BIVIGAM is an Immune Globulin Intravenous (Human), 10% Liquid, indicated for the treatment of patients with primary humoral immunodeficiency (PI). This includes, but is not limited to, the humoral immune defect in common variable immunodeficiency (CVID), X-linked agammaglobulinemia, congenital agammaglobulinemia, Wiskott-Aldrich syndrome, and severe combined immunodeficiencies.

**Thrombosis** may occur with human globulin (IGIV) products, including BIVIGAM. Risk factors may include: advanced age, prolonged immobilization, hypercoagulable conditions, history of venous or arterial thrombosis, use of estrogen-containing oral contraceptive, hypercholesterolemia, and cardiovascular risk factors. Thrombosis may occur in the absence of known risk factors.

**Use of Immune Globulin Intravenous (IGIV) products, particularly those containing sucrose, has been reported to be associated with acute nephrotoxic, acute renal failure, osmotic nephrosis, and death.** Patients at risk of acute renal failure include those with any degree of pre-existing renal insufficiency, diabetes mellitus, and cardiovascular risk factors. Thrombosis may occur in the absence of known risk factors.

**For patients at risk of thrombosis, renal dysfunction, or renal failure, administer BIVIGAM at the minimum dose and infusion rate practicable.** Ensure adequate hydration in patients before administration. Monitor for signs and symptoms of thrombosis and acute renal failure in patients at risk for hyperviscosity.

As there are significant differences in the half-life of IgG among patients with primary humoral immunodeficiency, 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 BIVIGAM for replacement therapy in primary humoral immunodeficiency (PI) is 300 to 800 mg/kg body weight administered every 3 to 4 weeks. The dosage may be adjusted over time to achieve the desired trough levels and clinical response.

BIVIGAM dose adjustments may be necessary in patients who fail to maintain trough total IgG concentrations of at least 500 mg/dL with a target of 600 mg/dL. Starting with the second infusion, the dose will be adjusted proportionately by a fraction of 0.9 mg/dL, based on the previous trough and the associated dose.

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BIVIGAM® CareLine: [Immune Globulin Intravenous (Human), 10% Liquid]
1-855-BIVIGAM (1-855-248-4426)

Once a patient is ready to begin therapy with BIVIGAM®, a reimbursement specialist will guide you through the process of securing payer approval and payment.

A Reimbursement specialist will assist healthcare providers appealing a payer's decision to deny or underpay a BIVIGAM® medical claim for a specific patient.

Verify patient-specific coverage and benefits for BIVIGAM® under various settings of care.

Priority Authorization Support

Case Management

Denied/Underpaid Claim Support

See full Bivigam Prescribing Information on page 3 to 6.

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BIVIGAM is a registered trademark of Biotest Pharmaceuticals Corporation

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BIVIGAM is an Immune Globulin Intravenous (Human), 10% Liquid, indicated for the treatment of patients with primary humoral immunodeficiency (PI). This includes, but is not limited to, the humoral immune defect in common variable immunodeficiency (CVID), X-linked agammaglobulinemia, congenital agammaglobulinemia, Wiskott-Aldrich syndrome, and severe combined immunodeficiencies.

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• Use of Immune Globulin Intravenous (IGIV) products, particularly those containing sucrose, has been reported to be associated with renal dysfunction, acute renal failure, osmotic nephrosis, and death. Patients at risk of acute renal failure include those with any degree of pre-existing renal insufficiency, diabetes mellitus, advanced age (above 65 years of age), volume depletion, sepsis, paraproteinemia, or receiving known nephrotoxic drugs.

• Renal dysfunction and acute renal failure occur more commonly in patients receiving IGIV products containing sucrose. BIVIGAM does not contain sucrose.

• For patients at risk of thrombosis, renal dysfunction, or renal failure, administer BIVIGAM 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.

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BIVIGAM dose adjustments may be required in patients who fail to maintain trough total IgG concentrations of at least 500 mg/dL with a target of 600 mg/dL. Starting with the second infusion, the dose will be adjusted proportionally, targeting a trough of □ 600 mg/dL, based on the previous trough and the associated dose.

ICD-9-CM DIAGNOSIS CODES*

- 279.00: Hypogammaglobulinemia, unspecified
- 279.03: Other selective immunoglobulin deficiencies
- 279.04: Congenital hypogammaglobulinemia
- 279.05: Immunodeficiency with increased IgM
- 279.06: Common variable immunodeficiency
- 279.09: Other deficiency of humoral immunity
- 279.12: Wiskott-Aldrich syndrome
- 279.2: Combined immunity deficiency

J1556: INJECTION, IMMUNE GLOBULIN (BIVIGAM), INTRAVENOUS, NON-LYOPHILIZED (eg., LIQUID), 500 mg

50 ml vial (5 g IgG): 59730-6502-1
100 ml vial (10 g IgG): 59730-6503-1

96365: Intravenous Infusion for therapy, prophylaxis, or diagnosis (specify substance or drug); initial up to 1 hour
96366: Intravenous Infusion for therapy, prophylaxis, or diagnosis each additional hour
99211-99215: Evaluation and management services
BIVIGAM® is an Immune Globulin Intravenous (Human). 10% Liquid, indicated for the treatment of primary humoral immunodeficiency (PI). [1]

DOSEAGE AND ADMINISTRATION

Intravenous Use Only

<table>
<thead>
<tr>
<th>Indication</th>
<th>Dose</th>
<th>Initial Infusion Rate</th>
<th>Maintenance Infusion Rate (if tolerated)</th>
</tr>
</thead>
<tbody>
<tr>
<td>PI</td>
<td>300–800 mg/kg every 3–4 weeks</td>
<td>0.5 mg/kg/min for the first 10 minutes.</td>
<td>Increase every 20 minutes (if tolerated) by 0.8 mg/kg/min up to 6 mg/kg/min.</td>
</tr>
</tbody>
</table>

• Ensure that patients with pre-existing renal insufficiency are not volume depleted; discontinue BIVIGAM if renal function deteriorates. [5.3]

• For patients at risk of renal dysfunction or thrombotic events, administer BIVIGAM at the minimum infusion rate practicable. [5.1, 5.3]

DOSEAGE FORMS AND STRENGTHS

BIVIGAM is a liquid solution containing 10% IgG (100mg/mL) for intravenous infusion: 5g in 50mL solution, 10g in 100mL solution. [3]

CONTRAINDICATIONS

• History of anaphylactic or severe systemic reactions to human immunoglobulin, [4]

• IgA deficient patients with antibodies to IgA and a history of hypersensitivity, [4, 5.2]

WARNINGS AND PRECAUTIONS

• Thrombotic events have occurred in patients receiving IGIV therapy. Monitor patients with known risk factors for thrombotic events; consider baseline assessment of blood viscosity for those at risk of hyperviscosity. [5.1, 5.5, 5.4]

• IgA deficient patients with antibodies against IgA are at greater risk of developing severe hypersensitivity and anaphylactic reactions. Have medications such as epinephrine available immediately to treat any acute severe hypersensitivity reactions. [4, 5.2]

• Monitor renal function, including blood urea nitrogen (BUN), serum creatinine, and urine output in patients at risk of developing acute renal failure. [5.3, 5.9]

• Hyperproteinemia, increased serum viscosity, and hyponatremia or pseudohyponatremia can occur in patients receiving IGIV therapy. [5.4]

• Aseptic meningitis syndrome (AMS) has been reported with IGIV treatments, especially with high doses or rapid infusion. [5.5]

• Hemolytic anemia can develop subsequent to treatment with IGIV products. Monitor patients for hemolysis and hemolytic anemia. [5.6]

• Monitor patients for pulmonary adverse reactions (Transfusion-related acute lung injury [TRALI]). If transfusion-related acute lung injury is suspected, test the product and patient for antineutrophil antibodies. [5.7]

• Because this product is made from human blood, it may carry a risk of transmitting infectious agents, e.g., viruses, and theoretically, the Creutzfeldt-Jakob disease (CJD) agent. [5.8]

ADVERSE REACTIONS

The most common adverse reactions to BIVIGAM (reported in ≥5% of clinical study subjects) were headache, fatigue, infusion site reaction, nausea, sinusitis, blood pressure increased, diarrhea, dizziness, and lethargy. [6]

To report SUSPECTED ADVERSE REACTIONS, contact Biotest Pharmaceuticals at (800) 458-4244 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

DRUG INTERACTIONS

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

• Passive transfer of antibodies may confound the results of serological testing. [5.10]

USE IN SPECIFIC POPULATIONS

• Pregnancy: Use in pregnant women has not been evaluated. Use BIVIGAM in pregnant women only if clearly needed. [8.1]

• Geriatric Use: In patients over age 65 or in any patient at risk of developing renal insufficiency, do not exceed the recommended dose, and infuse BIVIGAM at the minimum infusion rate practicable. [8.5]

See 17 for PATIENT COUNSELING INFORMATION

Issued: June 2013

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3 DOSAGE FORMS AND STRENGTHS

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5.2 Hypersensitivity

Thrombosis may occur with use of immune globulin (IGIV) products, including BIVIGAM. Risk factors may include: advanced age, prolonged immobilization, hypercoagulable conditions, a history of venous or arterial thrombosis, the 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 [17.2]).

Use of Immune Globulin Intravenous (IGIV) products, particularly those containing sucrose, has been reported to be associated with renal dysfunction, acute renal failure, osmotic nephrosis, and death.1,2

Patients at risk of acute renal failure include those with any degree of pre-existing renal insufficiency, diabetes mellitus, advanced age (above 65 years of age), volume depletion, sepsis, paraproteinemia, receiving known nephrotoxic drugs (see Warnings and Precautions [5.3]).

Renal dysfunction and acute renal failure occur more commonly in patients receiving IGIV products containing sucrose. BIVIGAM does not contain sucrose.

For patients with pre-existing renal insufficiency, the use of estrogens, indwelling central vascular catheters, hyperviscosity and renal dysfunction or, renal failure, administer BIVIGAM 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 [2.2, 2.3], Warnings and Precautions [5.2]).

5.3 Acute Renal Dysfunction and Acute Renal Failure

Acute renal dysfunction/failure, osmotic nephrosis, and death1,2 may occur upon use of human IgG products. Most patients are not volume depleted before administering BIVIGAM. Periodic monitoring of renal function and urine output is particularly important in patients judged to be at increased risk of developing acute renal failure.2 Assess renal function, including measurement of blood urea nitrogen (BUN) and serum creatinine, before the initial infusion of BIVIGAM and at appropriate intervals thereafter. If renal function deteriorates, consider discontinuing BIVIGAM (see Patient Counseling Information [17.1]). In patients who are at risk of developing renal dysfunction, because of pre-existing renal insufficiency or post-thrombotic syndrome, the use of estrogens, indwelling central vascular catheters, hyperviscosity and elevated osmolarg, because treatment aimed at decreasing serum free water in patients with pseudohypertonia may lead to volume depletion, a further increase in serum viscosity, and a possible exacerbation of hyperviscosity.

5.4 Hyperproteinemia, Increased Serum Viscosity, and Hyponatremia

Hyperproteinemia, increased serum viscosity, and hyponatremia may occur in patients receiving IGIV therapy. It is clinically to distinguish clinically true hyponatremia from a pseudohyponatremia that is associated with increased serum viscosity. Patients may exhibit decreased serum osmolality or elevated osmolarg, because treatment aimed at decreasing serum free water in patients with pseudohypertonia may lead to volume depletion, a further increase in serum viscosity, and a possible exacerbation of hyperviscosity.

5.5 Asyptic Meningitis Syndrome (AMS)

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

5.6 Hemolysis

IGIV products, including BIVIGAM, may contain blood group antibodies that can act as hemolysins and induce in vivo coating of red blood cells (RBCs) with immunoglobin, causing a positive direct antiglobulin reaction and, rarely, hemolysis.10,11,12 Delayed hemolytic anemia can develop subsequent to IGIV therapy due to increased RBC sequestration,13 and acute hemolysis, consistent with intravascular hemolysis, has been reported.

Monitor patients for clinical signs and symptoms of hemolysis (see Patient Counseling Information [17.4]). If these are present after BIVIGAM infusion, perform appropriate confirmatory laboratory testing. If thrombocytopenia is indicated for patients with pre-existing hemolysis or in patients after receiving BIVIGAM, perform adequate cross-matching to avoid exacerbating ongoing hemolysis.

5.7 Transfusion-Related Acute Lung Injury (TRALI)

Noncardiogenic pulmonary edema may occur in patients following IGIV treatment including BIVIGAM. 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 (see Patient Counseling Information [17.5]).

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

5.8 Transmissible Infectious Agents

Because BIVIGAM is made from human blood, it may carry a risk of transmitting infectious agents, e.g., viruses or bacterial pathogens, the Creutzfeldt-Jakob disease (CJD) agent. No cases of transmission of viral diseases or CJD have been associated with the use of BIVIGAM. All infections suspected by a physician possibly to have been transmitted by this product should be reported by the physician or other healthcare provider to Biotest Pharmaceuticals Corporation at 1-800-438-4244. Before producing BIVIGAM, the physician should discuss the risks and benefits of its use with the patient (see Patient Counseling Information [17.6]).

5.9 Monitoring Laboratory Tests

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

• Because of the potentially increased risk of thrombosis with IGIV treatment, consider baseline assessment of blood viscosity in patients at risk for hyperviscosity, including those with cryoglobulins, fasting chylomicronemia, markedly high triglycerides (triglycerides), or monocholin gammapathies.

• If signs and symptoms of hemolysis are present after an infusion of BIVIGAM, 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 the patient’s serum.

5.10 Intolerance with Laboratory Tests

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

6 ADVERSE REACTIONS

Serious adverse reactions observed in clinical trial subjects receiving BIVIGAM were vomiting and dehydration in one subject.

The most common adverse reactions to BIVIGAM (reported in >5% of clinical study subjects) were headache, fever, nausea, urticaria, rash, nausea, dizziness, and lethargy.

6.1 Clinical Trials Experience

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

In a multicenter, open-label, non-randomized clinical trial, 63 subjects with PI on regular IGIV replacement therapy, received doses of BIVIGAM ranging from 254 to 1029 mg/kg (median dose 402.8 mg/kg) every 3 weeks for 4 or weeks for up to 12 months (mean 37.3 days: range 66 – 386 days) (see Clinical Studies [7.4]). The study was pre-terminated due to worsening. However, if subjects required pre-medication (antihistamine, or antimalaric agent) for recurrent reactions to immunoglobulin, they were allowed to continue these medications for this trial. Of the 746 infusions administered, 41 (6%) subjects received medications prior to 415 (6%) infusions.

Fifty-nine subjects (94%) had an adverse reaction at some time during the study. The proportion of subjects who had at least one adverse reaction was the same for the 3- and 4-week cycles. The most common adverse reactions observed in a clinically related trial were headache (32 subjects, 51%), sinusitis (34 subjects, 54%), influenza (31 subjects, 38%), fatigue (18 subjects, 29%), upper respiratory tract infection (16 subjects, 25%), diarrhea (13 subjects, 21%), cough (14 subjects, 22%), bronchitis (12 subjects, 19%), pyrexia (12 subjects, 19%), and nausea (9 subjects, 14%).

Adverse reactions (ARs) are those occurring during or within 72 hours after the end of an infusion. In this study, the upper bound of the 1-sided 95% confidence interval for the proportion of BIVIGAM infusions with one or more temporally associated adverse reactions was 31%. The total number of adverse reactions was 453 (a rate of 5.08 ARs per infusion).
Precipitation and removal of fraction III eliminates both enveloped and non-enveloped viruses, solvent/detergent treatment represents a virus inactivation step for enveloped viruses, and 35 nm filters remove both enveloped and non-enveloped viruses by size exclusion. In addition to the steps above, low pH during several steps of the production process contributes to virus inactivation. The results of virus validation studies for BIVIGAM are shown in Table 3, expressed as log10 reduction factors.

### Table 3: Virus Validation Data for BIVIGAM

<table>
<thead>
<tr>
<th>Virus Type</th>
<th>Enveloped Viruses</th>
<th>Non-enveloped Viruses</th>
</tr>
</thead>
<tbody>
<tr>
<td>Retro</td>
<td>HIV, BVDV, SNV, WN</td>
<td>HIV, BVDV, SNV, WN</td>
</tr>
<tr>
<td>Flip</td>
<td>Flaviviruses</td>
<td>Flaviviruses</td>
</tr>
<tr>
<td>Herpes</td>
<td>Herpesvirus, CMV</td>
<td>Herpesvirus</td>
</tr>
<tr>
<td>Picorna</td>
<td>Picornaviruses</td>
<td>Picornaviruses</td>
</tr>
<tr>
<td>Parvovirus</td>
<td>Parvovirus, PRV</td>
<td>Parvovirus, PRV</td>
</tr>
<tr>
<td>Polyoma</td>
<td>Polyomaviruses, B19</td>
<td>Polyomaviruses, B19</td>
</tr>
</tbody>
</table>

### 2. Postmarketing Experience

Because postmarketing reporting of adverse reactions is voluntary and from a population of uncertain size, it is not always possible to reliably estimate the frequency of these reactions or establish a causal relationship to product exposure. The following adverse reactions have been identified and reported during the post-approval use of IG preparation.

- **Respiratory:** Apnea, Acute Respiratory Distress Syndrome (ARDS), Transfusion Associated Lung Injury (TRALI), cyanosis, hypoxemia, pulmonary edema, dyspnea, bronchospasm.
- **Cardiovascular:** Cardiac arrest, thromboembolism, vascular collapse, hypotension.
- **Neurological:** Cerebellar ataxia, peripheral neuropathy.
- **Integumentary:** Stevens-Johnson syndrome, epidermolysis, erythema multiforme, bullous dermatitis.
- **Hematologic:** Purpura, leucopenia, hemolysis, positive direct antiglobulin (Coombs’) test.
- **General/Body as a Whole:** Pyrexia, rigors.
- **Musculoskeletal:** Back pain.
- **Gastrointestinal:** Hepatic dysfunction, abdominal pain.

### 7. Drug Interactions

**7.1 Live Virus Vaccines**

Immunoglobulin administration may transiently impair the efficacy of live attenuated vaccines such as measles, mumps, rubella, and varicella because the continued presence of high levels of passively acquired antibody may interfere with an active antibody response.10,11 The immunizing physician should be informed of recent therapy with BIVIGAM so that appropriate measures may be taken (see Patient Counseling Information [17.7]).

### 8. USE IN SPECIFIC POPULATIONS

**8.1 Pregnancy**

Pregnancy Category C. Animal reproduction studies have not been conducted with BIVIGAM. It is not known whether BIVIGAM can cause fetal harm when administered to a pregnant woman or can affect reproduction capacity. BIVIGAM should be given to pregnant women only if clearly needed.11,14

**8.2 Nursing Mothers**

Use of BIVIGAM in nursing mothers has not been evaluated. BIVIGAM should be given to nursing mothers only if clearly needed.

**8.4 Pediatric Use**

BIVIGAM was evaluated in 9 pediatric patients (4 children ages 6 – 11 years and 5 adolescents ages 12 – 16 years) with PI. This number of pediatric patients was too small for safety or efficacy. The safety and effectiveness of BIVIGAM has not been established in pediatric patients with PI who are under the age of 6 (see Clinical Studies [14]).

**8.5 Geriatric Use**

BIVIGAM should be used with caution in patients age 65 and over who are judged to be at increased risk of developing renal insufficiency or thrombotic events (see Boxed Warning, Warnings and Precautions [5.1, 8.5 Geriatric Use]).

- **CNS:** Headache, insomnia, anxiety, paranoid thought.
- **Gastrointestinal:** Diarrhea, constipation.
- **Hematologic:** Thrombocytopenia, purpura, hemolysis, positive direct antiglobulin (Coombs’) test.
- **General/Body as a Whole:** Pyrexia, rigors.
- **Musculoskeletal:** Back pain.
- **Gastrointestinal:** Hepatic dysfunction, abdominal pain.

### 12. CLINICAL PHARMACOLOGY

**12.1 Mechanism of Action**

BIVIGAM is a replacement therapy in patients with primary humoral immunodeficiency (PI) (e.g. agammaglobulinemia, hypogammaglobulinemia, CVID, SCID).

The broad spectrum of neutralizing IgG antibodies against bacterial and viral pathogens and their toxins helps to avoid recurrent serious opportunistic infections. IgG antibodies are opsonins that increase phagocytosis and elimination of pathogens from the circulation. The mechanism of action has not been fully elucidated in PI.

**12.3 Pharmacokinetics**

In the clinical study assessing the efficacy and safety of BIVIGAM in 63 subjects with PI (see Clinical Studies [14.5]), serum concentrations of total IgG and IgG subclasses were measured in 21 subjects (ages 18 to 75) following the 4th infusion for the 5 subjects on the 3-week dosing interval and following the 5th infusion for the 16 subjects on the 4-week dosing interval. The dose of BIVIGAM used in these subjects ranged from 300 mg/kg to 800 mg/kg. After the infusion, blood samples were taken until Day 21 and Day 28 for the 3-week and 4-week dosing intervals, respectively. Table 4 summarizes the total IgG Pharmacokinetic Parameters of BIVIGAM based on serum concentrations of total IgG trough concentrations measured in 21 subjects. Serum concentrations of total IgG were measured throughout the study for both treatment cycles and mean trough concentrations were well above the target trough concentration of 500 mg/dL for both treatment cycles in pediatric (<6 years old) as well as adult subjects at all time points.

### Table 4: Total IgG Pharmacokinetic Parameter Estimates (PK Population) in Adults

<table>
<thead>
<tr>
<th>Parameter</th>
<th>3-week cycle</th>
<th>4-week cycle</th>
<th>Total (n = 21)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cmax (mg/L)</td>
<td>2164 (293)</td>
<td>2122 (425)</td>
<td>2137 (390)</td>
</tr>
<tr>
<td>Cmin (mg/dL)</td>
<td>996 (176)</td>
<td>1106 (396)</td>
<td>1108 (359)</td>
</tr>
<tr>
<td>AUC0-28 (mg*day/mL)</td>
<td>27841 (4925)</td>
<td>35089 (6472)</td>
<td>33592 (6309)</td>
</tr>
<tr>
<td>T1/2 (d)</td>
<td>19.6 (4.1)</td>
<td>21.1 (3.7)</td>
<td>20.6 (4.1)</td>
</tr>
<tr>
<td>CL (mL/d/kg)</td>
<td>0.0197 (0.002234)</td>
<td>0.0414 (0.004835)</td>
<td>0.0158 (0.004808)</td>
</tr>
<tr>
<td>Vd (mL/kg)</td>
<td>0.584 (0.125)</td>
<td>0.648 (0.141)</td>
<td>0.628 (0.138)</td>
</tr>
<tr>
<td>MRT (day)</td>
<td>29.5 (5.1)</td>
<td>17.54 (4.34)</td>
<td>20.3 (5.1)</td>
</tr>
</tbody>
</table>

### 11 DESCRIPTION

BIVIGAM is a purified, sterile, ready-to-use preparation of concentrated human immunoglobulin G (IgG) antibodies. The distribution of IgG subclasses is similar to that of normal plasma.12,13 The active ingredient is human immunoglobulin purified from source human plasma and processed using a modified classical Cohn Method 6 / (Onex) Method 9 fractionation procedure. BIVIGAM contains 100 ± 10 mg/mL protein, of which not less than 96% is human immunoglobulin obtained from source human plasma. It is formulated in water for injection containing 0.109-0.140 M sodium chloride, 0.20-0.29 M sodium glycine, 0.15-0.25% polysorbate 80, and 4.0-4.6% BIVIGAM. BIVIGAM contains ≤ 200 µg/mL of IgA.

Each plasma donation used for the manufacture of BIVIGAM is collected from FDA licensed facilities and each plasma sample is tested negative for hepatitis B virus (HBV) surface antigen (HBsAg), antibodies to human immunodeficiency virus (HIV) strains 1 and 2 (anti-HIV-1/2), and antibodies to the hepatitis C virus (anti-HCV) as determined by enzyme immuno assay (EIA). In addition, each plasma unit must be negative and/or non-reactive for HIV RNA, HCV RNA, HBV DNA, Hepatitis A Virus (HAV) RNA and Parvovirus B19 (B19 virus) DNA as determined by Nucleic Acid Amplification Testing (NAT) of plasma. For BIVIGAM, model virus for highly resistant non-enveloped viruses. BIVIGAM was evaluated in 9 patients age 65 and older with PI. This number of geriatric patients is not being sufficient to determine whether they respond differently from younger patients (see Clinical Studies [14]).

### 13 NONCLINICAL TOXICOLOGY

**13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility**

No animal studies were conducted to evaluate the carcinogenic or mutagenic effects of BIVIGAM or its effects on fertility.

**13.2 Animal Toxicology and/or Pharmacology**

No animal studies were conducted to evaluate possible toxicity of BIVIGAM in animals.

BIVIGAM contains Polysorbate 80 at a concentration of up to 2.5 mg/mL. Intravenous administrations of Polysorbate 80 in multiple species have been linked with a decrease in blood pressure. In rats, single doses of Polysorbate 80 that were up to 25 times higher than the amount from 800 mg/kg BIVIGAM resulted in an increase of liver enzymes and total bilirubin.

### 14 CLINICAL STUDIES

**14.1 Treatment of Primary Humoral Immunodeficiency**

A prospective, open-label, single-arm, multicenter trial assessed the efficacy, safety, and pharmacokinetics of BIVIGAM in adult and pediatric subjects with PI. Study subjects were receiving regular IgV replacement therapy, with a stable dose between 300 and 800 mg/kg for at least 3 months prior to participation. Subjects received a BIVIGAM infusion administered every 3 or 4 weeks (both the dose and schedule depending on their pathophysiology) for approximately 1 year.

A total of 63 subjects were enrolled in the trial, 31 men and 32 women with a mean age of 41 years. Forty-four subjects were adults (70%) between 18 and 64 years of age. There were 9 pediatric subjects (see Pediatric Use [8.4]), and 9 elderly subjects (14%, ≥65 years of age). The oldest subject was 75 years age.
BIVIGAM is supplied in the following sizes:

Refrigerate between 2 to 8°C (36 to 46°F).

### Special Precautions for Storage
Do not freeze or heat. Do not use any solutions that have been frozen or heated.

Allow refrigerated product to come to room temperature before use.

Do not use after expiration date.

### Shelf-life
BIVIGAM may be stored until expiration date on vial packaging at 2 to 8°C (36 to 46°F).

### Incompatibilities
Do not dilute.

BIVIGAM should be infused using a separate line by itself, without mixing with other intravenous fluids or medications the patient may be receiving.

### 17 PATIENT COUNSELLING INFORMATION

#### 17.1 Acute Renal Dysfunction and Acute Renal Failure

Instruct patients to immediately report symptoms of decreased urine output, sudden weight gain, fluid retention/edema, and/or shortness of breath. Such symptoms may suggest kidney damage (see Boxed Warning. Warnings and Precautions [5.3]).

#### 17.2 Thrombosis

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, acute chest pain or discomfort that worsens on deep breathing, unexplained rapid pulse, numbness or weakness on one side of the body, (see Warnings and Precautions [5.1]).

#### 17.3 Aseptic Meningitis Syndrome (AMS)

Instruct patients to immediately report signs and symptoms of AMS. These symptoms include severe headache, neck stiffness, drowsiness, fever, sensitivity to light, painful eye movements, nausea and vomiting (see Warnings and Precautions [5.5]).

#### 17.4 Hemolysis

Instruct patients to immediately report signs and symptoms of hemolysis. These symptoms include fatigue, increased heart rate, yellowing of skin or eyes, dark-colored urine (see Warnings and Precautions [5.6]).

#### 17.5 Transfusion-Related Acute Lung Injury (TRALI)

Instruct patients to immediately report signs and symptoms of TRALI. These symptoms include trouble breathing, chest pain, blue lips or extremities, fever (see Warnings and Precautions [5.7]).

#### 17.6 Transmissible Infectious Agents

Inform patients that BIVIGAM is made from human plasma and may contain infectious agents that can cause disease. While the risk that BIVIGAM 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 Description [11] and Warnings and Precautions [5.8]).

#### 17.7 Live Virus Vaccines

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