Product Monograph

Cytogam®
CYTOMEGALOVIRUS IMMUNOGLOBULIN INTRAVENOUS (HUMAN)

Liquid Formulation, Solvent Detergent Treated
Passive Immunizing Agent
Pharmaceutical Standard: Professed

Manufactured by:
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MP Negev 8532500
Israel

For:

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ACTION AND CLINICAL PHARMACOLOGY

Cytogam®, Cytomegalovirus Immunoglobulin Intravenous (Human) (CMV-IGIV), contains IgG antibodies representative of the large number of normal persons who contributed to the plasma pools from which the product was derived. The globulin contains a relatively high concentration of antibodies directed against Cytomegalovirus (CMV). In the case of persons who may be exposed to CMV, Cytogam® can raise the relevant antibodies to levels sufficient to attenuate or reduce the incidence of serious CMV disease.

In two separate clinical trials, Cytogam® was shown to provide effective prophylaxis in renal transplant recipients at risk for primary CMV disease. In the first randomized trial,[1] the incidence of virologically confirmed CMV-associated syndromes was reduced from 60% in controls (n=35) to 21% in recipients of CMV immunoglobulin (n=24) ($P < 0.01$); marked leukopenia was reduced from 37% in controls to 4% in globulin recipients ($P < 0.01$); and fungal or parasitic superinfections were not seen in globulin recipients but occurred in 20% of controls ($P = 0.05$). Serious CMV disease was reduced from 46% to 13%. There was a concomitant but not statistically significant reduction in the incidence of CMV pneumonia (17% of controls as compared with 4% of globulin recipients). There was no effect on rates of viral isolation or seroconversion although the rate of viremia was less in Cytogam® recipients. In a subsequent non-randomized trial in renal transplant recipients (n=36),[2] the incidence of virologically confirmed CMV-associated syndrome was reduced to 36% in the globulin recipients in comparison to a 60%

incidence in control patients (n=35) in the randomized trial. The rates of CMV- associated pneumonia, CMV-associated hepatitis, and concomitant fungal and parasitic superinfection were similar to those in the first trial.

INDICATIONS AND CLINICAL USE

Cytomegalovirus Immunoglobulin Intravenous (Human) is indicated for the attenuation of primary (1°) Cytomegalovirus disease associated with kidney transplantation. Specifically, the product is indicated for kidney transplant recipients who are seronegative for CMV and who receive a kidney from a CMV seropositive donor. In a population of seronegative recipients of seropositive kidneys approximately 75% of the untreated recipients would be expected to develop CMV disease.[3,4] Clinical studies have shown a 50% reduction in 1° CMV disease in renal transplant patients given Cytomegalovirus Immunoglobulin Intravenous (Human).[1,2,5]

CONTRAINDICATIONS

Cytogam®, Cytomegalovirus Immunoglobulin Intravenous (Human), should not be used in individuals with a history of a prior severe reaction associated with the administration of this or other human immunoglobulin preparations. Persons with selective immunoglobulin A deficiency have the potential for developing antibodies to immunoglobulin A and could have anaphylactic reactions to subsequent administration of blood products that contain immunoglobulin A, including Cytogam®.

WARNINGS

Cytogam®, Cytomegalovirus Immunoglobulin Intravenous (Human) is made from human plasma and, like other plasma products, carries the possibility for transmission of blood-borne viral agents, and theoretically, the Creutzfeldt-Jakob disease (CJD) agent. The risk of transmission of recognized blood-borne viruses is considered to be low because of the viral inactivation and removal properties in the Cohn-Oncley cold ethanol precipitation procedure used for purification of immunoglobulin products.[13-15] Until 1993, cold ethanol manufactured immunoglobulins licensed in the United States had not been documented to transmit any viral agent. However, during a brief period in late 1993 to

early 1994, intravenous immunoglobulin made by one U.S. manufacturer was associated with transmission of Hepatitis C virus.[16] To further guard against possible transmission of blood-borne viruses, including Hepatitis C, CMV-IGIV is treated with a solvent detergent viral inactivation procedure[17] known to inactivate a wide spectrum of lipid enveloped viruses, including HIV-1, HIV-2, Hepatitis B, and Hepatitis C.[18] However, because new blood-borne viruses may yet emerge, some of which may not be inactivated by the manufacturing process or by solvent detergent treatment, CMV-IGIV, like any other blood product, should be given only if a benefit is expected.

Immunoglobulin Intravenous (Human) products have been reported to be associated with renal dysfunction, acute renal failure, osmotic nephrosis and death.[6-8] Patients predisposed to acute renal failure include patients with any degree of pre-existing renal insufficiency, diabetes mellitus, age greater than 65, volume depletion, sepsis, paraproteinemia or patients receiving known nephrotoxic drugs. Especially in such patients, IGIV products should be administered at the minimum concentrations available and the minimum rate of infusion practical. While these reports of renal dysfunction and acute renal failure have been associated with the use of many IGIV products, those containing sucrose as a stabilizer (and given at daily doses of 350 mg/kg or greater) account for a disproportionate share of the total number. Cytogam® contains sucrose as a stabilizer. See PRECAUTIONS and DOSAGE AND ADMINISTRATION sections for important information intended to reduce the risk of acute renal failure.

During administration, the patient's vital signs should be monitored continuously and careful observation made for any symptoms throughout the infusion. Epinephrine should be available for the treatment of an acute anaphylactic reaction (see PRECAUTIONS section).

PRECAUTIONS

General:

Cytogam® does not contain a preservative. The vial should be entered only once for administration purposes and the infusion should begin within 6 hours. The infusion schedule should be adhered to closely (see INFUSION section). Do not use if the solution is turbid.

Although systemic allergic reactions are rare (see ADVERSE REACTIONS section), epinephrine and diphenhydramine should be available for treatment of acute allergic symptoms. If hypotension or anaphylaxis occur, the administration of the immunoglobulin should be discontinued immediately and an antidote should be given as noted above.

Renal Function:

Assure that patients are not volume depleted prior to the initiation of IGIV. Periodic monitoring of renal function tests and urine output is particularly important in patients judged to have a potential increased risk for developing acute renal failure. Renal function, including the measurement of blood urea nitrogen (BUN) or serum creatinine should be assessed prior to the initial infusion of Cytogam® and again at appropriate intervals thereafter. If renal function deteriorates, discontinuation of the product should be considered. For patients judged to be at risk for developing renal dysfunction, it may be prudent to reduce the amount of product infused per unit time. The recommended rate of Cytogam® infusion for prophylaxis of CMV disease in kidney transplant patients should NOT EXCEED 60 mg Ig/kg/hr (see DOSAGE AND ADMINISTRATION).

Aseptic Meningitis Syndrome:

An aseptic meningitis syndrome (AMS) has been reported to occur infrequently in association with Immunoglobulin Intravenous (Human) (IGIV) treatment.[9-12] The syndrome usually begins within several hours to two days following IGIV treatment. It is characterized by symptoms and signs including severe headache, nuchal rigidity, drowsiness, fever, photophobia, painful eye movements, and nausea and vomiting.

Cerebrospinal fluid studies are frequently positive with pleocytosis up to several thousand cells/mm^3, predominantly from the granulocytic series, and elevated protein levels up to several hundred mg/dl. Patients exhibiting such symptoms and signs should receive a thorough neurological examination, including CSF studies, to rule out other causes of meningitis. AMS may occur more frequently in association with high dose (2 g/kg) IGIV treatment. Discontinuation of IGIV treatment has resulted in remission of AMS within several days without sequelae.

Hemolysis:

Immunoglobulin Intravenous (Human) (IGIV) products can contain blood group antibodies which may act as hemolysins and induce *in vivo* coating of red blood cells with immunoglobulin, causing a positive direct antiglobulin reaction and, rarely, hemolysis.[19-21] Hemolytic anemia can develop subsequent to IGIV therapy due to enhanced RBC sequestration[22] [See ADVERSE REACTIONS]. IGIV recipients should be monitored for clinical signs and symptoms of hemolysis [See PRECAUTIONS: Laboratory Tests].

Transfusion-Related Acute Lung Injury (TRALI):

There have been reports of noncardiogenic pulmonary edema [Transfusion-Related Acute Lung Injury (TRALI)] in patients administered IGIV.[23] TRALI is characterized by severe respiratory distress, pulmonary edema, hypoxemia, normal left ventricular function, and fever and typically occurs within 1-6 hours after transfusion. Patients with TRALI may be managed using oxygen therapy with adequate ventilatory support.

IGIV recipients should be monitored for pulmonary adverse reactions. If TRALI is suspected, appropriate tests should be performed for the presence of anti-neutrophil antibodies in both the product and patient serum [See PRECAUTIONS: Laboratory Tests].

Thrombotic Events:

Thrombotic events have been reported in association with IGIV[24-26] (See ADVERSE REACTIONS). Patients at risk may include those with a history of atherosclerosis, multiple cardiovascular risk factors, advanced age, impaired cardiac output, and/or known or suspected hyperviscosity. The potential risks and benefits of IGIV should be weighed against those of alternative therapies for all patients for whom IGIV administration is being considered. Baseline assessment of blood viscosity should be considered in patients at risk for hyperviscosity, including those with cryoglobulins, fasting chylomicronemia/ markedly high triacylglycerols (triglycerides), or monoclonal gammopathies [See PRECAUTIONS: Laboratory Tests].

Laboratory Tests:

If signs and/or symptoms of hemolysis are present after IGIV infusion, appropriate confirmatory laboratory testing should be done [See PRECAUTIONS].

If TRALI is suspected, appropriate tests should be performed for the presence of anti-neutrophil antibodies in both the product and patient serum [See PRECAUTIONS].

Because of the potentially increased risk of thrombosis, baseline assessment of blood viscosity should be considered in patients at risk for hyperviscosity, including those with cryoglobulins, fasting chylomicronemia/markedly high triacylglycerols (triglycerides), or monoclonal gammopathies [See PRECAUTIONS].

Drug Interactions:

Antibodies present in immunoglobulin preparations may interfere with the immune response to live virus vaccines such as measles, mumps, and rubella; therefore, vaccination with live virus vaccines should be deferred until approximately three months after administration of Cytogam®. If such vaccinations were given shortly after Cytogam®, a revaccination may be necessary. Admixtures of Cytogam® with other drugs have not been evaluated. It is recommended that Cytogam® be administered separately from other drugs or medications which the patient may be receiving (see DOSAGE AND ADMINISTRATION section).

Pregnancy Category C:

Animal reproduction studies have not been conducted with Cytomegalovirus Immunoglobulin Intravenous (Human). It is also not known whether Cytomegalovirus Immunoglobulin Intravenous (Human) can cause fetal harm when administered to a pregnant woman or can affect reproduction capacity. Cytomegalovirus Immunoglobulin Intravenous (Human) should be given to a pregnant woman only if clearly needed.

ADVERSE REACTIONS

Minor reactions such as flushing, chills, muscle cramps, back pain, fever, nausea, vomiting, arthralgia, and wheezing were the most frequent adverse reactions observed during the clinical trials of Cytogam®, Cytomegalovirus Immunoglobulin Intravenous (Human). The incidence of these reactions during the clinical trials was less than 6.0% of all infusions and were most often related to infusion rates. If a patient develops a minor side effect, slow the rate immediately or temporarily interrupt the infusion.

Increases in serum creatinine and blood urea nitrogen (BUN) have been observed as soon as one to two days following IGIV infusion. Progression to oliguria or anuria requiring dialysis has been observed. Types of severe renal adverse events that have been seen following IGIV therapy include acute renal failure, acute tubular necrosis, proximal tubular nephropathy and osmotic nephrosis.[6-9]

Severe reactions such as angioneurotic edema and anaphylactic shock, although not observed during clinical trials, are a possibility. Clinical anaphylaxis may occur even when the patient is not known to be sensitized to immunoglobulin products. A reaction may be related to the rate of infusion; therefore, carefully adhere to the infusion rates as outlined under “DOSAGE AND ADMINISTRATION”. If anaphylaxis or drop in blood pressure occurs, discontinue infusion and use antidote such as diphenhydramine and adrenalin.

Postmarketing:

In addition to adverse events reported during clinical trials, the following events have been reported during the post-approval use of Cytogam®: Acute Respiratory Distress Syndrome (ARDS), cyanosis, pulmonary edema, dyspnea, cardiac arrest, circulatory collapse, hypotension, convulsions, bullous dermatitis, hemolysis, hepatic failure, and abdominal pain.

In addition to the adverse reactions seen with the use of Cytogam®, the following adverse reactions have been identified and reported during the post-approval use of IGIV products[27]:

Respiratory: Apnea, Transfusion Associated Lung Injury (TRALI), hypoxemia, bronchospasm

Cardiovascular: Thromboembolism

Neurological: Coma, loss of consciousness, tremor

Integumentary: Stevens-Johnson syndrome, epidermolysis, erythema multiforme

Hematologic: Pancytopenia, leukopenia, positive direct antiglobulin (Coombs) test

Because postmarketing reporting of these reactions is voluntary and the at-risk populations are of uncertain size, it is not always possible to reliably estimate the frequency of the reaction or establish a causal relationship to exposure to the product. Such is also the case with literature reports authored independently.

SYMPTOMS OF OVERDOSAGE

Although little data are available, clinical experience with other immunoglobulin preparations suggests that the major manifestations would be those related to volume overload.

DOSAGE AND ADMINISTRATION

The maximum recommended total dosage per infusion is 150 mg Ig/kg, administered according to the following schedule:

Within 72 hours of transplant: 150 mg/kg
2 weeks post transplant: 100 mg/kg
4 weeks post transplant: 100 mg/kg
6 weeks post transplant: 100 mg/kg
8 weeks post transplant: 100 mg/kg
12 weeks post transplant: 50 mg/kg
16 weeks post transplant: 50 mg/kg

Preparation for Administration. Bring the product vial to room temperature. Remove the tab portion of the vial cap and clean the rubber stopper with 70% alcohol or equivalent. DO NOT SHAKE VIAL; AVOID FOAMING.

Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration whenever solution and container permit. Infuse the solution only if it is colorless, free of particulate matter and not turbid. Cytogam®, Cytomegalovirus Immunoglobulin Intravenous (Human), does not contain a preservative. The vial should be entered only once for administration purposes.

Infusion should begin within 6 hours after entering the vial and should be complete within 12 hours of entering the vial. Vital signs should be taken pre-infusion, mid-way and post-infusion as well as before any rate increase. Cytogam® should be administered through an intravenous line using an administration set that contains an in- line filter (pore size 15μ) and a constant infusion pump (i.e., IVAC pump or equivalent). A smaller in-line filter (0.2μ) is also acceptable. Pre-dilution of Cytogam® before infusion is not recommended. Cytogam® should be administered through a separate intravenous line. If this is not possible, Cytogam® may be "piggybacked" into a pre- existing line if that line contains either Sodium Chloride, Injection, USP, or one of the following dextrose solutions (with or without NaCl added): 2.5% dextrose in water, 5% dextrose in water, 10% dextrose in water, 20% dextrose in water. If a pre-existing line must be used, the Cytogam® should not be diluted more than 1:2 with any of the above- named solutions. Admixtures of Cytogam® with any other solutions have not been evaluated.

Initial Dose. Administer intravenously at 15 mg Ig per kg body weight per hour. If no adverse reactions occur after 30 minutes, the rate may be increased to 30 mg Ig/kg/hr; if no adverse reactions occur after a subsequent 30 minutes, then the infusion may be increased to 60 mg Ig/kg/hr (volume not to exceed 75 mL/hour). DO NOT EXCEED THIS RATE OF ADMINISTRATION. The patient should be monitored closely during and after each rate change.

Subsequent Doses. Administer at 15 mg Ig/kg/hr for 15 minutes. If no adverse reactions occur, increase to 30 mg Ig/kg/hr for 15 minutes and then increase to a **maximum rate of 60 mg Ig/kg/hr** (volume not to exceed 75 mL/hour). DO NOT EXCEED THIS RATE OF ADMINISTRATION. The patient should be monitored closely during each rate change.

Cytogam® should be used with caution in patients with pre-existing renal insufficiency and in patients judged to be at increased risk of developing renal insufficiency (including, but not limited to those with diabetes mellitus, age greater than 65, volume

depletion, paraproteinemia, sepsis and patients receiving known nephrotoxic drugs). In these cases especially, it is important to assure that patients are not volume depleted prior to Cytogam® infusion. While most cases of renal insufficiency have occurred in patients receiving total doses of 350 mg lg/kg or greater, no prospective data are presently available to identify a maximum safe dose, concentration or rate of infusion in patients determined to be at increased risk of acute renal failure. In the absence of prospective data, recommended doses should not be exceeded and the concentration and infusion rate selected should be the minimum practicable.

Potential adverse reactions are: flushing, chills, muscle cramps, back pain, fever, nausea, vomiting, wheezing, drop in blood pressure. Minor adverse reactions have been infusion rate related - if the patient develops a minor side effect (i.e., nausea, back pain, flushing), slow the rate or temporarily interrupt the infusion. If anaphylaxis or drop in blood pressure occurs, *discontinue infusion* and use antidote such as diphenhydramine and adrenalin.

To prevent the transmission of hepatitis viruses or other infectious agents from one person to another, sterile disposable syringes and needles should be used. The syringes and needles should not be reused.

PHARMACEUTICAL INFORMATION

Cytogam®, Cytomegalovirus Immunoglobulin Intravenous (Human), is an immunoglobulin G (IgG) product containing a standardized amount of antibody to Cytomegalovirus (CMV). Cytogam® is formulated in final vial as a sterile liquid. The globulin is stabilized with 5% sucrose and 1% Albumin (Human). Cytogam® contains no preservative. The purified immunoglobulin is derived from pooled adult human plasma selected for high titers of antibody for Cytomegalovirus (CMV).[3] Source material for fractionation may be obtained from another U.S. licensed manufacturer. Pooled plasma was fractionated by ethanol precipitation of the proteins according to Cohn Methods 6 and 9, modified to yield a product suitable for intravenous administration.

A widely utilized solvent-detergent viral inactivation process is also used.[14] Certain manufacturing operations may be performed by other firms. Each milliliter contains: 50 ± 10 mg of immunoglobulin, primarily IgG, and trace amounts of IgA and IgM; 50 mg of sucrose; 10 mg of Albumin (Human). The sodium content is 20-30 mEq per liter; i.e. 1.0-1.5 mEq per 50 mL. The solution should appear colorless and translucent. Cytogam® is supplied in a single use vial and therefore, any product remaining after administration should be discarded.

Stability and Recommendations. Cytogam® should be stored between 2-8°C (36-46°F) and used within 6 hours after entering the vial. The product is stable up to the expiration date which is stamped on the outer carton and vial label. It should not be used after that date.

AVAILABILITY OF DOSAGE FORMS

Cytogam®, Cytomegalovirus Immunoglobulin Intravenous (Human), is supplied in a single use vial containing 2500 mg ± 500 mg of immunoglobulin. DIN 02231962.

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