

# HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use GAMMAPLEX® 10% safely and effectively. See full prescribing information for GAMMAPLEX 10%.

GAMMAPLEX 10% Immune Globulin Intravenous [Human], 10% Liquid

Initial U.S. Approval: 2017

## WARNING: THROMBOSIS, RENAL DYSFUNCTION and ACUTE RENAL FAILURE

See full prescribing information for complete boxed warning.

- **Thrombosis may occur with immune globulin products, including GAMMAPLEX 10%. Risk factors may include: advanced age, prolonged immobilization, hypercoagulable conditions, history of venous or arterial thrombosis, use of estrogens, indwelling vascular catheters, hyperviscosity and cardiovascular risk factors (5.2)**
- **Renal dysfunction, acute renal failure, osmotic nephrosis, and death<sup>1</sup> may occur in predisposed patients with immune globulin intravenous (IGIV) products, including GAMMAPLEX 10%**
- **Renal dysfunction and acute renal failure occur more commonly with IGIV products containing sucrose. GAMMAPLEX 10% does not contain sucrose (5.1)**
- **For patients at risk of thrombosis, renal dysfunction or acute renal failure, administer GAMMAPLEX 10% at the minimum dose and infusion rate practicable. Ensure adequate hydration in patients before administration. Monitor for signs and symptoms of thrombosis and assess blood viscosity in patients at risk for hyperviscosity (2.3, 5.2)**

## RECENT MAJOR CHANGES

Indications and Usage (1.1)

04/2018

## INDICATIONS AND USAGE

GAMMAPLEX 10% is an Immune Globulin Intravenous (Human) 10% Liquid indicated for the treatment of:

- primary humoral immunodeficiency (PI) in adults and pediatric patients 2 years of age and older (1.1)
- chronic immune thrombocytopenic purpura (ITP) in adults (1.2)

## DOSAGE AND ADMINISTRATION

For Intravenous Use Only

Indication	Dose	Initial infusion rate	Maintenance infusion rate (if tolerated)
PI	300-800 mg/kg (3-8 mL/kg) every 3-4 weeks	0.5 mg/kg/min (0.005 mL/kg/min) for 15 minutes	Increase gradually every 15 minutes to 8 mg/kg/min (0.08 mL/kg/min)
ITP	1 g/kg (10 mL/kg) for 2 consecutive days	0.5 mg/kg/min (0.005 mL/kg/min) for 15 minutes	Increase gradually every 15 minutes to 8 mg/kg/min (0.08 mL/kg/min)

- Ensure that patients with pre-existing renal insufficiency are not volume depleted; discontinue GAMMAPLEX 10% if renal function deteriorates (2.3, 5.1)
- For patients at risk of renal dysfunction, thrombotic events or volume overload, administer GAMMAPLEX 10% at the minimum infusion rate practicable (2.3, 5.1, 5.2, 5.8)

## DOSAGE FORMS AND STRENGTHS

GAMMAPLEX 10% is a liquid solution containing 10% IgG (100 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 (5.3)
- Hyperproteinemia, increased serum viscosity, and hyponatremia may occur in patients receiving IGIV therapy (5.4)
- Aseptic meningitis syndrome may occur, especially with high doses or rapid infusion (5.5)
- Hemolysis, either intravascular or due to enhanced red blood cell sequestration, can develop subsequent to GAMMAPLEX 10% treatments. Risk factors include high doses and non-O blood group. Closely monitor patients for hemolysis and hemolytic anemia (5.6)
- Monitor patients for pulmonary adverse reactions (transfusion-related acute lung injury [TRALI]) (5.7)
- Volume overload can occur. Monitor for signs and symptoms (5.8)
- Consider risks and benefits before prescribing the high dose regimen for chronic ITP in patients at risk of thrombosis, hemolysis, acute kidney injury, or volume overload (5)
- GAMMAPLEX 10% is made from human plasma and may contain infectious agents, e.g. viruses and, theoretically, the Creutzfeldt-Jakob disease agent (5.9)
- Passive transfer of antibodies may confound serologic testing (5.10)

## ADVERSE REACTIONS

- **PI** - The most common adverse reactions reported in ≥5% of clinical trial subjects were headache, migraine and pyrexia (6)
- **Chronic ITP** - The safety of GAMMAPLEX 10% has not been established in patients with ITP. However, the safety of GAMMAPLEX 5% has been studied in subjects with ITP, and it is anticipated that the safety profile for both formulations are comparable for ITP patients. Hence adverse reaction information is presented for GAMMAPLEX 5% where relevant. The most common adverse reactions reported with GAMMAPLEX 5% in ≥5% of clinical trial subjects with ITP were headache, vomiting, pyrexia, nausea, arthralgia and dehydration (6)

To report SUSPECTED ADVERSE REACTIONS, contact BPL Inc. (1-844-427-5872) or MedInfo@BPL-US.com, FDA (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, e.g. measles, mumps, and rubella (7)
- Therapy with GAMMAPLEX 10% may confound serological testing (7)

## USE IN SPECIFIC POPULATIONS

- **Pediatrics:** In pediatric patients 2 years of age and older, the pharmacokinetics, dosage and safety are similar to those in adults (8.4)
- **Geriatrics:** In patients over the age of 65 years or in any patient at risk of developing renal insufficiency, do not exceed the recommended dose and infuse GAMMAPLEX 10% at the minimum rate practicable (8.5)

See 17 for PATIENT COUNSELING INFORMATION.

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**WARNING: THROMBOSIS, RENAL DYSFUNCTION and ACUTE RENAL FAILURE**

- Thrombosis may occur with immune globulin products, including GAMMAPLEX 10%. Risk factors may include: advanced age, prolonged immobilization, hypercoagulable conditions, history of venous or arterial thrombosis, use of estrogens, indwelling central vascular catheters, hyperviscosity and cardiovascular risk factors. Thrombosis may occur in the absence of known risk factors [see Warnings and Precautions (5.2), Patient Counseling Information (17)].
- Renal dysfunction, acute renal failure, osmotic nephrosis, and death<sup>1</sup> may occur in predisposed patients who receive immune globulin intravenous (IGIV) products.
- Patients predisposed to renal dysfunction include those with any degree of pre-existing renal insufficiency, diabetes mellitus, age greater than 65 years, volume depletion, sepsis, paraproteinemia, or patients receiving known nephrotoxic drugs [see Warnings and Precautions (5.1)]. Renal dysfunction and acute renal failure occur more commonly in patients receiving IGIV products containing sucrose. GAMMAPLEX 10% does not contain sucrose.
- For patients at risk of thrombosis, renal dysfunction or acute renal failure, administer GAMMAPLEX 10% at the minimum dose and infusion rate practicable. Ensure adequate hydration in patients before administration. Monitor for signs and symptoms of thrombosis and assess blood viscosity in patients at risk for hyperviscosity [see Dosage and Administration (2.1, 2.3), Warnings and Precautions (5.2)].

**1 INDICATIONS AND USAGE**

- 1.1 Primary Humoral Immunodeficiency (PI)** – GAMMAPLEX 10% is an Immune Globulin Intravenous (Human), 10% Liquid indicated for replacement therapy in primary humoral immunodeficiency (PI) in adults and pediatric patients 2 years of age and older. 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.
- 1.2 Chronic Immune Thrombocytopenic Purpura (ITP)** – GAMMAPLEX 10% is indicated for the treatment of chronic immune thrombocytopenic purpura (ITP) in adults to raise platelet counts.

**2 DOSAGE AND ADMINISTRATION**

**For Intravenous Use Only**

**2.1 Dosage**

**Table 1: Recommended Dosage and Administration for GAMMAPLEX 10%**

Indication	Dose	Initial infusion rate	Maintenance infusion rate (if tolerated)
PI	300-800 mg/kg (3-8 mL/kg) every 3-4 weeks	0.5 mg/kg/min (0.005 mL/kg/min) for 15 minutes	Increase gradually every 15 minutes to 8 mg/kg/min (0.08 mL/kg/min)
ITP	1 g/kg (10 mL/kg) for 2 consecutive days	0.5 mg/kg/min (0.005 mL/kg/min) for 15 minutes	Increase gradually every 15 minutes to 8 mg/kg/min (0.08 mL/kg/min)

**Treatment of Primary Humoral Immunodeficiency**

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 10% for patients with PI is 300 to 800 mg/kg (3 to 8 mL/kg), administered every 3 to 4 weeks. If a patient routinely receives a dose of less than 400 mg/kg of GAMMAPLEX 10% every 3 to 4 weeks (less than 4 mL/kg), and is at risk of measles exposure (i.e. traveling to a measles endemic area), administer a dose of at least 400 mg/kg (4 mL/kg) just prior to the expected measles exposure. If a patient has been exposed to measles, a dose of 400 mg/kg (4 mL/kg) should be administered as soon as possible after exposure. Adjust the dosage over time to achieve the desired serum trough levels and clinical response. 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.

**Treatment of Chronic Immune Thrombocytopenic Purpura**

The recommended dose of GAMMAPLEX 10% for patients with ITP is 1 g/kg (10 mL/kg) on 2 consecutive days, providing a total dose of 2 g/kg. Carefully consider the relative risks and benefits before prescribing the high dose regimen (i.e. 1 g/kg/day for 2 days) in patients at increased risk of thrombosis, hemolysis, acute kidney injury, or volume overload [see Warnings and Precautions (5)]. Adequate data on the platelet response to the low dose regimen (e.g. 400 mg/kg per day for 5 consecutive days) are not available for GAMMAPLEX 10%.

**2.2 Preparation and Handling**

- GAMMAPLEX 10% is a clear or slightly opalescent, colorless solution. Visually inspect parenteral drug products 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
- GAMMAPLEX 10% vials are for single use only. Dispose of partially used or unused product
- GAMMAPLEX 10% contains no antimicrobial preservatives. Therefore, prompt administration after preparation is necessary
- Do not shake
- Administer GAMMAPLEX 10% at room temperature (up to 25°C [77°F])
- Do not use any solution that has been frozen [see How Supplied/Storage and Handling (16)]
- Infuse GAMMAPLEX 10% using a separate infusion line
- Do not mix GAMMAPLEX 10% with other intravenous medications (including normal saline) or other IGIV products
- An infusion pump may be used to control the rate of administration
- For administration of large doses, pool multiple vials using aseptic technique

**2.3 Administration**

- Hydrate the patient adequately prior to the initiation of infusion
- Infuse GAMMAPLEX 10% intravenously using an intravenous infusion set. See Table 1 for recommended infusion rates
- Monitor vital signs throughout the infusion
- Slow or stop the infusion if adverse reactions occur
- If symptoms subside, the infusion may be resumed at a lower rate that is comfortable for the patient
- The observation time of patients after GAMMAPLEX 10% administration may vary. If the patient (a) has not received GAMMAPLEX 10% 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 10% infusion
- Certain severe adverse reactions may be related to the rate of infusion. Slowing or stopping the infusion often allows the reaction to disappear
- Close monitoring of the infusion rate in pediatric patients is recommended
- Ensure that patients with pre-existing renal insufficiency are not volume depleted
- For patients at increased risk of renal dysfunction, thrombotic events, or volume overload, administer GAMMAPLEX 10% at the minimum infusion rate practicable. Consider discontinuing GAMMAPLEX 10% administration if renal function deteriorates [see Boxed Warning, Warnings and Precautions (5.1, 5.2, 5.8)]

**3 DOSAGE FORMS AND STRENGTHS**

GAMMAPLEX 10% is a liquid solution containing 10% IgG (100 mg/mL).

**4 CONTRAINDICATIONS**

- GAMMAPLEX 10% is contraindicated in patients who have had an anaphylactic or severe systemic reaction to the administration of human immune globulin
- GAMMAPLEX 10% is contraindicated in IgA-deficient patients with antibodies to IgA and a history of hypersensitivity

**5 WARNINGS AND PRECAUTIONS**

**5.1 Renal Dysfunction/Failure**

Acute renal dysfunction/failure, osmotic nephropathy, and death<sup>1</sup> may occur upon use of human IGIV products. Ensure that patients are not volume depleted before administering GAMMAPLEX 10%. In patients who are at risk of developing renal dysfunction, because of pre-existing renal insufficiency, predisposition to acute renal failure (such as diabetes mellitus, hypovolemia, overweight, use of concomitant nephrotoxic medicinal products or age >65 years), administer GAMMAPLEX 10% 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 10% and at appropriate intervals thereafter. If renal function deteriorates, consider discontinuing GAMMAPLEX 10%.

**5.2 Thrombotic Events**

Thrombosis may occur following treatment with immune globulin products, including GAMMAPLEX 10%.<sup>2</sup> Risk factors may include: advanced age, prolonged immobilization, hypercoagulable conditions, history of venous or arterial thrombosis, use of estrogens, indwelling central vascular catheters, hyperviscosity and cardiovascular risk factors. Thrombosis may occur in the absence of known risk factors.

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 at risk of thrombosis, administer GAMMAPLEX 10% at the minimum dose and infusion rate practicable. Ensure adequate hydration in patients before administration. Monitor for signs and symptoms of thrombosis and assess blood viscosity in patients at risk for hyperviscosity [see Boxed Warning, Dosage and Administration (2.3), Patient Counseling Information (17)].

**5.3 Hypersensitivity**

Severe hypersensitivity reactions may occur [see Contraindications (4)]. In case of hypersensitivity, discontinue GAMMAPLEX 10% infusion immediately and institute appropriate treatment. Medications such as epinephrine should be available for immediate treatment of acute hypersensitivity reactions.

GAMMAPLEX 10% contains trace amounts of IgA (<20 micrograms/mL) [see Description (11)]. Patients with known antibodies to IgA may have a greater risk of developing potentially severe hypersensitivity and anaphylactic reactions. GAMMAPLEX 10% is contraindicated in patients with antibodies against IgA and a history of hypersensitivity reaction [see Contraindications (4)].



## 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.

GAMMAPLEX 10% Postmarketing Experience

The following adverse reactions have been identified and reported during the postmarketing use of GAMMAPLEX 10%:

- **Cardiovascular:** Tachycardia, Thromboembolism, Hypertension, Flushing
- **Gastrointestinal:** Nausea
- **General/Body as a Whole:** Chills, Chest discomfort, Pyrexia
- **Musculoskeletal:** Back pain, Polymyositis
- **Neurological:** Headache
- **Respiratory:** Dyspnea
- **Integumentary:** Rash, Urticaria
- **Investigations:** Blood Pressure increased, Blood Pressure diastolic decreased

The following adverse reactions have been identified during postmarketing use of intravenous immune globulins<sup>9</sup>:

- **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, pulmonary embolism
- **Cardiovascular:** Cardiac arrest, thromboembolism, vascular collapse, hypotension, myocardial infarction
- **Neurological:** Coma, loss of consciousness, seizures, tremor, aseptic meningitis syndrome, migraine
- **Integumentary:** Stevens-Johnson syndrome, epidermolysis, erythema multiforme, dermatitis (e.g. bullous dermatitis)
- **Hematologic:** Pancytopenia, leukopenia, hemolysis, positive direct antiglobulin (Coombs') test
- **Musculoskeletal:** Musculoskeletal pain
- **Gastrointestinal:** Hepatic dysfunction, abdominal pain
- **General/Body as a Whole:** Pyrexia, rigors

## 7 DRUG INTERACTIONS

- Transitory rise of the various passively transferred antibodies in the patient's blood after infusion of immunoglobulin 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
- Passive transfer of antibodies may transiently interfere with the immune response to live virus vaccines such as measles, mumps, rubella and varicella.<sup>10, 11</sup>  
Inform the immunizing physician of recent therapy with GAMMAPLEX 10% so that appropriate measures may be taken [see Patient Counseling Information (17)]

## 8 USE IN SPECIFIC POPULATIONS

### 8.1 Pregnancy

#### Risk Summary

Animal reproduction studies have not been conducted with GAMMAPLEX 10%. It is also not known whether GAMMAPLEX 10% can cause fetal harm when administered to a pregnant woman or can affect reproduction capacity. GAMMAPLEX 10% should be given to a pregnant woman only if clearly needed. Immunoglobulins cross the placenta from maternal circulation increasingly after 30 weeks of gestation.<sup>12</sup>

### 8.2 LACTATION

#### Risk Summary

Use of GAMMAPLEX 10% has not been evaluated in breast-feeding mothers.

### 8.4 PEDIATRIC USE

In pediatric subjects 3 years of age and older, the pharmacokinetics, dosage and safety are similar to those in adults.

#### Treatment of Primary Humoral Immunodeficiency

GAMMAPLEX 10% was evaluated in 13 pediatric patients with primary humoral immunodeficiency (2 between ages of 3 to 5, 6 between ages of 6 to 11, and 5 between ages of 12 to 15). No pediatric-specific dose requirements were necessary to achieve the desired serum IgG levels [see Clinical Studies (14)]. The safety and pharmacokinetics of GAMMAPLEX 10% were assessed in pediatric subjects 3 years of age and older with PI [see Clinical Studies (14)].

#### Treatment of Chronic Immune Thrombocytopenic Purpura

The safety and effectiveness of GAMMAPLEX 10% has not been established in pediatric patients with ITP. GAMMAPLEX 5% was evaluated in three (3) pediatric subjects with chronic ITP (two aged 6 years and one aged 12 years). This number of pediatric patients was too small for separate evaluation from the adult patients for efficacy [see Clinical Studies (14)].

### 8.5 Geriatric Use

Use caution when administering GAMMAPLEX 10% to patients aged 65 years and over who are judged to be at increased risk of developing renal insufficiency or thrombotic events [see Boxed Warning, Warnings and Precautions (5.1, 5.2)]. Do not exceed recommended doses, and administer GAMMAPLEX 10% at the minimum infusion rate practicable. No subjects over the age of 55 years were included in the clinical study of GAMMAPLEX 10%. Eight (8) patients with PI at or over the age of 65 years were included within the clinical evaluation of GAMMAPLEX 5%. The number of geriatric patients was too small for separate evaluation from the younger patients for safety or efficacy [see Clinical Studies (14)].

### 10 OVERDOSAGE

Overdosage may lead to fluid overload and hyperviscosity, particularly in the elderly and in patients with renal impairment.

### 11 DESCRIPTION

GAMMAPLEX 10% is a ready to use sterile solution of polyclonal human Immunoglobulin G for intravenous administration that contains glycine and polysorbate 80 as stabilizers. Specifically, GAMMAPLEX 10% contains approximately 10 g normal human immunoglobulin and 200-300 mM glycine in 100 mL of buffer solution containing: <30 mM acetate, <30 mM sodium chloride and 1-6 mg polysorbate 80. Immunoglobulin G purity is ≥98%, the pH is in the range of 4.9 to 5.2, and osmolality is not less than 240 mOsmol/kg (typically 280 mOsmol/kg). The distribution of the four IgG subclasses reflects that of normal plasma. The content of IgA is less than 20 micrograms/mL. The anti-D and anti-A/anti-B hemagglutinin content of the drug product is strictly controlled to specification. GAMMAPLEX 10% contains no reducing carbohydrate stabilizers (e.g. sucrose, maltose) and no preservative.

GAMMAPLEX 10% 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 10% 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.

All plasma donations are screened for antibody to HIV-1/2 and hepatitis C virus (HCV), and hepatitis B surface antigen (HBsAg). Additional testing of donations is carried out in plasma mini-pools (512 donations per pool) that 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 10<sup>4</sup> 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 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. Table 5 presents the contribution of each process step to virus reduction and the overall process reduction.

Table 5: Viral Reduction by Process Step

Virus	Type (Envelope/ Genome)	Size (nm)	Process Log <sub>10</sub> 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	1	6.0	>12.8
SIN	Env/RNA	70	>6.7	6.2	>5.4	>18.3
WNV	Env/RNA	50	>6.4	1	NT	>6.4
BVDV	Env/RNA	40-60	>5.6	1	>4.0	>9.6
IBR	Env/DNA	200	>5.0	1	>5.4	>10.4
HAV	Non-Env/RNA	30	NA	>4.8	1.5	>6.3
EMC	Non-Env/RNA	30	NA	>4.8	3.4	>8.2
CPV	Non-Env/RNA	18-24	NA	3.2	1.0	4.2

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 herpes virus model for enveloped DNA viruses including hepatitis B

HAV: Hepatitis A virus

EMC: Encephalomyocarditis, model for HAV

CPV: Canine parvovirus, model for human parvovirus B19

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

1: 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

**Treatment of Primary Humoral Immunodeficiency** - GAMMAPLEX 10% is a replacement therapy for primary humoral immunodeficiency. GAMMAPLEX 10% acts through a broad spectrum of opsonic and neutralizing IgG antibodies against pathogens and their toxins involving antigen binding and effector functions.<sup>13,14</sup> However, the mechanism of action in PI has not been fully elucidated.

**Treatment of Chronic Immune Thrombocytopenic Purpura** - The mechanism of action of high doses of immunoglobulins in the treatment of chronic ITP has not been fully elucidated.

### 12.3 Pharmacokinetics

#### Treatment of Primary Humoral Immunodeficiency

In the cross-over clinical trial assessing bioequivalence, safety and tolerability between

GAMMAPLEX 10% and GAMMAPLEX 5% in PI, the pharmacokinetics (PK) of these products was assessed after administration to 30 adult subjects on 28-day (n = 16) or 21-day (n = 14) infusion cycles. Blood samples for PK analysis were obtained after at least five infusions.

The dose of GAMMAPLEX 10% ranged from 361-691 mg/kg for subjects on a 28-day cycle and from 254-794 mg/kg for those on a 21-day cycle. The doses of GAMMAPLEX 5% were similar to those of GAMMAPLEX 10% in this cross-over study. Table 6 compares the other PK variables parameters for GAMMAPLEX 10% and GAMMAPLEX 5% for both the 21-day and 28-day cycle regimens.

GAMMAPLEX 10% was pharmacokinetically equivalent to GAMMAPLEX 5% in adults.

PK outcomes after administration of GAMMAPLEX 10% were assessed in 13 pediatric subjects. Six subjects were on a 28-day regimen and 7 were on a 21-day regimen; doses for the PK assessments ranged from 400 to 745 mg/kg and 355 to 702 mg/kg respectively. Results are shown in Table 6 together with those from the adults in the study.

**Table 6: Pharmacokinetic Parameters of GAMMAPLEX 10% compared with GAMMAPLEX 5% in Adults, and GAMMAPLEX 10% in Pediatric Subjects (corrected for baseline concentration)**

Indication: Parameter (unit)	ADULTS				PEDIATRICS		
	GAMMAPLEX 10%		GAMMAPLEX 5%		GAMMAPLEX 10%		
	28-day Dosing Interval (n=16)	21-day Dosing Interval (n=14)	28-day Dosing Interval (n=16)	21-day Dosing Interval (n=14)	2-5 years (n=2)	6-11 years (n=6)	12-15 years (n=5)
	Mean§ (CV%)	Mean§ (CV%)	Mean§ (CV%)	Mean§ (CV%)	Mean§ (CV%)	Mean§ (CV%)	Mean§ (CV%)
C <sub>max</sub> (mg/dL)	1090 (20.5)	1150 (27.6)	1020 (23.6)	1090 (21.6)	1120 (33.5)	907 (37.9)	977 (34.9)
T <sub>max</sub> (hr) <sup>a</sup>	2.87 (1.6-31)	2.70 (1.8-7.8)	3.73 (2.1-9.0)	3.68 (2.2-5.7)	3.24 (2.8-3.7)	2.76 (2.0-5.1)	2.33 (1.7-4.5)
AUC <sub>0-τ</sub> † (days*mg/dL)	7830 (30.2)	6980 (33.0)	7230 (35.3)	6380 (32.8)	7620 (70.0)	6160 (71.1)	6650 (31.9)
Half-Life (hr)	123 (32.3)	118 (39.3)	132 (45.8)	119 (48.7)	167 (9.14)	111 (37.3)	144 (16.0)
Clearance (dL/day/kg)	0.0635 (24.0)	0.0674 (21.9)	0.0684 (37.6)	0.0743 (38.6)	0.0716 (19.3)	0.0845 (39.7)	0.0787 (19.3)
Volume of Distribution (dL/kg)	0.498 (27.4)	0.528 (50.3)	0.569 (38.4)	0.536 (32.6)	0.688 (7.45)	0.571 (28.8)	0.711 (26.4)

† AUC<sub>0-τ</sub> = area under the concentration versus time curve within a dosing interval, τ = dosing interval

C<sub>max</sub> = maximum observed concentration

T<sub>max</sub> = time at which C<sub>max</sub> was apparent

<sup>a</sup> Median and range are presented for t<sub>max</sub>

§ Geometric mean

## 14 CLINICAL STUDIES

### 14.1 Treatment of Primary Humoral Immunodeficiency

#### Pharmacokinetics, Safety and Tolerability study

A cross-over clinical trial assessed bioequivalence, safety and tolerability between GAMMAPLEX 10% and GAMMAPLEX 5% in PI after administration to 33 adult subjects on 28-day (n = 19) or 21-day (n = 14) infusion cycles, of whom 30 (90.9%) completed the PK component [see *Pharmacokinetics* (12.3)]. Thirty-two subjects completed the study of whom 12 were male and 20 were female. All adults were aged between 17 and 55 years. The mean doses of GAMMAPLEX 10% were 491.7 mg/kg for those on a 28-day cycle and 499.0 mg/kg for those on a 21-day cycle. For GAMMAPLEX 5%, the doses were similar: 473.5 and 502.1 mg/kg respectively. The maximum infusion rate was 0.08 mL/kg/min for each product and this rate was achieved by all adult subjects. In this study, PK bioequivalence was used as a surrogate marker for efficacy. Nevertheless, an *ad hoc* comparison was made between the products for the number of subjects reporting an infection while on each product. Comparing the number of subjects developing infections of any severity or type while on GAMMAPLEX 10% (22/32) with the period on GAMMAPLEX 5% (17/32) using the McNemar test provided an exact p value of 0.180, confirming the relevance of PK as a surrogate marker. No subject had an acute serious bacterial infection (SABI) during the study.

The pediatric population in the study comprised 15 subjects who received only GAMMAPLEX 10%, of whom 8 were on a 28-day cycle and 7 on a 21-day cycle. Of these, 13 completed the PK component (6 on a 28-day cycle and 7 on a 21-day cycle) [see *Pharmacokinetics* (12.3)]. There were two subjects in the 2-5 year age group, 7 in the 6-11 year age group and 6 in the 12-15 year age group. The mean dose across all infusions was 535.1 mg/kg. All pediatric subjects tolerated an infusion rate of 0.04 mL/kg/min and 8 subjects (53.3%) tolerated an infusion rate of 0.08 mL/kg/min for all infusions.

Overall, in the population receiving GAMMAPLEX 10%, the PK results (the surrogate for efficacy in this study) and the types and frequencies of adverse reactions were similar for the adult and pediatric populations.

### 14.2 Treatment of Chronic Immune Thrombocytopenic Purpura

The crossover bioequivalence study described in 14.1, above, did not include subjects with ITP. The results of the bioequivalence study comparing GAMMAPLEX 10% to GAMMAPLEX 5% in subjects with PI are supportive of the potential effectiveness of GAMMAPLEX 10% in the treatment of chronic ITP.

In a Phase 3 multicenter, open-label clinical trial to evaluate the efficacy and safety of GAMMAPLEX 5% in chronic ITP, of the 35 subjects enrolled from various ethnic groups, 9 were male and 26 were female. The age range was between 6 and 69 years. Subjects received intravenous infusions on two consecutive days (1 course) and then observed for a further 30 days. Individuals were given the option of a further two courses of treatment (if required), where only safety variables were assessed. Doses of GAMMAPLEX 5% ranged from 482 to 1149 mg/kg on Day 1 and Day 2. The median total dose per subject was 2035 mg/kg. Subjects received a total of 94 infusions (48 treatment courses). All 35 subjects received at least one infusion of clinical trial drug, and all but one subject completed the first course of treatment.

The primary analysis was based on the platelet count achieved by Day 9 after the first course of treatment with GAMMAPLEX 5%, response being defined as a platelet count of 50 x 10<sup>9</sup>/L or greater. Response to treatment on or before Day 9 was achieved by 29 of 35 subjects (82.9%), and the one-sided 97.5% lower confidence limit of the response rate was 66.4%, which met the *a priori* success criterion that required it to be greater than 60%.

Efficacy analyses included the duration of response, and changes in the incidences of bleeding or hemorrhage. At Day 32, the median (+ SD) platelet count (24 + [90] x 10<sup>9</sup>/L) was still higher than the baseline value, and 11 of 33 subjects (33.3%) continued to show response of platelet counts of 50 x 10<sup>9</sup>/L or greater. The median duration of platelet count response for the responders was 10 days.

**Table 7: Median Platelet Count (Standard deviation) and Number and Percent of Subjects with a Platelet Count > 50 x 10<sup>9</sup>/L during the clinical trial.**

Number of days in clinical trial	Day 1	Day 2	Day 3	Day 5	Day 9	Day 14	Day 21	Day 32
Median Platelet count (x 10 <sup>9</sup> /L) (Std Dev)	12.0 (11.4)	50.0 (36.4)	93.0 (97.3)	121.5 (151.9)	100.5 (201.3)	15.5 (113.0)	30.0 (80.0)	24.0 (89.9)
Number (n/N) and percent of subjects with a platelet count ≥ 50 x 10 <sup>9</sup> /L	0/35 (0.0%)	18/35 (51.4%)	22/32 (68.8%)	25/32 (78.1%)	22/32 (68.8%)	11/30 (36.7%)	10/29 (34.5%)	11/33 (33.3%)

GAMMAPLEX 5% infusions given on Days 1 and 2.

There was an increase in platelet counts for the majority of subjects, and an overall reduction in the manifestations of bleeding after treatment compared to baseline (Day 1). Petechiae, hematomas and gastrointestinal, pulmonary and genitourinary bleeds were all either reduced or absent by Day 32. There were no thromboembolic episodes reported in the clinical trial; and vital signs, biochemical, hematological and virology tests did not reveal any unexpected pathophysiology or toxicity.

## 15 REFERENCES

- Gupta N, Ahmed I, Nissel-Horowitz S, Patel D, Mehrotra B. Intravenous gammaglobulin-associated acute renal failure. *Am J Hematol* 2001; 66:151-152.
- Dalakas MC. High-dose intravenous immunoglobulin and serum viscosity: risk of precipitating thromboembolic events. *Neurology* 1994; 44:223-226.
- Gabor EP. Meningitis and skin reaction after intravenous immune globulin therapy. *Ann Intern Med* 1997; 127:1130.
- Wilson JR, Bhoopalani N, Fisher M. Hemolytic anemia associated with intravenous immunoglobulin. *Muscle Nerve* 1997; 20:1142-1145.
- Kessary-Shoham H, Levy Y, Shoenfeld Y, Lorber M, Gershon H. *In vivo* administration of intravenous immunoglobulin (IVIg) can lead to enhanced erythrocyte sequestration. *J Autoimmun* 1999; 13:129-135.
- Kahwaji J, Barker E, Pepkowitz S, et al. Acute Hemolysis After High-Dose Intravenous Immunoglobulin Therapy in Highly HLA Sensitized Patients. *Clin J Am Soc Nephrol* 2009;4:1993-1997.
- Daw Z, Padmore R, Neurath D, et al. Hemolytic transfusion reactions after administration of intravenous immune (gamma) globulin: A case series analysis. *Transfusion* 2008;48:1598-1601.
- Rizk A, Gorson KC, Kenney L, Weinstein R. Transfusion-related acute lung injury after the infusion of IVIG. *Transfusion* 2001; 41:264-268.
- Pierce LR, Jain N. Risks associated with the use of intravenous immunoglobulin. *Trans Med Rev* 2003; 17:241-251.
- Siber GA, Werner BG, Halsey NA, Reid R, Almeida-Hill J, Garrett SC, Thompson C, Santosham M. Interference of immune globulin with measles and rubella immunization. *J Pediatr* 1993; 122:204-211.
- Salisbury D, Ramsay M, Noakes K, eds. Immunisation against infectious disease. The Stationery Office (TSO), London: UK Department of Health, 2009; p426.
- Sidiropoulos D, Herrmann U, Morell A, von Muralt G, Barandun S. Transplacental passage of intravenous immunoglobulin in the last trimester of pregnancy. *J Pediatr* 1986; 109:505-508.
- Wood P, Stanworth S, Burton J, Jones A, Peckham DG, Chapel H. Recognition, clinical diagnosis and management of patients with primary antibody deficiencies: a systematic review. *Clin Exp Immunol* 2007; 149:410-423.
- Simon H, Späth P. IVIG – Mechanisms of action. *Allergy* 2003; 58(7):543-52.

**16 HOW SUPPLIED/STORAGE AND HANDLING**

GAMMAPLEX 10% is supplied in a single use, clear Type II glass bottle, closed with a stopper and oversealed with a tamper-evident cap.

The components used in the packaging for GAMMAPLEX 10% are not made with natural rubber latex.

The following presentations of GAMMAPLEX 10% are available:

Grams and Fill Size	Carton NDC Number	Vial NDC Number
5 g in 50 mL	64208-8235-5	64208-8235-1
10 g in 100 mL	64208-8235-6	64208-8235-2
20 g in 200 mL	64208-8235-7	64208-8235-3

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 10% has a shelf life of 36 months.

Keep GAMMAPLEX 10% in its original carton to protect it from light.

Do not shake.

Do not use GAMMAPLEX 10% beyond the expiration date on the product label.

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 (5.1)*]
- Acute chest pain, shortness of breath, leg pain, and swelling of the legs/feet [see *Warnings and Precautions (5.2)*]
- 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 10% is made from human plasma and may contain infectious agents that can cause disease. While the risk that GAMMAPLEX 10% 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 (5.9)*].

Inform patients that GAMMAPLEX 10% 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)*].

Instruct patients to immediately report symptoms of thrombosis. These symptoms may include: pain and/or swelling of an arm or leg with warmth over the affected area, discoloration of an arm or leg, unexplained shortness of breath, chest pain or discomfort that worsens on deep breathing, unexplained rapid pulse, numbness or weakness on one side of the body.

Manufactured by:

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United Kingdom.

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