficiency suffer from recurrent bacterial infections, principally *Haemophilus influenzae* and *Streptococcus pneumoniae*. For this reason, it is important that IGIV preparations contain antibodies to these and other common pathogens. Gammalex® contains a broad spectrum of IgG antibodies that are enriched over the manufacturing process and that exceed the European Pharmacopoeia requirement for enrichment factors ≥ 3 for both viral and bacterial antibodies (Gammalex Product Monograph 2011).

Biologic activity is a key property of IgG and is important in its role in humoral and innate immunity. Biologic functionality is measured by the ability of IgG to bind and neutralize toxins and viruses, using specific tests for antibodies to measles, polio-1, and diphtheria that comply with USP 21CFR640.104, as follows: diphtheria antitoxin, not less than 0.61 antitoxin units/mL; neutralization of measles virus, not less than 0.18 × NIH reference lot 176; and neutralization of polio virus, not less than 0.085 × NIH reference lot 176. Gammalex® exceeds these limits: diphtheria antitoxin ~4 (range: 3–6); measles antibody ~0.4 (range: 0.38–0.5); and polio-1 antibody ~0.35 (range: 0.12–0.5) (Gammalex Product Monograph 2011).

Gammalex® contains a number of excipients that render it suitable for IV administration (by helping to maintain the natural monomeric state of the IgG) and that stabilize the IgG for long-term storage in the container. These excipients are used at strictly controlled concentrations (Gammalex Product Monograph 2011). Gammalex® contains sorbitol as a stabilizer, thereby reducing the risk of renal adverse events seen with IGIV products (particularly those containing sucrose) in at-risk patients (FDA 2008, Gammalex PI 2010). Gammalex® is also formulated at a slightly acidic pH (typically 4.9–5.0) for improved stability and to provide additional virus inactivation during incubation in the final container (Gammalex PI 2010, Gammalex Product Monograph 2011).

THE MANUFACTURE OF GAMMAPLEX®

The quality assurance process employed by Bio Products Laboratory helps ensure that Gammalex® is produced to strict standards of quality and safety (Gammalex Product Monograph 2011):

- Manufactured from an FDA-accredited plasma source
- Manufactured to Good Manufacturing Practice standards at an FDA-inspected processing facility
- Produced using a manufacturing process based on cold ethanol fractionation followed by ion exchange chromatography
- Manufactured using specific virus inactivation/removal procedures: solvent/detergent, virus filtration, and low-pH incubation

In conformance with US Pharmacopeia and European Pharmacopoeia requirements, each batch of Gammalex® contains many thousands of donations from more than 1,000 different donors. This ensures that a wide spectrum of antibodies is present in the product. Bio Products Laboratory draws its plasma from collection centers in the United States. These centers are licensed by the FDA and are members of the Plasma Protein Therapeutics Association (Gammalex Product Monograph 2011).

For the preparation of Gammalex®, IgG is isolated and purified from plasma by a multistage fractionation process. Cold ethanol fractionation is used to isolate the IgG-rich Fraction II precipitate in a series of steps. The Fraction II precipitate is then purified to approximately 100% IgG using ion exchange chromatography to remove impurities, such as IgA, IgM, and prekallikrein activator (Gammalex Product Monograph 2011).

Several specific and well proven virus inactivation steps (solvent/detergent treatment, virus filtration, and low-pH incubation) have been incorporated in the manufacture of Gammalex®. The solvent/detergent procedure was designed to inactivate enveloped viruses, such as hepatitis B virus, hepatitis C virus, and HIV, which are the viruses of principal concern in plasma products. It will also inactivate more recently described enveloped viruses, such as hepatitis G virus and West Nile virus. Virus filtration, the second specific virus-reduction step in the Gammalex® process, involves passing the immunoglobulin solution through a filter with a small pore size of 20 nm; the immunoglobulin molecules can pass through the filter, but any virus of approximately 20 nm or larger is trapped. Since the removal process is based on size, it is effective against both enveloped and nonenveloped viruses. Finally, viruses are inactivated during low-pH incubation. The filled product in its final closed container is incubated at 30°C (86°F) for 2 weeks. Under these conditions, the low-pH formulation and temperature contribute to effective inactivation of lipid-enveloped viruses and some nonenveloped viruses (Gammalex Product Monograph 2011).

CLINICAL EFFICACY

In a pivotal Phase 3 study conducted in the United States Gammalex® was shown to be clinically effective in patients with PI diseases. Fifty patients on regular IGIV replacement therapy for at least 3 months prior to participation were enrolled in the study. Twenty-six patients were male and 24 were female, with a mean age of 44 years (range: 9–78 years) (Gammalex PI 2010, Moy 2010).

Gammalex® was administered intravenously for a planned treatment period of 12 months, at 21-day (22 patients) or 28-day (28 patients) dosing intervals. The mean dose for the 21-day interval was 465 mg/kg (range: 330–693 mg/kg), and the mean dose for the 28-day interval was 458 mg/kg (range: 326–790 mg/kg). The maximum infusion rate allowed during the study was 0.08 mL/kg/min (Gammalex PI 2010, Moy 2010).

During the 12-month study period, no aSBIs occurred in any patient with an onset date between the first infusion of Gammalex® and the first follow-up visit, inclusive. The mean event rate of aSBIs per year was therefore zero (Gammalex PI 2010, Moy 2010).

IMPORTANT SAFETY INFORMATION

Contraindications

Gammalex® is contraindicated in patients who have had an anaphylactic or severe systemic reaction to the administration of human immunoglobulin. Gammalex® is also contraindicated in IgA-deficient patients with antibodies to IgA and a history of hypersensitivity reaction (Gammalex PI 2010).

Boxed Warning

The use of IGIV products, particularly those containing sucrose, has been reported to be associated with renal dysfunction, acute renal failure, osmotic nephropathy, and death (Gupta 2001). Patients at risk of acute renal failure include those with any degree of preexisting renal insufficiency, diabetes mellitus, advanced age (>65 years), volume depletion, sepsis, or paraproteinemia, or those receiving known nephrotoxic drugs (Gammalex PI 2010). Gammalex® does not contain sucrose (Gammalex PI 2010); the FDA, however, requires that a Black Box Warning be included in the prescribing information for all IGIV products (FDA 1998).

For patients at risk of renal dysfunction or failure, Gammalex® should be administered at the minimum infusion rate practicable (Gammalex PI 2010).

Warnings and Precautions

Hypersensitivity. Severe hypersensitivity reactions may occur. In case of hypersensitivity, the Gammalex® infusion should be discontinued immediately and appropriate treatment instituted. Medications, such as epinephrine, should be available for immediate treatment of acute hypersensitivity reactions (Gammalex PI 2010).

Gammalex® contains trace amounts of IgA (<10 mcg/mL).

Patients with known antibodies to IgA may have a greater risk of developing potentially severe hypersensitivity and anaphylactic reactions. Gammalex® is contraindicated in patients with antibodies against IgA and a history of hypersensitivity reaction (Gammalex PI 2010).

Renal dysfunction/failure. Acute renal dysfunction or failure, osmotic nephropathy, and death may occur during the use of human IGIV products. Physicians should ensure that patients are not volume depleted before administering Gammalex®. In patients who are at risk of developing renal dysfunction because of preexisting renal insufficiency or predisposition to acute renal failure (eg, diabetes mellitus, hypovolemia, overweight, use of concomitant nephrotoxic medicinal products, or age >65 years), Gammalex® should be administered at the minimum infusion rate practicable (Gammalex PI 2010).

Hyperproteinemia, increased serum viscosity, and hyponatremia. Hyperproteinemia, increased serum viscosity, and hyponatremia may occur in patients receiving IGIV therapy. It is critical to clinically distinguish true hyponatremia from a pseudohyponatremia that is associated with or causally related to hyperproteinemia with concomitant decreased calculated serum osmolality or elevated osmolar gap, because treatment aimed at decreasing serum-free water in patients with pseudohyponatremia may lead to volume depletion, a further increase in serum viscosity, and a possible predisposition to thrombotic events (Gammalex PI 2010).

Thrombotic events. Thrombotic events may occur following treatment with Gammalex® and other IGIV products. Patients at risk include those with a history of atherosclerosis, multiple cardiovascular risk factors, advanced age, impaired cardiac output, coagulation disorders, prolonged periods of immobilization, and/or known/suspected hyperviscosity. For at-risk patients, Gammalex® should be administered at the minimum rate of infusion practicable (Gammalex PI 2010).

Aseptic meningitis syndrome (AMS). AMS may occur infrequently with IGIV treatment. AMS usually begins within several hours to 2 days following IGIV treatment.

Discontinuation of IGIV treatment has resulted in remission of AMS within several days without sequelae. AMS may occur more frequently in association with high doses (2 g/kg) and/or rapid infusion of IGIV (Gammalex PI 2010).

Hemolysis. IGIV products may contain blood group antibodies that may act as hemolysins and induce in vivo coating of red blood cells (RBCs) with immunoglobulin, causing a positive direct antiglobulin reaction and, rarely, hemolysis. Delayed hemolytic anemia can develop subsequent to IGIV therapy because of enhanced RBC sequestration, and acute hemolysis, consistent with intravascular hemolysis, has been reported (Gammalex PI 2010).

Patients should be monitored for clinical signs and symptoms of hemolysis. If these are present after

Gammalex® infusion, the physician should perform appropriate confirmatory laboratory testing. If transfusion is indicated for patients who develop hemolysis with clinically compromising anemia after receiving IGIV, the physician should perform adequate cross-matching to avoid exacerbating ongoing hemolysis (Gammalex PI 2010).

Transfusion-related acute lung injury (TRALI). Noncardiogenic pulmonary edema may occur in patients following IGIV treatment. TRALI is characterized by severe respiratory distress, pulmonary edema, hypoxemia, normal left ventricular function, and fever. Symptoms typically appear within 1 to 6 hours after treatment. Physicians should monitor patients for pulmonary adverse reactions. If TRALI is suspected, physicians should perform appropriate tests for the presence of antineutrophil antibodies in both the product and the patient's serum. TRALI may be managed using oxygen therapy with adequate ventilatory support (Gammalex PI 2010).

Transmissible infectious agents. Gammalex® is made from human plasma. Based on effective donor screening and product manufacturing processes, Gammalex® carries an extremely remote risk of transmission of viral diseases. A theoretical risk for transmission of Creutzfeldt-Jakob disease (CJD) also is considered to be extremely remote. No cases of transmission of viral diseases or CJD have been associated with the use of Gammalex®. Before prescribing Gammalex®, the physician should discuss the risks and benefits of its use with the patient (Gammalex PI 2010).

Monitoring: laboratory tests. Periodic monitoring of renal function and urine output is particularly important in patients judged to be at increased risk of developing acute renal failure. Physicians should assess renal function, including measurement of blood urea nitrogen and serum creatinine, before the initial infusion of Gammalex® and at appropriate intervals thereafter. If signs and/or symptoms of hemolysis are present after an infusion of Gammalex®, physicians should perform appropriate laboratory testing for confirmation. If TRALI is suspected, physicians should perform appropriate tests for the presence of antineutrophil antibodies in both the product and the patient's serum (Gammalex PI 2010).

Interference with laboratory tests. After infusion of immunoglobulin, the transitory rise of the various passively transferred antibodies in the patient's blood may yield positive serologic testing results, with the potential for misleading interpretation. Passive transmission of antibodies to erythrocyte antigens (eg, A, B, and D) may cause a positive direct or indirect antiglobulin (Coombs') test (Gammalex PI 2010).

Use in Specific Populations

Pregnancy. Gammalex® is a Pregnancy Category C drug. Animal reproduction studies have not been conducted with Gammalex®. It is not known whether

Gammaplex® can cause fetal harm when administered to a pregnant woman or can affect reproduction capacity. Gammaplex® should be given to a pregnant woman only if clearly needed. Immunoglobulins cross the placenta from maternal circulation increasingly after 30 weeks of gestation (Gammaplex PI 2010).

Nursing mothers. The use of Gammaplex® has not been evaluated in nursing mothers (Gammaplex PI 2010).

Pediatric use. Six pediatric patients with PI (2 between the ages of 9 and 10 years, and 4 between ages 12 and 16 years) were included within the clinical evaluation of Gammaplex®. This number of pediatric patients was too small for separate evaluation from the adult patients for safety or efficacy (Gammaplex PI 2010).

Geriatric use. Physicians should use caution when administering Gammaplex® to patients aged ≥65 years who are judged to be at increased risk of developing renal insufficiency or thrombotic events. Physicians should not exceed recommended doses and should administer Gammaplex® at the minimum infusion rate practicable. Eight patients with PI ages ≥65 years were included within the clinical evaluation of Gammaplex®. This number of geriatric patients was too small for separate evaluation from the younger patients for safety or efficacy (Gammaplex PI 2010).

Adverse Reactions

Two serious adverse reactions, thrombosis and chest pain, were observed in a single clinical study subject receiving Gammaplex®. The most common adverse reactions to Gammaplex® (reported in >5% of clinical trial subjects) were headache, fatigue, nausea, pyrexia, hypertension, myalgia, pain, and vomiting (Gammaplex PI 2010).

Drug Interactions

Passive transfer of antibodies may transiently interfere with the immune response to live virus vaccines, such as measles, mumps, rubella, and varicella. The immunizing physician should be informed of recent therapy with Gammaplex® so that appropriate measures may be taken (Gammaplex PI 2010).

HOW SUPPLIED

Gammaplex® is a clear or slightly opalescent, colorless solution. The product is supplied in a single-use, clear Type II glass bottle, closed with a latex-free stopper (13% natural rubber) and oversealed with a tamper-evident cap. Each bottle has a label with a peel-off strip showing the product name and batch number (Gammaplex PI 2010, Gammaplex Product Monograph 2011). The label may be removed and applied to the patient's notes to maintain a record of the batches used.

Gammaplex® is available in the following presentations: 2.5 g in a 50-mL solution, 5 g in a 100-mL solution, and 10 g in a 200-mL solution (Gammaplex PI 2010).

STORAGE

Gammaplex® has been designed to be stored at room temperature, removing the constraints on patient usage and providing a product that is easier for hospitals and pharmacies to store (FDA 2008). Since Gammaplex can be stored throughout its shelf life at room temperature, the product can be used directly from the pharmacy, saving time for pharmacists and patients.

When Gammaplex® is stored between 2°C (35.6°F) and 25°C (77°F), it has a shelf life of 24 months. The drug product should be kept in its original carton to protect it from light. It should not be frozen (Gammaplex PI 2010).

Conclusion

In view of the economic and overall health impact of immunodeficiency disorders, P&T decision makers are aware of the need to optimize the clinical management of patients with these diseases. Gammaplex® (Immune Globulin Intravenous [Human], 5% Liquid) offers an effective treatment option for patients with PI. When evaluating Gammaplex® for inclusion in a formulary, P&T committee members should consider the product's proven clinical efficacy and tolerability along with cost implications. Selection or rejection of a drug based on acquisition cost alone may be more costly in the long run if biologic function or efficacy is compromised or if adverse events are higher and need to be managed (Gelfand 2003).

Therapy with IV immunoglobulin is a mainstay of treatment for a number of PI disorders. Gammaplex® is FDA-approved for replacement therapy of PI. This includes, but is not limited to, the humoral immune defect in common variable immunodeficiency, X-linked agammaglobulinemia, congenital agammaglobulinemia, Wiskott-Aldrich syndrome, and severe combined immunodeficiencies (Gammaplex PI 2010).

Gammaplex® offers the following clinical benefits (Gammaplex PI 2010):

- Proven protection against infections in PI patients (0% incidence of serious, acute bacterial infections in the pivotal Phase 3 trial)
- Low incidence of infusion-associated adverse events (most common: headache [7.5% of infusions], pyrexia [1.4%], fatigue [1.3%], sinusitis [1.3%], and nausea [1.0%])
- Mean half-life: 41 to 42 days
- Trace amounts of IgA (<10 mcg/mL)
- A broad spectrum of IgG antibodies against endemic pathogens
- The complete range of IgG subclasses
- Optimal pH (4.8–5.1) for stability and virus safety
- Three dedicated virus inactivation/removal steps incorporated into the manufacturing process
- 24-month shelf life with storage at room temperature (up to 25°C [77°F]); full storage range: 2–25°C (36–77°F)

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HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use Gammaplex® safely and effectively. See full prescribing information for Gammaplex®.

GAMMAPLEX, IMMUNE GLOBULIN INTRAVENOUS (HUMAN), 5% LIQUID

Initial U.S. Approval: 2009

WARNING: RENAL DYSFUNCTION/ ACUTE RENAL FAILURE

See full prescribing information for complete boxed warning.

- Renal dysfunction, acute renal failure, osmotic nephropathy, and death may be associated with the administration of Immune Globulin Intravenous (Human) (IGIV) products in predisposed patients.
- Renal dysfunction and acute renal failure occur more commonly in patients receiving IGIV products containing sucrose. Gammaplex does not contain sucrose.
- For patients at risk of renal dysfunction or failure, administer Gammaplex at the minimum infusion rate practicable.

INDICATIONS AND USAGE

Gammaplex is an Immune Globulin Intravenous (Human) indicated for the treatment of primary humoral immunodeficiency (PI).

DOSAGE AND ADMINISTRATION**Intravenous Use Only**

Indication	Dose	Initial infusion rate	Maintenance rate (if tolerated)
PI	300-800 mg/kg every 3-4 weeks	0.5 mg/kg/min (0.01 mL/kg/min) for 15 minutes	Increase to 4 mg/kg/min (0.08 mL/kg/min)

Infuse Gammaplex intravenously using an intravenous infusion set preferably fitted with an in-line 15-20 micron filter (2.3). Ensure that patients with pre-existing renal insufficiency are not volume depleted; discontinue Gammaplex if renal function deteriorates (5.1).

For patients at risk of renal dysfunction or thrombotic events, administer Gammaplex at the minimum infusion rate practicable (5.1, 5.2).

Dosage forms and strengths

Gammaplex is a liquid solution containing 5% IgG (50 mg/mL).

CONTRAINDICATIONS

- History of anaphylactic or severe systemic reactions to human immunoglobulin (4).
- IgA-deficient patients with antibodies against IgA and a history of hypersensitivity (4).

WARNINGS AND PRECAUTIONS

- IgA-deficient patients with antibodies to IgA are at greater risk of developing severe hypersensitivity and anaphylactic reactions (5.1).
- Monitor renal function, including blood urea nitrogen (BUN) and serum creatinine, and urine output in patients at risk of developing acute renal failure (5.2).
- Hyperproteinemia, increased serum viscosity, and hyponatremia may occur in patients receiving IGIV therapy (5.3).
- Thrombotic events may occur. Monitor patients with known risk factors for thrombotic events; consider baseline assessment of blood viscosity for those at risk of hyperviscosity (5.4).
- Aseptic meningitis syndrome may occur, especially with high doses or rapid infusion (5.5).
- Hemolysis can develop subsequent to IGIV treatments. Monitor patients for hemolysis and hemolytic anemia (5.6).
- Monitor patients for pulmonary adverse reactions (transfusion-related acute lung injury [TRALI]) (5.7).
- Gammaplex is made from human plasma and may contain infectious agents, e.g., viruses and, theoretically, the Creutzfeldt-Jakob disease agent (5.8).
- Passive transfer of antibodies may confound serologic testing (5.10).

ADVERSE REACTIONS

The most common adverse reactions during clinical trial (reported in >5% of subjects) were headache, fatigue, nausea, pyrexia, hypertension, myalgia, pain, and vomiting (6).

To report SUSPECTED ADVERSE REACTIONS, contact FFF on behalf of Bio Products Laboratory at 1-800-843-7477 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

DRUG INTERACTIONS

Passive transfer of antibodies may transiently interfere with the immune response to live virus vaccines, such as measles, mumps, and rubella (7).

USE IN SPECIFIC POPULATIONS

- Pregnancy: No human or animal data. Use only if clearly indicated. (8.1)
- Geriatrics: In patients over age 65 or in any patient at risk of developing renal insufficiency, do not exceed the recommended dose and infuse Gammaplex at the minimum rate practicable. (8.5)

See 17 for PATIENT COUNSELING INFORMATION.

Issued: SEP 2009

FULL PRESCRIBING INFORMATION: CONTENTS*

WARNING – ACUTE RENAL DYSFUNCTION/FAILURE

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FULL PRESCRIBING INFORMATION

Gammaplex®
Immune Globulin Intravenous (Human)
5% Liquid

WARNING: ACUTE RENAL DYSFUNCTION and ACUTE RENAL FAILURE

- Use of Immune Globulin Intravenous (IGIV) products, particularly those containing sucrose, have been reported to be associated with renal dysfunction, acute renal failure, osmotic nephropathy, and death. Patients at risk of acute renal failure include those with any degree of pre-existing renal insufficiency, diabetes mellitus, advanced age (above 65 years of age), volume depletion, sepsis, paraproteinemia, or receiving known nephrotoxic drugs (see *Warnings and Precautions [5.2]*). Gammaplex does not contain sucrose.
- For patients at risk of renal dysfunction or failure, administer Gammaplex at the minimum infusion rate practicable (see *Dosage and Administration [2.3]*, *Warnings and Precautions [5.2]*).

1 INDICATIONS AND USAGE

Gammaplex is an Immune Globulin Intravenous (Human), 5% Liquid indicated for the replacement therapy of primary humoral immunodeficiency (PI). This includes, but is not limited to, the humoral immune defect in common variable immunodeficiency, X-linked agammaglobulinemia, congenital agammaglobulinemia, Wiskott-Aldrich syndrome, and severe combined immunodeficiencies.

2 DOSAGE AND ADMINISTRATION**For Intravenous Use Only****2.1 Preparation and Handling**

- Gammaplex is a clear or slightly opalescent, colorless solution. Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit. Do not use if the solution is cloudy or turbid, or if it contains particulate matter.
- Do not freeze, and do not use any solution that has been frozen.
- DO NOT SHAKE.
- Gammaplex should be at room temperature (up to 25°C [77°F]) at the time of administration.
- Do not use Gammaplex beyond the expiration date on the product label.
- The Gammaplex vial is for single use only. Due to the absence of anti-microbial preservatives, promptly administer Gammaplex after piercing the cap. Dispose of partially used or unused product in accordance with local requirements.
- Infuse Gammaplex using a separate infusion line.
- Do not mix Gammaplex with other intravenous medications (including normal saline) or other IGIV products.
- An infusion pump may be used to control the rate of administration.
- If large doses of Gammaplex are to be administered, several vials may be pooled using aseptic technique. Begin infusion within 2 hours after pooling.

2.2 Recommended Dose

As there are significant differences in the half-life of IgG among patients with PI, the frequency and amount of immunoglobulin therapy may vary from patient to patient. The proper amount can be determined by monitoring clinical response.

The recommended dose of Gammaplex for patients with PI is 300 to 800 mg/kg (6 to 16 mL/kg), administered every 3 to 4 weeks. Adjust the dosage over time to achieve the desired serum trough levels and clinical responses. If a patient misses a dose, administer the missed dose as soon as possible, and then resume scheduled treatments every 3 or 4 weeks, as applicable.

2.3 Administration

- Hydrate the patient adequately prior to the initiation of infusion.
- Due to the absence of anti-microbial preservatives, promptly administer Gammaplex after piercing the cap.
- Infuse Gammaplex intravenously using an intravenous infusion set preferably fitted with an in-line 15-20 micron filter.

Table 1: Recommended Infusion Rates for Gammaplex

Indication	Initial infusion rate for first 15 minutes	Maintenance infusion rate (if tolerated)
PI	0.5 mg/kg/min (0.01 mL/kg/min)	Increase gradually every 15 minutes to 4 mg/kg/min (0.08 mL/kg/min)

Monitor vital signs throughout the infusion. Slow or stop the infusion if adverse reactions occur. If symptoms subside promptly, the infusion may be resumed at a lower rate that is comfortable for the patient.

The observation time of patients after Gammaplex administration may vary. If the patient (a) has not received Gammaplex or another IgG product, (b) is switched from an alternative IGIV product or (c) has had a long interval since the previous infusion, prolong the observation time for adverse reactions after Gammaplex infusion.

Certain severe adverse drug reactions may be related to the rate of infusion. Slowing or stopping the infusion often allows the reaction to disappear promptly.

Ensure that patients with pre-existing renal insufficiency are not volume depleted. For patients judged to be at risk for renal dysfunction or thrombotic events, administer Gammaplex at the minimum infusion rate practicable, and discontinue Gammaplex administration if renal function deteriorates (see *Boxed Warning, Warnings and Precautions [5.2]*).

3 DOSAGE FORMS AND STRENGTHS

Gammaplex is a liquid solution containing 5% IgG (50 mg/mL).

4 CONTRAINDICATIONS

- Gammaplex is contraindicated in patients who have had an anaphylactic or severe systemic reaction to the administration of human immune globulin.
- Gammaplex is contraindicated in IgA-deficient patients with antibodies to IgA and a history of hypersensitivity.

5 WARNINGS AND PRECAUTIONS

- Weigh the potential risks and benefits of Gammaplex against those of alternative therapies in all patients for whom Gammaplex is being considered.
- Before prescribing Gammaplex, the physician should discuss the risks and benefits of its use with the patient.

5.1 Hypersensitivity

Severe hypersensitivity reactions may occur (see *Contraindications [4]*). In case of hypersensitivity, discontinue Gammaplex infusion immediately and institute appropriate treatment. Medications such as epinephrine should be available for immediate treatment of acute hypersensitivity reactions.

Gammaplex contains trace amounts of IgA (<10 µg/mL) (see *Description [11]*). Patients with known antibodies to IgA may have a greater risk of developing potentially severe hypersensitivity and anaphylactic reactions. Gammaplex is contraindicated in patients with antibodies against IgA and a history of hypersensitivity reaction (see *Contraindications [4]*).

5.2 Renal Dysfunction/Failure

Acute renal dysfunction/failure, osmotic nephropathy, and death¹ may occur upon use of human IGIV products. Ensure that patients are not volume depleted before administering Gammaplex. In patients who are at risk of developing renal dysfunction, because of pre-existing renal insufficiency or predisposition to acute renal failure (such as diabetes mellitus, hypovolemia, overweight, use of concomitant nephrotoxic medicinal products or age of >65 years), administer Gammaplex at the minimum infusion rate practicable (see *Dosage and Administration* [2.3]).

Periodic monitoring of renal function and urine output is particularly important in patients judged to be at increased risk of developing acute renal failure. Assess renal function, including measurement of blood urea nitrogen (BUN) and serum creatinine, before the initial infusion of Gammaplex and at appropriate intervals thereafter. If renal function deteriorates, consider discontinuing Gammaplex.

5.3 Hyperproteinemia, Increased Serum Viscosity, and Hyponatremia

Hyperproteinemia, increased serum viscosity, and hyponatremia may occur in patients receiving IGIV therapy. It is critical to clinically distinguish true hyponatremia from a pseudohyponatremia that is associated with or causally related to hyperproteinemia with concomitant decreased calculated serum osmolality or elevated osmolar gap, because treatment aimed at decreasing serum free water in patients with pseudohyponatremia may lead to volume depletion, a further increase in serum viscosity, and a possible predisposition to thrombotic events.²

5.4 Thrombotic Events

Thrombotic events may occur following treatment with Gammaplex and other IGIV products.^{2,3} Patients at risk include those with a history of atherosclerosis, multiple cardiovascular risk factors, advanced age, impaired cardiac output, coagulation disorders, prolonged periods of immobilization, and/or known/suspected hyperviscosity.

Consider baseline assessment of blood viscosity in patients at risk for hyperviscosity, including those with cryoglobulins, fasting chylomicronemia/ markedly high triacylglycerols (triglycerides), or monoclonal gammopathies. For patients judged to be at risk of developing thrombotic events, administer Gammaplex at the minimum rate of infusion practicable (see *Dosage and Administration* [2.3]).

5.5 Aseptic Meningitis Syndrome (AMS)

AMS may occur infrequently with IGIV treatment. AMS usually begins within several hours to 2 days following IGIV treatment. Discontinuation of IGIV treatment has resulted in remission of AMS within several days without sequelae.⁴

AMS is characterized by the following signs and symptoms: severe headache, nuchal rigidity, drowsiness, fever, photophobia, painful eye movements, nausea, and vomiting (see *Patient Counseling Information* [17]). Cerebrospinal fluid (CSF) studies frequently reveal pleocytosis up to several thousand cells per cubic millimeter, predominantly from the granulocytic series, and elevated protein levels up to several hundred mg/dL, but negative culture results. Conduct a thorough neurological examination on patients exhibiting such signs and symptoms, including CSF studies, to rule out other causes of meningitis.

AMS may occur more frequently in association with high doses (2 g/kg) and/or rapid infusion of IGIV.

5.6 Hemolysis

IGIV products can contain blood group antibodies that may act as hemolysins and induce in vivo coating of red blood cells (RBCs) with immunoglobulin, causing a positive direct antiglobulin reaction and, rarely, hemolysis^{5,7}. Delayed hemolytic anemia can develop subsequent to IGIV therapy due to enhanced RBC sequestration⁸, and acute hemolysis, consistent with intravascular hemolysis, has been reported.

Monitor patients for clinical signs and symptoms of hemolysis (see *Patient Counseling Information* [17]). If these are present after Gammaplex infusion, perform appropriate confirmatory laboratory testing. If transfusion is indicated for patients who develop hemolysis with clinically compromising anemia after receiving IGIV, perform adequate cross-matching to avoid exacerbating on-going hemolysis.

5.7 Transfusion-related Acute Lung Injury (TRALI)

Noncardiogenic pulmonary edema may occur in patients following IGIV treatment⁹. TRALI is characterized by severe respiratory distress, pulmonary edema, hypoxemia, normal left ventricular function, and fever. Symptoms typically appear within 1 to 6 hours following treatment.

Monitor patients for pulmonary adverse reactions. If TRALI is suspected, perform appropriate tests for the presence of anti-neutrophil antibodies in both the product and the patient's serum.

TRALI may be managed using oxygen therapy with adequate ventilatory support.

5.8 Transmissible Infectious Agents

Gammaplex is made from human plasma. Based on effective donor screening and product manufacturing processes (see *Description* [11]), Gammaplex carries an extremely remote risk of transmission of viral diseases. A theoretical risk for transmission of Creutzfeldt-Jakob disease (CJD) also is considered to be extremely remote. No cases of transmission of viral diseases or CJD have been associated with the use of Gammaplex. All infections suspected by a physician possibly to have been transmitted by this product should be reported by the physician or other healthcare provider to FFF on behalf of Bio Products Laboratory (800) 843-7477. Before prescribing Gammaplex, the physician should discuss the risks and benefits of its use with the patient (see *Patient Counseling Information* [17]).

5.9 Monitoring: Laboratory Tests

- Periodic monitoring of renal function and urine output is particularly important in patients judged to be at increased risk of developing acute renal failure. Assess renal function, including measurement of BUN and serum creatinine, before the initial infusion of Gammaplex and at appropriate intervals thereafter.
- Because of the potentially increased risk of thrombosis, consider baseline assessment of blood viscosity in patients at risk for hyperviscosity, including those with cryoglobulins, fasting chylomicronemia/ markedly high triacylglycerols (triglycerides), or monoclonal gammopathies.
- If signs and/or symptoms of hemolysis are present after an infusion of Gammaplex, perform appropriate laboratory testing for confirmation.
- If TRALI is suspected, perform appropriate tests for the presence of anti-neutrophil antibodies in both the product and patient's serum.

5.10 Interference with Laboratory Tests

- After infusion of immunoglobulin, the transitory rise of the various passively transferred antibodies in the patient's blood may yield positive serological testing results, with the potential for misleading interpretation. Passive transmission of antibodies to erythrocyte antigens (e.g., A, B, and D) may cause a positive direct or indirect antiglobulin (Coombs') test.

6 ADVERSE REACTIONS

Two serious adverse reactions, thrombosis and chest pain, were observed in a clinical study subject receiving Gammaplex.

The most common adverse reactions to Gammaplex (reported in >5% of clinical trial subjects) were headache, fatigue, nausea, pyrexia, hypertension, myalgia, pain, and vomiting.

6.1 Clinical Studies Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in clinical practice.

In a multicenter, open-label, non-randomized clinical study, 50 subjects with primary humoral immunodeficiency received doses of Gammaplex ranging from 279 to 799 mg/kg every 21 days (mean dose 465 mg/kg) or 28 days (mean dose 458 mg/kg), for up to 12 months (see *Clinical Studies* [14.1]). Routine premedication was not allowed. Of the 703 infusions administered, 2 (4%) subjects received premedication (antipyretic, antihistamine, or antiemetic agent) prior to 2 courses of treatment, because of experience with consecutive infusion-related adverse reactions.

All 50 subjects had an adverse event at some time during the study. Twenty-four subjects (48.0%) had an adverse reaction at some time during the study that was considered product-related. More subjects with the 21-day infusion cycle had at least one adverse reaction (14 of 22 subjects, 63.6%) than subjects with the 28-day infusion cycle (10 of 28 subjects, 35.7%). Of these 24 subjects who showed adverse reactions, only 3 subjects had adverse reactions that were considered definitely related to Gammaplex: headache, pyrexia, tachycardia, chest discomfort, and hypertension.

The most common adverse reactions observed in this clinical trial were headache (18 subjects, 36.0%), fatigue (6 subjects, 12.0%), nausea (6 subjects, 12.0%), pyrexia (6 subjects, 12.0%), hypertension (3 subjects, 6.0%), myalgia (3 subjects, 6.0%), pain (3 subjects, 6.0%), and vomiting (3 subjects, 6.0%).

Temporally associated adverse events (AEs) are those occurring during or within 72 hours after the end of an infusion, *irrespective of causality*. In this study, the upper bound of the 1-sided 97.5% confidence interval for the proportion of Gammaplex infusions temporally associated with one or more AEs was 24.2% (actual proportion: 21.2%). This is below the target of 40% for this safety endpoint. The total number of temporally associated AEs was 237 (a rate of 0.34 AEs per infusion), reflecting that some subjects experienced more than one AE during the observation period.

Table 2 lists the temporally associated AEs that occurred in more than 5% of subjects during a Gammaplex infusion or within 72 hours after the end of an infusion, *irrespective of causality*.

Table 2: Adverse Events Occurring in >5% of Subjects with PI during a Gammaplex Infusion or within 72 Hours after the End of an infusion, Irrespective of Causality

Adverse Event	Subjects (%) [n=50]	Infusions (%) [n=703]
Headache	18 (36%)	53 (7.5%)
Sinusitis	8 (16%)	9 (1.3%)
Pyrexia	7 (14%)	10 (1.4%)
Nausea	6 (12%)	7 (1.0%)
Pain	5 (10%)	5 (0.7%)
Chills	3 (6%)	5 (0.7%)
Fatigue	3 (6%)	9 (1.3%)
Hypertension	3 (6%)	4 (0.6%)
Insomnia	3 (6%)	3 (0.4%)
Nasal Congestion	3 (6%)	3 (0.4%)
Upper respiratory tract infection	3 (6%)	5 (0.7%)
Vomiting	3 (6%)	3 (0.4%)

Of the 237 temporally associated AEs reported for the 50 subjects, the investigators judged 115 to be related to the infusion of Gammaplex. The most common temporally associated AEs judged to be related to Gammaplex infusion were headache (32% of subjects), pyrexia (8% of subjects), and nausea (8% of subjects).

Five subjects (10%) experienced seven serious AEs. Two of these serious AEs were considered related to Gammaplex treatment (thrombosis and chest pain). Three other subjects withdrew from the study due to the following AEs: paresthesia, bronchospasm, and pregnancy.

Forty-seven of the 50 subjects enrolled in this study had a negative direct antiglobulin test (DAT) at baseline. Of these 47 subjects, 4 (8.5%) developed a positive DAT at some time during the study. However, no subjects showed evidence of hemolytic anemia.

During this study, no subjects tested positive for infection due to human immunodeficiency virus (HIV), hepatitis B virus (HBV), hepatitis C virus (HCV), or B19 virus (B19V).

6.2 Postmarketing Experience

Because adverse reactions are voluntarily reported post-approval from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to product exposure. The following adverse reactions have been identified during post-approval use of intravenous immune globulins¹⁰:

- **Infusion reactions:** hypersensitivity (e.g., anaphylaxis), headache, diarrhea, tachycardia, fever, fatigue, dizziness, malaise, chills, flushing, urticaria or other skin reactions, wheezing or other chest discomfort, nausea, vomiting, rigors, back pain, myalgia, arthralgia, and changes in blood pressure
- **Renal:** Acute renal dysfunction/failure, osmotic nephropathy
- **Respiratory:** Apnea, Acute Respiratory Distress Syndrome (ARDS), TRALI, cyanosis, hypoxemia, pulmonary edema, dyspnea, bronchospasm
- **Cardiovascular:** Cardiac arrest, thromboembolism, vascular collapse, hypotension
- **Neurological:** Coma, loss of consciousness, seizures, tremor, aseptic meningitis syndrome
- **Integumentary:** Stevens-Johnson syndrome, epidermolysis, erythema multiforme, dermatitis (e.g., bullous dermatitis)
- **Hematologic:** Pancytopenia, leukopenia, hemolysis, positive direct antiglobulin (Coombs') test
- **Gastrointestinal:** Hepatic dysfunction, abdominal pain
- **General/Body as a Whole:** pyrexia, rigors

7 DRUG INTERACTIONS

Passive transfer of antibodies may transiently interfere with the immune response to live virus vaccines such as measles, mumps, rubella and varicella.^{11,12} Inform the immunizing physician of recent therapy with Gammaplex so that appropriate measures may be taken (see *Patient Counseling Information* [17]).

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Category C. Animal reproduction studies have not been conducted with Gammaplex. It is also not known whether Gammaplex can cause fetal harm when administered to a pregnant woman or can affect reproduction capacity. Gammaplex should be given to a pregnant woman only if clearly needed. Immunoglobulins cross the placenta from maternal circulation increasingly after 30 weeks of gestation^{13, 14}.

8.3 Nursing Mothers

Use of Gammaplex has not been evaluated in nursing mothers.

8.4 Pediatric Use

Six (6) pediatric patients with primary humoral immunodeficiency (2 between ages of 9 and 10, and 4 between ages 12 and 16) were included within the clinical evaluation of Gammaplex. This number of pediatric patients was too small for separate evaluation from the adult patients for safety or efficacy (see *Clinical Studies* [14]).

8.5 Geriatric Use

Use caution when administering Gammaplex to patients age 65 and over who are judged to be at increased risk of developing renal insufficiency or thrombotic events (see *Boxed Warning, Warnings and Precautions* [5.2, 5.4]). Do not exceed recommended doses, and administer Gammaplex at the minimum infusion rate practicable.

Eight (8) patients with primary humoral immunodeficiency at or over the age of 65 were included within the clinical evaluation of Gammaplex. This number of geriatric patients was too small for separate evaluation from the younger patients for safety or efficacy (see *Clinical Studies* [14]).

11 DESCRIPTION

Gammaplex is a ready to use sterile solution of polyclonal human Immunoglobulin G for IV administration that contains sorbitol, glycine and polysorbate 80 as stabilizers. Specifically, Gammaplex contains approximately 5 g normal human immunoglobulin and 5 g D-sorbitol in 100 mL of buffer solution containing: 0.6 g glycine, 0.2 g sodium acetate, 0.3 g sodium chloride, and ~5 mg polysorbate 80. Immunoglobulin G purity is > 95%, the pH is in the range of 4.8 to 5.1, and osmolality is not less than 240 mOsmol/kg (typically 420 to 500 mOsmol/kg). The distribution of the four IgG subclasses is approximately 64% IgG1, 30% IgG2, 5% IgG3, and 1% IgG4. The content of IgA is lower than 10 µg/mL. The anti-D and anti-A/anti-B hemagglutinin content of the drug product is strictly controlled to specification. Gammaplex contains no reducing carbohydrate stabilizers (e.g. sucrose, maltose) and no preservative.

Gammaplex is prepared from large pools of human plasma by a combination of cold ethanol fractionation and ion exchange chromatography. Fab functions tested include antigen binding activity, and Fc functions tested include complement activation and rubella antibody-mediated hemolysis.

Gammaplex is manufactured from plasma, obtained from healthy US donors, that have passed viral screening tests. All donors are subjected to medical examinations, laboratory tests, and a review of their medical history before being allowed to donate blood or plasma. There are several stages within this manufacturing process that contribute to viral reduction, including management of donors, screening of donations and specific virus removal steps during manufacturing.

All plasma donations are screened for antibody to HIV-1/2 and HCV, and hepatitis B surface antigen (HBsAg). Furthermore, plasma mini-pools (512 donations per pool) undergo nucleic acid amplification testing (NAT) for HIV, hepatitis B virus (HBV), HCV, hepatitis A virus (HAV) and Parvovirus B19. Further testing is carried out on the manufacturing pools for HBsAg, and antibody to HIV-1/2; HCV and Parvovirus B19 are also tested by NAT, with the limit for B19 set to not exceed 10⁴ IU B19 DNA per mL plasma.

There are three processing steps specifically designed to remove or inactivate viruses:

- 1) Solvent/Detergent treatment is targeted to enveloped viruses;
 - 2) A virus filtration step using Pall Ultipor DV20 is designed to remove small viruses including non-enveloped viruses, on a size exclusion basis; and
 - 3) The terminal low pH incubation step is identified as contributing to the overall viral clearance capacity for enveloped and non-enveloped viruses.
- 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. Overall virus reduction was calculated only from steps that were mechanistically independent from each other. In addition, each step was validated to provide robust virus reduction. The table below presents the contribution of each process step to virus reduction and the overall process reduction.

Table 3: Viral Reduction by Process Step

Virus	Type (Envelope/ Genome)	Size (nm)	Process Log ₁₀ Reduction of Virus (LRV) over manufacturing step			Total LRV
			Solvent Detergent	20 nm filtration	Terminal low pH/elevated temperature incubation	
HIV	Env/RNA	80-100	>6.8	I	>6.1	>12.9
SIN	Env/RNA	70	>6.7	6.2	>7.3	>20.2
WNV	Env/RNA	50	>6.4	I	NT	>6.4
BVDV	Env/RNA	40-60	>5.6	I	>6.1	>11.7
IBR	Env/DNA	200	>5.0	I	>6.3	>11.3
HAV	Non-Env/RNA	30	NA	>4.8	1.1	>5.9
EMC	Non-Env/RNA	30	NA	>4.8	2.7	>7.5

HIV: Human immunodeficiency virus

SIN: Sindbis virus, model for hepatitis C virus (HCV)

WNV: West Nile Virus

BVDV: Bovine viral diarrhea virus, model for HCV

IBR: Infectious bovine rhinotracheitis, bovine herpesvirus model for enveloped DNA viruses including hepatitis B

HAV: Hepatitis A virus

EMC: Encephalomyocarditis, model for HAV

NA: Not applicable, solvent detergent step is limited to the inactivation of enveloped viruses

I: Inactivation by the product intermediate precluded the accurate estimation of the removal of these viruses by the filtration step

NT: Not tested

B19: Viral clearance of Human Parvovirus B19 was investigated experimentally at the 20 nm filtration step. The estimated Log reduction Factor obtained was 6.0

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Gammplex is a replacement therapy for primary humoral immunodeficiency. It acts through a broad spectrum of opsonic and neutralizing IgG antibodies against pathogens and their toxins involving antigen binding and effector functions^{15,16}. However, the mechanism of action in PI has not been fully elucidated.

12.3 Pharmacokinetics

In the clinical study assessing safety and efficacy in primary humoral immunodeficiency, the pharmacokinetics of Gammplex was assessed for 28 days after administration to 24 subjects on 21- or 28-day infusion cycles. Blood samples for pharmacokinetic (PK) analysis were obtained after Infusion 9 for subjects on a 21-day schedule (9 subjects) and after infusion 7 for subjects on a 28-day schedule (15 subjects), i.e., during the sixth month after initiation of Gammplex treatment.

The mean dose (range) for those on the 21-day schedule was 476 mg/kg (range: 330 to 721 mg/kg), and it was 468 mg/kg (range: 324 to 799 mg/kg) for those on the 28-day schedule. Table 4 summarizes the PK parameters of Gammplex, measured as serum concentrations of total IgG.

Assessment of the clinical relevance of half-life measurements in this study should be viewed with caution. Although half-life estimates are provided for total IgG and the specific antibodies, drug elimination half-lives should be measured over a minimum period of at least 3 half-lives. However, the short dosing intervals relative to the long half-life of IgG in this clinical trial do not permit accurate assessment of half-life.

Table 4: Pharmacokinetic Parameters of Gammplex in Subjects with PI

Parameter (unit)	21-day Dosing Interval (n=9)	28-day Dosing Interval (n=15)
	Mean ± SD (Range)	Mean ± SD (Range)
C _{max} (mg/mL)	21.6 ± 3.8 (16.3-27.3)	21.4 ± 4.3 (15.9-31.0)
T _{max} (hr)	5.4 ± 7.2 (2.1-24.5)	6.1 ± 11.6 (2.4-48.1)
AUC _{0-tau} (days*mg/mL)	289 ± 41 (214-365)	346 ± 52 ^a (262-455) ^a
Half-Life (days)	42 ± 26 (22-108)	41 ± 14 ^a (22-70) ^a
Clearance (mL/days/kg)	0.59 ± 0.24 (0.19-1.02)	0.58 ± 0.27 ^a (0.24-1.28) ^a

a: n=14 for these calculations ; tau = dosing interval

14 CLINICAL STUDIES

In a Phase 3 multicenter, open-label study to evaluate the efficacy, safety, and pharmacokinetics of Gammalex in primary humoral immunodeficiency, 50 subjects on regular IGIV replacement therapy for at least 3 months prior to participation were treated for 12 months at 21-day (22 subjects) or 28-day (28 subjects) dosing intervals. Out of the 50 subjects, 26 were male and 24 were female, and 46 were Caucasian. They were in the age range of 9 to 78 years.

Doses ranged from 279 mg/kg to 799 mg/kg. The mean dose (range) for the 21-day interval was 465 mg/kg (330 - 693 mg/kg); the mean dose (range) for the 28-day interval was 458 mg/kg (326 - 790 mg/kg). Subjects received a total of 703 infusions of Gammalex. The maximum infusion rate allowed during this study was 0.08 mL/kg/min.

The primary analysis for efficacy was based on the annual rate of acute serious bacterial infections (aSBIs), defined as pneumonia, bacteremia/septicemia, osteomyelitis/septic arthritis, visceral abscess, and bacterial meningitis, per subject per year¹⁷. Other important clinical analyses for efficacy were based on the annual rate of infections, antibiotic use, days out of work/school/day care or unable to perform normal activities due to illness, and days of hospitalization.

During the 12-month study period, no serious acute bacterial infections occurred in any subject with an onset date between the first infusion of Gammalex and the first follow-up visit, inclusive. Thus, the mean event rate of serious, acute, bacterial infections per year was zero (with an upper 1-sided 99% confidence interval of 0.101).

Table 5: Summary of Efficacy Results in Subjects with PI

Number of Subjects	50
Total Number of Subject Days	16715
Infections	
Annual rate of confirmed serious acute bacterial infections*	0 /subject year †
Annual rate of other infections (median)	3.07 infections/subject year
Antibiotic use (therapeutic)	
Number of subjects (%)	40 (80%)
Annual rate	47.2 days/subject year
Out of work/school/day care or unable to perform normal activities due to illness	
Number of subjects (%)	23 (46%)
Number of days (%)	394 (2.36%)
Annual rate	8.73 days/subject year
Hospitalization	
Number of subjects (%)	4 (8%)
Number of days (%)	29 (0.17%)
Annual rate	0.75 days/subject year

*Defined as pneumonia, bacterial meningitis, bacteremia/septicemia, osteomyelitis/septic arthritis, and visceral abscess.

†Upper 1-sided 99% confidence interval: 0.101

Duration of exposure in all tables relating to GMX01 was calculated as the difference between the date of the last visit (first follow-up visit) i.e. approximately 10-14 days following the last dose of Gammalex and the date of the first Gammalex infusion (plus one day).

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16 HOW SUPPLIED/STORAGE AND HANDLING

Gammaplex is supplied in a single use, clear Type II glass bottle, closed with a stopper (13% natural rubber) and oversealed with a tamper-evident cap.

The following presentations of Gammaplex are available:

NDC Number	Grams and Fill Size
64208-8234-1	2.5g in 50 mL
64208-8234-2	5 g in 100 mL
64208-8234-3	10 g in 200 mL

Each vial has a label with a peel-off strip showing the product name and batch number.

When stored between 2 °C [35.6 °F] and 25 °C [77 °F], Gammaplex has a shelf life of 24 months, as indicated by the expiration date printed on the outer carton and vial label.

Keep Gammaplex in its original carton to protect it from light.

DO NOT FREEZE.

17 PATIENT COUNSELING INFORMATION

Inform patients to immediately report the following signs and symptoms to their healthcare professional:

- Decreased urine output, sudden weight gain, fluid retention/edema, and/or shortness of breath (see *Warnings and Precautions* [5.2]).
- Acute chest pain, shortness of breath, leg pain, and swelling of the legs/feet (see *Warnings and Precautions* [5.4]).
- Severe headache, neck stiffness, drowsiness, fever, sensitivity to light, painful eye movements, nausea and vomiting (see *Warnings and Precautions* [5.5]).
- Increased heart rate, fatigue, yellowing of skin or eyes, dark-colored urine (see *Warnings and Precautions* [5.6]).
- Trouble breathing, chest pain, blue lips or extremities, fever (see *Warnings and Precautions* [5.7]).

Inform patients that Gammaplex is made from human plasma and may contain infectious agents that can cause disease. While the risk that Gammaplex can transmit an infection has been reduced by screening plasma donors for prior exposure, testing donated plasma, and inactivating or removing certain viruses during manufacturing, patients should report any symptoms that concern them (see *Warnings and Precautions* [5.8]).

Inform patients that Gammaplex can interfere with their immune response to live viral vaccines (e.g., measles, mumps, and rubella), and instruct patients to notify their healthcare professional of this potential interaction when they are receiving vaccinations (see *Drug Interactions* [7]).

Manufactured by:
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