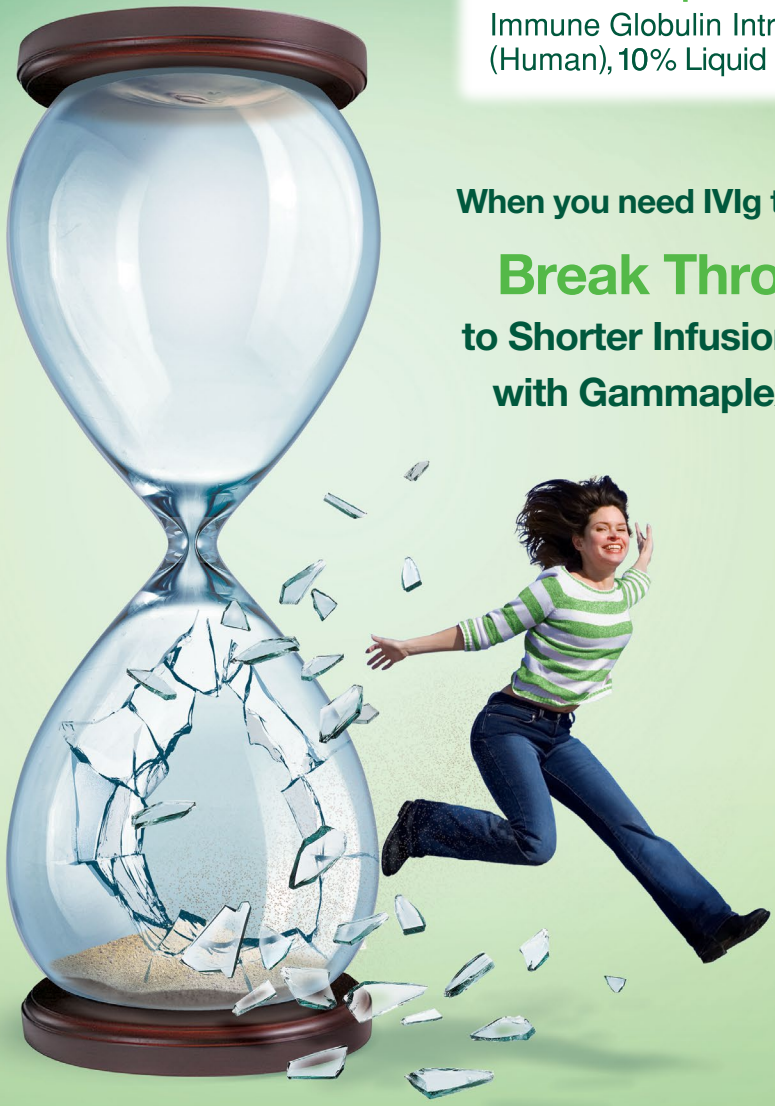
Gammaplex® 10%
Immune Globulin Intravenous
(Human), 10% Liquid

When you need IVIg therapy…

Break Through

to Shorter Infusion Times with Gammaplex 10%



Information for Patients

Please see Important Safety Information on pages 18-19 and Full Prescribing Information in pocket.

bpl
Bio Products Laboratory
a commitment for life

Get to know the terms used in this brochure

Antibodies: proteins produced by the immune system to defend the body against threats like viruses or bacteria

Autoimmune disorder: a disease caused by the immune system attacking the body's own healthy tissue

Clot: collection of platelets and other proteins that stick together to stop blood flow

Hematomas: a collection of clotted or partially clotted blood under the skin that looks or feels like a lump

Hereditary: runs in families; a parent can pass changes in the genes to a child

Intravenous: entering the blood stream through a vein; also called IV

Immune globulins: antibodies

Immune system: the cells, tissues, and organs that work together to protect the body against threats, such as bacteria and viruses

Petechiae: small red dots caused by minor bleeding under the skin; often looks like a rash

Plasma: liquid part of blood

Platelet: a type of blood cell that helps with blood clotting

Prophylactic: intended to prevent disease

Purpura: purple bruises on skin or mucous membranes

Spleen: an organ that filters blood and helps the body fight infection

Thrombocyte: also called a platelet; a type of blood cell that helps with blood clotting

Thrombocytopenia: low numbers of thrombocytes (platelets) in the blood; also called low platelet count

Table of contents

What is Primary Immunodeficiency (PI)?

PI is a group of conditions found in people who are born with a genetic error that affects their immune system.

In PI, one or more of the key parts of the immune system is missing or does not work the way it should. This can lead to problems with infections since the immune system helps protect the body against infection.

Getting an infection once in awhile may not be serious. But it can be more serious if infections become repeated or don't go away.

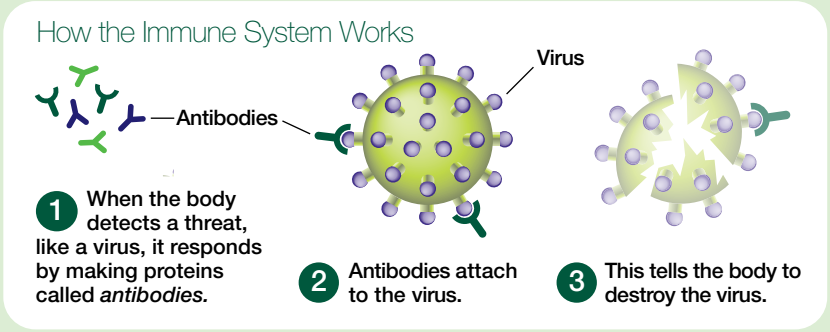
What causes PI?

PI is caused by one or more genetic errors. In many cases, these errors are hereditary (run in families). However, not everyone diagnosed with PI has a family history of PI.

- Different genetic errors can cause different types of PI. More than 400 different primary immunodeficiencies have been identified.

What is the immune system?

The immune system helps the body fight infection. It is made up of cells, tissues, and organs that work together to protect against outside threats like bacteria or viruses. The immune system works to destroy the threat and prevent infection.



Please see Important Safety Information on pages 18-19 and Full Prescribing Information in pocket.

Who can have Primary Immunodeficiency (PI)?

PI can affect anyone—male or female, any age, any race. Some types of PI affect the immune system from birth or early childhood. Other types may not cause problems until later in life.

How common is PI?

About 1 in every 1,200 to 2,000 people has some form of PI.

What are the signs of PI?

Infections are a common sign of PI because people with PI have a higher chance of getting infected. Infections may occur in the skin, sinuses, throat, ears, lungs, kidney or bladder (urinary tract), intestines (gut), and brain or spinal cord.

People with PI may have infections that are:

- Severe (requiring hospitalization or intravenous antibiotics)
- Persistent (hard to cure)
- Unusual (caused by a bacteria or virus that is not common)
- Recurrent (keep coming back, even with treatment)

How is PI diagnosed?

A doctor will ask about personal and family history of infections, such as severe or recurrent infections.

PI is diagnosed using blood tests.

- The most common test looks at levels of immune globulins, or antibodies. People with PI usually have low levels of one or more types of antibodies.
- If PI is suspected based on blood tests, more tests may be needed.

How is Primary Immunodeficiency (PI) treated?

PI cannot be cured, but most types of PI can be treated and managed. The goal of treatment is to reduce the severity and number of infections.

There are 3 main treatment options:

Prevention of infections: See page 7 to learn more.

Preventive antibiotics: Some patients with a history of certain respiratory tract infections may take antibiotics every day to help prevent infection. This may not be right for everyone—talk with your doctor to learn more.

Immune globulin (Ig) replacement therapy: Patients with some types of PI are not able to make enough immune globulins (antibodies).

- Ig replacement products contain antibodies. The products are made by purifying blood plasma donated by people without PI, who have a wide range of antibodies.
- Ig replacement products contain mainly immune globulin G (IgG), the most common antibody in the immune system.

How does Gammaplex 10% fit in?

Gammaplex 10% is an IgG replacement product that replaces the missing antibodies.

- In most cases, Gammaplex 10% is given once every 3 to 4 weeks.
- Gammaplex 10% is given using a small needle inserted into a vein. This is called an intravenous (IV) infusion, so you may hear Gammaplex 10% called IVIG (intravenous immune globulin).

You should not receive Gammaplex 10% if you have had an allergic reaction to an intravenous Ig treatment, or your doctor has told you that you are IgA-deficient with anti-IgA antibodies. Your doctor will discuss with you if there are any other reasons you should not take Gammaplex 10%.

Please see Important Safety Information on pages 18-19 and Full Prescribing Information in pocket.

In addition to medicine, how can infections be prevented?

Anyone can help prevent infections by using one or more of these tips:

Wash your hands before eating and after using the bathroom

Brush your teeth at least twice a day

Eat a healthy, well-balanced diet

Be physically active. Ask your doctor what activities are best for you

Get enough sleep, and try to keep a regular sleep schedule

Manage stress. Some studies suggest that stress can affect your immune system. To keep stress under control, consider massage, meditation, yoga, or hobbies

Avoid exposure. Stay away from people with colds or other infections and avoid crowds

Get vaccinated. Ask your doctor about which vaccines are right for you

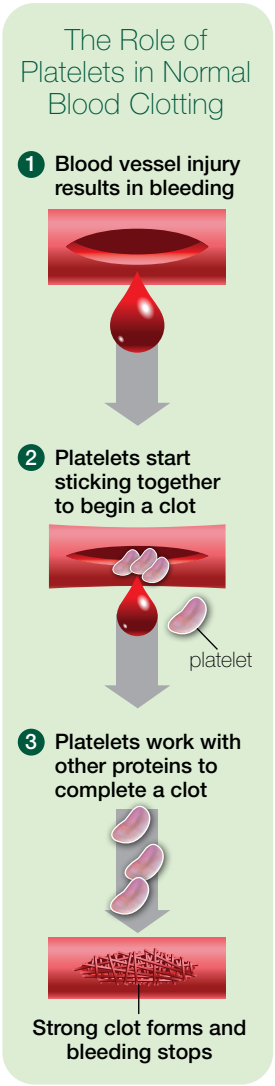
What is chronic immune thrombocytopenic purpura (ITP)?

ITP is a disorder where blood does not clot like it should. This is due to a low number of platelets. Platelets are tiny cells that stick together to help make clots and stop bleeding.

Chronic ITP can be easier to understand if you look at each word by itself:

- **Chronic**—long term (for ITP, this is 12 months or longer)
- **Immune**—dealing with the system that protects the body from infection
- **Thrombocytopenic**—low numbers of thrombocytes, also called platelets, which are needed for blood clotting
- **Purpura**—bruises

Without enough platelets, it takes longer than normal for blood to clot to stop bleeding. While major bleeding is rare in people with chronic ITP, bleeding in the brain can be life-threatening.



What causes ITP?

In most cases, ITP is caused by the immune system attacking the body's platelets by mistake.

- ITP is a type of autoimmune disorder. An autoimmune disorder occurs when the body attacks itself. The cause of this is not known.

Please see Important Safety Information on pages 18-19 and Full Prescribing Information in pocket.

Who can get chronic ITP?

Chronic ITP occurs most often in adults, and women are more likely than men to have it. About 1 in every 4,000 adults has chronic ITP.

What are the signs of ITP?

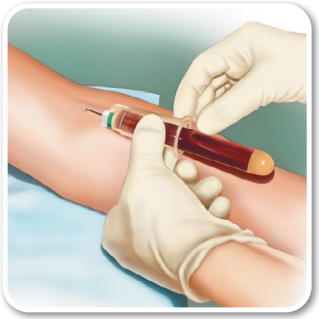
The most common sign of ITP is bleeding. People with ITP may have:

- Purpura—purple bruises on skin or mucous membranes, like inside the mouth
- Petechiae—tiny red dots caused by minor bleeding under the skin; often looks like a rash
- Hematomas—clotted or partly clotted blood under the skin that looks or feels like a lump
- Nosebleeds or bleeding from the gums
- Blood in the urine or stool
- Heavy menstrual bleeding (heavy periods) in women
- Any kind of bleeding that is hard to stop
- Fatigue or tired feeling

How is ITP diagnosed?

Your doctor will check to see if you have a low platelet count.

- A blood test is used to count the number of platelets in the blood.
- If the platelet count is low, more tests will be needed to find out if the cause is ITP or another cause.



Treatment of ITP

- The goal of treatment is to keep the platelet count at a safe level to prevent serious bleeding.
- People with mild ITP may not need to be treated.
- People with ITP who have heavy or serious bleeding and/or low platelet counts may be helped by treatment.

If ITP treatment is needed, treatment options include:

1. **Medicines to increase the platelet count**—This is often the first choice for treatment.
2. **Removal of the spleen**—The spleen is the organ that makes antibodies that attack the body's platelets in ITP.
3. **Platelet transfusions**—These replace the missing platelets with platelets from another person.

How does Gammaplex 10% fit in?

Gammaplex 10% immune globulin (IG) is one type of medicine that increases platelet counts.

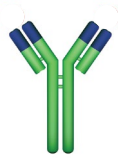
- Gammaplex 10% is given on 2 consecutive days.
- Gammaplex 10% is given using a small needle inserted into a vein. This is called an intravenous (IV) infusion, so you may hear Gammaplex 10% called IVIG (intravenous immune globulin).

The amount of Gammaplex 10% given will depend on your body weight. The infusion time will vary depending on the amount given and how well you tolerate it. During your first infusion, you will be watched closely and have your blood pressure, heart rate, and temperature checked regularly. If you feel well during the first 15 minutes of the infusion, the rate of the infusion will be increased gradually.

Please see Important Safety Information on pages 18-19 and Full Prescribing Information in pocket.

What is Gammaplex 10%?

Gammaplex 10% is a medicine that contains a type of antibody called immunoglobulin G (IgG). Because it is given by intravenous (IV) infusion, it is also called IVIG (intravenous immune globulin).



Immunoglobulin G (IgG)

What is Gammaplex 10% used for?

Gammaplex 10% is approved by the FDA for two different uses:

- **Primary Immunodeficiencies (PI):** In adult and pediatric patients 2 years of age and older with PI, Gammaplex 10% raises the level of antibodies to help prevent infections.
- **Chronic Immune Thrombocytopenic Purpura (ITP):** In adult patients with ITP, Gammaplex 10% helps to raise the level of platelets so that blood can clot normally.

How is Gammaplex 10% given?

Gammaplex 10% is given by an IV infusion administered by a healthcare professional. It can be given at a hospital, doctor's office, special infusion center, or in your home.

- **For PI,** Gammaplex 10% is usually given once every 3 to 4 weeks. Most patients will need to take Ig replacement therapy for their whole lives.
- **For ITP,** Gammaplex 10% is given once a day for 2 consecutive days when patients have low platelet levels.

Please see Important Safety Information on pages 18-19 and Full Prescribing Information in pocket.

Gammaplex 10% offers shorter infusion times*

- **The Gammaplex 10% infusion rate can be increased every 15 minutes until it reaches the highest recommended rate**
- **Gammaplex 10% reaches the highest recommended infusion rate faster than IVIG products that have infusion rate increases every 30 minutes**
- **The Gammaplex 10% infusion rate schedule offers a shorter infusion time if you are able to tolerate the medicine well**

Did you know?

People receiving a 35 g dose of Gammaplex 10% with infusion rate increases every 15 minutes could save approximately 1.5 hours in infusion time

*IVIG products are usually infused at a very slow rate to begin and then the infusion rate is slowly increased as long as you are doing well or any side effects are minor. A nurse or other healthcare professional will monitor your health during your infusion. They will slow or stop it if side effects cause discomfort or there is a risk to your health. Tell your doctor and the healthcare professional assisting with your infusion if you have any history of kidney disease or blood clots.

Who makes Gammaplex 10%?

Gammaplex 10% is made by Bio Products Laboratory (BPL). BPL has been producing plasma products for conditions like PI and ITP for over 60 years.

How is Gammaplex 10% made?

Gammaplex 10% is made from plasma donated by healthy individuals at collection centers across the US. Each center is inspected and licensed by the US Food and Drug Administration (FDA).

- After the plasma is collected, it is thoroughly screened and tested to make sure it is free from viruses and other infectious agents.
- The manufacturing process that purifies Gammaplex 10% from plasma includes three steps to remove or inactivate any viruses that might be present.

Even though Gammaplex 10% is highly purified, because it is made from human plasma there is a risk it may contain infectious agents, such as viruses and, theoretically, the Creutzfeldt-Jakob disease agent. There has never been a confirmed case of virus transmission with Gammaplex 10%.

Please see Important Safety Information on pages 18-19 and Full Prescribing Information in pocket.

What are the most common side effects with Gammaplex 10%?

The most common side effects with Gammaplex 10% in adults are:

- Headache
- Migraine
- Fever

Who should not take Gammaplex 10%?

You should not take Gammaplex 10% if:

- You have had a history of allergic reactions to human immune globulin
- You have an IgA deficiency and have antibodies to IgA and a history of hypersensitivity

If you have been told you have a risk factor for thrombosis (clot formation) or kidney damage, Gammaplex 10% may not be right for you—talk with your doctor.

BPL is committed to helping patients with the cost of their medicine

BPL provides reimbursement support for patients receiving Gammaplex 10%. Contact us for help with any insurance coverage questions, including out-of-pocket cost reimbursement

For assistance, you or your doctor can call or email BPL:

Call:
1-844-4BPLUSA
(844-427-5872)

Email:
reimbursement@bpl-us.com

BPL is here to answer your questions about GAMMAPLEX 10%

844-4BPLUSA

(844-427-5872)

For more information

To learn more about PI or ITP, visit these independent websites:

PI

Immune Deficiency Foundation
www.primaryimmune.org

Jeffrey Modell Foundation
www.jmfworld.com

International Patient Organization for Primary Immunodeficiencies
www.ipopi.org

ITP

Platelet Disorder Support Association
www.pdsa.org

To learn more about Gammaplex 10%, visit **www.gammaplex.com**

Important Safety Information for Gammaplex 10%

Gammaplex 10% (immune globulin intravenous [human], 10% liquid) is 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. Gammaplex 10% is also indicated for the treatment of chronic immune thrombocytopenic purpura (ITP) in adults.

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.**
- **Renal dysfunction, acute renal failure, osmotic nephrosis, and death may occur in predisposed patients who receive immune globulin intravenous (IGIV) products, including Gammaplex 10%.**
- **Patients predisposed to renal dysfunction include those with any degree of pre-existing renal insufficiency, diabetes mellitus, age greater than 65, volume depletion, sepsis, paraproteinemia, or patients receiving known nephrotoxic drugs. 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.**

Gammaplex 10% is contraindicated in patients who have had a history of anaphylactic or severe systemic reactions to human immune globulin and IgA deficient patients with antibodies to IgA and a history of hypersensitivity.

In patients at risk of developing acute renal failure, monitor renal function, including blood urea nitrogen (BUN), serum creatinine and urine output. Hyperproteinemia, increased serum viscosity, and hyponatremia may occur in patients receiving IGIV therapy.

Aseptic meningitis syndrome (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.

Hemolysis and hemolytic anemia can develop subsequent to IGIV treatments. Patient risk factors that may be associated with development of hemolysis include high dose (>2 g/kg), non-O blood group, and underlying inflammatory state. Noncardiogenic pulmonary edema may occur in patients following IGIV treatment (i.e. transfusion-related acute lung injury [TRALI]). Monitor patients for pulmonary adverse reactions. If TRALI is suspected, test product and patient's serum for anti-neutrophil antibodies.

Gammaplex 10% is made from human plasma and may contain infectious agents, e.g. viruses and, theoretically, the Creutzfeldt-Jakob disease agent. No cases of transmission of viral diseases or CJD have been associated with the use of Gammaplex 10%.

The most common adverse reactions in adult subjects receiving Gammaplex 10% in the PI clinical trial were headache, migraine, and pyrexia. The most common adverse reaction in pediatric subjects receiving Gammaplex 10% in the PI clinical trial was headache. There were no serious product-related adverse reactions observed in adult or pediatric clinical trial subjects with PI. The safety of Gammaplex 10% has not been established in patients with ITP. However, the safety profile for 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. The most common adverse reactions in adult subjects receiving Gammaplex 5% in the chronic ITP clinical trial were headache, vomiting, nausea, pyrexia, arthralgia, and dehydration. Serious adverse reactions observed in clinical trial subjects with ITP were headache, vomiting and dehydration.

Please see accompanying Full Prescribing Information for complete prescribing details.

When you need IVIg therapy…

Break Through

to Shorter Infusion Times with Gammaplex 10%

For more information about Gammaplex 10%, please visit
www.gammaplex.com

You are encouraged to report negative side effects of prescription drugs to the FDA. Visit www.fda.gov/medwatch, or call 1-800-FDA-1088.

Please see Important Safety Information on pages 18-19 and Full Prescribing Information in pocket.

Gammaplex® 10%
Immune Globulin Intravenous (Human), 10% Liquid

bpl
Bio Products Laboratory
a commitment for life

Manufactured by:
Bio Products Laboratory Limited, Dagger Lane, Elstree, Hertfordshire, WD6 3BX, United Kingdom
U.S. License No. 1811

www.bpl-us.com
www.gammaplex.com

For medical information queries, please call 844-4BPLUSA (844-427-5872) or email MedInfo@bpl-us.com

Individual HCPCS code for Gammaplex 10% **J1557**
US-Gx-2000014e Date of preparation: October 2020

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[1] 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
Dosage (2.1)	12/2018

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.

Revised: 09/2019

FULL PRESCRIBING INFORMATION: CONTENTS*

* Sections or subsections omitted from the full prescribing information are not listed.

FULL PRESCRIBING INFORMATION

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[1] 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 has been exposed to measles, it may be prudent to administer an extra dose of Immune Globulin Intravenous as soon as possible and within 6 days of exposure. A dose of 400 mg/kg should provide a serum level > 240 mIU/mL of measles antibodies for at least two weeks. If a patient is at risk of future measles exposure and receives a dose of less than 530 mg/kg every 3-4 weeks, the dose should be increased to at least 530 mg/kg. This should provide a serum level of 240 mIU/mL of measles antibodies for at least 22 days after infusion. 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[1] 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%[2]. 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)]*.

5.4 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].

5.5 Aseptic Meningitis Syndrome (AMS)

AMS may occur 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[3].

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

GAMMAPLEX 10% may contain blood group antibodies that can act as hemolysins and induce *in vivo* coating of red blood cells (RBCs) with immunoglobulin, causing a positive direct antiglobulin test (DAT) (Coombs' test) result and hemolysis[4]. Delayed hemolytic anemia can develop subsequent to IGIV therapy due to enhanced RBC sequestration; acute hemolysis, consistent with intravascular hemolysis, has been reported[5]. Cases of severe hemolysis-related renal dysfunction/failure or disseminated intravascular coagulation have occurred following infusion of IGIV.

The following risk factors may be associated with the development of hemolysis following IGIV administration: high doses (e.g. ≥2 g/kg), given either as a single administration or divided over several days, and non-O blood group[6]. Other individual patient factors, such as an underlying inflammatory state (as may be reflected by, for example, elevated C-reactive protein or erythrocyte sedimentation rate), have been hypothesized to increase the risk of hemolysis following administration of IGIV[7], but their role is uncertain. Hemolysis has been reported following administration of IGIV for a variety of indications, including ITP and PI[4].

Closely monitor patients for clinical signs and symptoms of hemolysis, particularly patients with risk factors noted above. Consider appropriate laboratory testing in higher risk patients, including measurement of hemoglobin or hematocrit prior to infusion and within approximately 36 to 96 hours post infusion. If clinical signs and symptoms of hemolysis or a significant drop in hemoglobin or hematocrit have been observed, perform 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 treatment[8]. 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 Volume Overload

Carefully consider the relative risks and benefits before prescribing the high dose regimen (for chronic ITP) in patients at increased risk of volume overload.

5.9 Transmissible Infectious Agents

As GAMMAPLEX 10% is made from human blood, it may carry a risk of transmitting infectious agents, e.g. viruses, the variant Creutzfeldt-Jakob disease (vCJD) agent and, theoretically, the Creutzfeldt-Jakob disease (CJD) agent. No cases of transmission of viral diseases or CJD have been associated with the use of GAMMAPLEX 10%. All infections suspected by a physician possibly to have been transmitted by this product should be reported by the physician or other healthcare providers to **BPL Inc. 1-844-427-5872 or MedInfo@BPL-US.com.**

Before prescribing GAMMAPLEX 10%, the physician should discuss the risks and benefits of its use with the patient *[see Patient Counseling Information (17)]*.

5.10 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
- Clinically assess patients with known renal dysfunction, diabetes mellitus, age greater than 65 years, volume depletion, sepsis, paraproteinemia, or those receiving nephrotoxic agents, and monitor as appropriate (BUN, serum creatinine, urine output) during therapy with GAMMAPLEX 10%
- Consider baseline assessment of blood viscosity in patients at risk for hyperviscosity, including those with polycythemia, cryoglobulins, fasting chylomicronemia/markedly high triglycerides, or monoclonal gammopathies
- Consider measuring hemoglobin or hematocrit at baseline and approximately 36 to 96 hours post infusion in patients at higher risk of hemolysis. If signs and/or symptoms of hemolysis are present after an infusion of GAMMAPLEX 10%, 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

6 ADVERSE REACTIONS

The safety information for GAMMAPLEX 10% is based on the clinical trial evaluating the bioequivalence of GAMMAPLEX 10% to GAMMAPLEX 5% in subjects with PI. The safety of GAMMAPLEX 10% has not been established in patients with ITP. However, the safety profile for 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 (AR) information is presented for GAMMAPLEX 5% where relevant. ARs are adverse events that were deemed by the investigators as causally related to GAMMAPLEX 10%.

There were no serious ARs observed with GAMMAPLEX 10% in the clinical trial in adult or pediatric subjects with PI.

Serious ARs observed with GAMMAPLEX 5% clinical trial subjects with ITP were headache, vomiting and dehydration. In addition, following a review of the data, 4 subjects (11%) were considered to have experienced asymptomatic suspected treatment-emergent hemolysis *[see Clinical Trials Experience (6.1)]*.

The following potential serious ARs are described above and/or elsewhere in the labeling:

- Thrombotic Events *[see Warnings and Precautions (5.2)]*
- Hemolysis *[see Warnings and Precautions (5.6)]*

The most common ARs occurring in ≥5% of adult subjects receiving GAMMAPLEX 10% in the PI clinical trial were headache (4 subjects, 12.5%), migraine (2 subjects, 6.3%) and pyrexia (2 subjects, 6.3%) and for pediatric subjects 3 years of age and older, in the same study, headache (3 subjects, 20.0%); other ARs occurred in a single pediatric subject. Overall, ARs which occurred in ≥5% of the adult and pediatric subjects combined are shown in Table 2.

The most common ARs occurring in ≥5% of adult subjects receiving GAMMAPLEX 5% in the chronic ITP clinical trial were headache (10 subjects, 28.6%), vomiting (6 subjects, 17.1%), pyrexia (5 subjects, 14.3%), nausea (3 subjects, 8.6%), arthralgia (2 subjects, 5.7%) and dehydration (2 subjects, 5.7%).

6.1 Clinical Trials 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.

Primary Humoral Immunodeficiency Study

A multicenter, open-label, randomized two-period crossover study (bioequivalence study) evaluated the PK, safety and tolerability of GAMMAPLEX 10% and GAMMAPLEX 5% in 33 adults aged 17 to 55 years with PI. Twenty one (63.6%) subjects were female and 12 (36.4%) were male; 33 (100%) were White, of which 1 (3.0%) was Hispanic or Latino. The safety analysis included all 33 subjects for GAMMAPLEX 5% and 32 subjects for GAMMAPLEX 10%. One subject withdrew consent during the first infusion of GAMMAPLEX 5%, citing inconvenience of the study visits. Thirty two subjects received at least five infusions of each product either on a 28-day or 21-day cycle. The mean doses per infusion for GAMMAPLEX 10% were 491.7 mg/kg and 499 mg/kg respectively, and were similar for GAMMAPLEX 5% *[see Clinical Studies (14.1)]*. No subjects were on regular systemic corticosteroids at entry to, or during the study. Twelve (36.4%) adult subjects received short courses of corticosteroids, from a single dose to a maximum of 6 days duration, for various clinical conditions. No subjects received corticosteroids as premedications for GAMMAPLEX infusions. The use of local anesthetics, antipyretics, antihistamines, analgesics, and antiemetics before infusion was allowed; three (9.1%) adult subjects received a total of 5 courses of such premedication.

While on GAMMAPLEX 10%, 10 of the adults (31.3%) had an adverse reaction (AR) with a similar proportion (12; 36.4%) when on GAMMAPLEX 5%. Headache was the most commonly reported AR with both formulations of GAMMAPLEX. In total, 166 infusions of GAMMAPLEX 10% and 163 infusions of GAMMAPLEX 5% were given to adults during the study.

Two subjects had a positive direct antiglobulin (Coombs') test (DAT; DCT) result at some stage in the study. For one adult, the test was positive before starting in the study and it remained positive throughout, but without evidence of hemolysis. One other adult had a positive DAT one week after an infusion of GAMMAPLEX 5% but there was no evidence of hemolysis and no positive DAT results when receiving GAMMAPLEX 10%. No other adults had a positive DAT during the study.

In the same study, 15 pediatric subjects with PI, 3 years of age and older, received GAMMAPLEX 10%. All subjects were White, of which 2 (13.3%) were Hispanic or Latino. The mean doses per infusion were 552.9 mg/kg for subjects on the 28-day cycle (n=8) and 514.7 mg/kg for subjects on the 21-day cycle (n=7), overall range 343 to 745 mg/kg. Two subjects were in the 2-5 year age group, 7 were in the 6-11 year age group and 6 were in the 12-15 year age group. Fourteen subjects completed the study with at least 5 infusions of GAMMAPLEX 10% (pediatric subjects only received GAMMAPLEX 10% in this study); 82 infusions were given in total. Two pediatric subjects received IV methylprednisolone as premedication for each infusion. Local anesthetics, antipyretics, antihistamines and analgesics were allowed.

While on GAMMAPLEX 10%, 6 (40%) pediatric subjects had an AR. Headache was the most common with 3 subjects (20%) reporting a total of 4 events. All other ARs were not reported by more than a single pediatric subject. One pediatric subject had a positive direct antiglobulin (Coombs') test without evidence of hemolysis.

Table 2 lists the ARs occurring in at least 5% of all subjects (adult and pediatric combined) with PI treated with GAMMAPLEX 10% in the clinical study.

Table 2: Adverse Reactions (ARs*) Occurring in ≥5% of Subjects with PI Receiving GAMMAPLEX 10% (Adult and Pediatric Subjects Combined)

Preferred Term	Subjects (%) [n=32]	Events
Headache	7 (14.9)	16
Migraine	3 (6.4)	3
Pyrexia	3 (6.4)	3

* Adverse Reactions (ARs) are defined as adverse events considered by the investigators to have been possibly, probably, or definitely related to administration of GAMMAPLEX.

Chronic Immune Thrombocytopenic Purpura Study

The safety of GAMMAPLEX 10% has not been established in patients with ITP. However, the safety profile for 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. The following is a summary of the study of GAMMAPLEX 5% in chronic ITP. In a multicenter, open-label, non-randomized clinical trial, 35 subjects with chronic ITP were treated with a nominal dose of 1000 mg/kg on each of two consecutive days (total dose 2000 mg/kg). Doses of GAMMAPLEX 5% ranged from 482 to 1149 mg/kg on an infusion day. The median total dose per subject was 2035 mg/kg. Pre-medication with antihistamine or analgesic drugs was permitted if required, but corticosteroids were not permitted prior to infusion as pre-medication. Ten subjects received corticosteroids for ITP during the trial and one additional subject received corticosteroids as pre-medication in violation of the protocol. All 35 subjects received at least one infusion of clinical trial drug, and all but one subject completed the first course of treatment.

Fifteen subjects (42.9%) reported at least one AR (63 in total); the most commonly reported being headache (10 subjects, 28.6%), vomiting (6 subjects, 17.1%), pyrexia (5 subjects, 14.3%), nausea (3 subjects, 8.6%), arthralgia (2 subjects, 5.7%) and dehydration (2 subjects, 5.7%). Three subjects experienced a total of five serious ARs. Of the five serious ARs, one subject had three concurrently (vomiting, dehydration and headache) and two subjects each had one serious AR (headache). One of these latter two subjects discontinued from the clinical trial because of the severe headache. Table 3 lists the ARs in more than ≥5% of subjects.

Based on a review of clinical and laboratory data, 4/35 subjects (11%) with drops in hemoglobin exceeding 2 g/dL following administration of GAMMAPLEX 5% were considered to have experienced suspected treatment-emergent hemolysis. Milder treatment-emergent hemolysis could not be excluded for an additional 7 subjects, giving a total of 11 of 35 subjects (31%) for whom hemolysis could not be excluded (not including an additional two subjects who lacked follow-up testing for hemolysis, so their hemolysis status was considered unassessable). Data for two subjects were consistent with possible intravascular hemolysis, including one subject who may also have had an element of extravascular hemolysis. Nine of the possible hemolysis cases were mild and appeared consistent with possible extravascular hemolysis.

There was no evidence of transmission of HBV, HCV, HIV and parvovirus B19 during this clinical trial.

Table 3: Adverse Reactions (ARs*) Occurring in ≥5% of Subjects with ITP

Adverse Reactions	Subjects % [n=35]	Events
Headache	10 (28.6)	19
Vomiting	6 (17.1)	8
Pyrexia	5 (14.3)	6
Nausea	3 (8.6)	3
Arthralgia	2 (5.7)	3
Dehydration	2 (5.7)	2

* Adverse Reactions (ARs) are defined as adverse events considered by the investigators to have been possibly, probably, or definitely related to administration of GAMMAPLEX.

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[9]:

- *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.[10, 11] 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.[12]

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 10^4 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_{10} Reduction of Virus (LRV) over manufacturing step			
			Solvent Detergent	20 nm filtration	Terminal low pH/ elevated temperature incubation	Total LRV
HIV	Env/RNA	80-100	›6.8	I	6.0	›12.8
SIN	Env/RNA	70	›6.7	6.2	›5.4	›18.3
WNV	Env/RNA	50	›6.4	I	NT	›6.4
BVDV	Env/RNA	40-60	›5.6	I	›4.0	›9.6
IBR	Env/DNA	200	›5.0	I	›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
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

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.[13,14] 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:	ADULTS				PEDIATRICS		
Parameter (unit)	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_{max} (mg/dL)	1090 (20.5)	1150 (27.6)	1020 (23.6)	1090 (21.6)	1120 (33.5)	907 (37.9)	977 (34.9)
T_{max} (hr)[a]	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¶ (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)

¶ $AUC_{0\text{-}tau}$ = area under the concentration versus time curve within a dosing interval, tau = dosing interval
C_{max} = maximum observed concentration
T_{max} = time at which C_{max} was apparent
[a] Median and range are presented for t_{max}
§ 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 10^9/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] × 10^9/L) was still higher than the baseline value, and 11 of 33 subjects (33.3%) continued to show response of platelet counts of 50 × 10^9/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 10^9/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 10^9/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 x10^9/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

1. Gupta N, Ahmed I, Nissel-Horowitz S, Patel D, Mehrotra B. Intravenous gammaglobulin-associated acute renal failure. Am J Hematol 2001; 66:151-152.
2. Dalakas MC. High-dose intravenous immunoglobulin and serum viscosity: risk of precipitating thromboembolic events. Neurology 1994; 44:223-226.
3. Gabor EP. Meningitis and skin reaction after intravenous immune globulin therapy. Ann Intern Med 1997; 127:1130.
4. Wilson JR, Bhoopalam N, Fisher M. Hemolytic anemia associated with intravenous immunoglobulin. Muscle Nerve 1997; 20:1142-1145.
5. 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.
6. 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.
7. 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.
8. Rizk A, Gorson KC, Kenney L, Weinstein R. Transfusion-related acute lung injury after the infusion of IVIG. Transfusion 2001; 41:264-268.
9. Pierce LR, Jain N. Risks associated with the use of intravenous immunoglobulin. Trans Med Rev 2003; 17:241-251.
10. Siber GA, Werner BG, Halsey NA, Reid R, Almeido-Hill J, Garrett SC, Thompson C, Santosham M. Interference of immune globulin with measles and rubella immunization. J Pediatr 1993; 122:204-211.
11. Salisbury D, Ramsay M, Noakes K, eds. Immunisation against infectious disease. The Stationery Office (TSO), London: UK Department of Health, 2009; p426.
12. 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.
13. 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.
14. 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:
Bio Products Laboratory Ltd.,
Elstree,
WD6 3BX.
United Kingdom.
U.S. License No. 1811

U.S. Distributor:
BPL Inc.,
302 E. Pettigrew Street,
Suite C-190,
Durham, NC 27701
U.S.A.