1.0 VACCINIA IMMUNE GLOBULIN INTRAVENOUS (HUMAN) PACKAGE INSERT

DESCRIPTION

Vaccinia Immune Globulin Intravenous (Human) (VIGIV) is a sterile liquid immunoglobulin (Ig) stabilized with 5% sucrose and 1% albumin (human). Each lot of VIGIV contains anti-vaccinia antibody that is isolated from units of Source Plasma that meet the minimum potency specifications as compared to the validated reference standard. The purified immunoglobulin is derived from pooled human plasma collected from donors who received booster immunizations with the Dryvax® smallpox vaccine.

All units of plasma were tested for alanine transaminase, and were found to be negative for hepatitis C antibody and hepatitis B surface antigen. All units of plasma were found to be negative for antibodies against human immunodeficiency virus (HIV). In addition, all plasma pools were negative for HIV RNA by reverse transcriptase polymerase chain reaction. The pooled plasma was fractionated by cold ethanol precipitation according to the Cohn Method 6 and the Oncley Method 9, modified to yield a product suitable for intravenous administration.[1,2] Several steps in the manufacturing process have been validated for their ability to inactivate or remove potential viruses.[1-4] These include Cohn/Oncley fractionation (Fraction I through Supernatant III Filtrate); nanofiltration through one 75-nm and two 35-nm filters; and solvent/detergent viral inactivation. The viral reduction steps have been validated in a series of *in vitro* experiments for their capacity to inactivate and/or remove HIV type 1 (HIV-1) and the following model viruses: bovine viral diarrhea virus (BVDV) as a model for hepatitis C virus; mouse encephalomyelitis virus

(MEMV) as a model for hepatitis A virus; and pseudorabies virus (PRV), feline calicivirus (FCV), and Sindbis virus to provide data for a wide range of physiochemical properties in the model viruses studied. Total mean $\log_{10}$ reductions in viable virus count range from 6.07 to greater than 16 $\log_{10}$ as shown in the following table.

Table 1. Viral Reduction by the Manufacturing Process for IGIV

Process step	Mean Reduction Factor ($\log_{10}$)					
	Enveloped Viruses (size in nm)				Non-Enveloped Viruses (size in nm)	
	BVDV (40-60)	Sindbis (60-70)	HIV-1 (80-100)	PRV (120-200)	MEMV (22-30)	FCV (35-39)
Cohn/Oncley fractionation	6.25	6.6	> 9.44	> 10.37	4.06	Not done
Nanofiltration	≥ 5.4	≥ 6.84	Not done	Not done	Not done	≥ 6.92
Solvent/detergent treatment	> 4.85	Not done	> 4.51	> 5.53	0.57*†	Not done
Cumulative Reduction Factor ($\log_{10}$)	≥ 16.5	≥ 13.44	> 13.95	> 15.9	4.06	≥ 6.92

* Included hydrophobic chromatography after solvent/detergent treatment.

† $\log_{10}$ values less than 1 were not considered significant and were therefore not included in the cumulative reduction factor.

BVDV: bovine viral diarrhea virus, as a model for hepatitis C virus.

HIV-1: human immunodeficiency virus type 1.

PRV: pseudorabies virus, as a model for large enveloped DNA viruses.

MEMV: mouse encephalomyelitis virus, as a model for hepatitis A virus.

FCV: feline calicivirus, as a model for small non-enveloped DNA viruses.

Additional testing performed with bovine parvovirus (as a model for parvovirus B19) showed a mean cumulative reduction factor of greater than 7.34 $\log_{10}$ for Cohn/Oncley fractionation and solvent/detergent treatment followed by hydrophobic chromatography. A mean cumulative reduction factor of 2.55 $\log_{10}$ was observed for removal of porcine parvovirus by nanofiltration.

Based on the size of vaccinia virus (350 × 270 nm), it is anticipated that it would be removed by the nanofiltration steps in the manufacturing process of VIGIV and inactivated by the presence of anti-vaccinia antibodies in the product. In addition, solvent/detergent treatment of bulk VIGIV material is capable of reducing vaccinia virus to undetectable levels. Treatment of bulk VIGIV material with solvent and detergent at the same concentrations used in the VIGIV manufacturing process led to a greater than 4 $\log_{10}$ reduction in vaccinia virus titers. Virus was reduced to undetectable levels at 25ºC, the temperature at which this treatment is performed during the manufacture of VIGIV, and to similarly low levels after treatment at 5ºC. Robust viral reduction was also observed after treatment at half-strength concentration of both solvent and detergent.

Each cubic centimeter (milliliter) of VIGIV contains approximately 50 ± 10 mg immunoglobulin, primarily IgG, and trace amounts of immunoglobulin A (IgA) and immunoglobulin M (IgM); 50 mg sucrose; and 10 mg albumin (human). The sodium content is 19.5 to 22.5 mEq per liter (i.e., 1.0 to 1.5 mEq per 50 mL). The solution should appear colorless, free of particulate matter, and not turbid.

CLINICAL PHARMACOLOGY

VIGIV contains vaccinia-specific immunoglobulin G (IgG) representative of the immunized donors who contributed to the plasma pool from which the product is derived. The immunoglobulin contains a relatively high concentration of antibodies directed against vaccinia virus. The potency of VIGIV is based on the ability of VIGIV to neutralize vaccinia virus as measured by the plaque reduction neutralization (PRN) assay. The concentration of anti-vaccinia antibodies in a sample, expressed in units/milliliter (U/mL), is defined as the inverse of the dilution of the sample that results in a 50% reduction in viral plaques (PRN_{50} titer). The circulating serum half-life of injected VIGIV has been shown to be approximately 22 days in adults, which is consistent with existing data for other immunoglobulin preparations.[5,6]

INDICATIONS AND USAGE

VIGIV is indicated for the treatment and/or modification of the following conditions:

- Aberrant infections induced by vaccinia virus that include its accidental implantation in eyes (except in cases of isolated keratitis), mouth, or other areas where vaccinia infection would constitute a special hazard.
- Eczema vaccinatum
- Progressive vaccinia
- Severe generalized vaccinia, and
- Vaccinia infections in individuals who have skin conditions such as burns, impetigo, varicella-zoster, or poison ivy; or in individuals who have eczematous skin lesions because of either the activity or extensiveness of such lesions.

Treatment of complications that include vaccinia keratitis with VIGIV should be performed with caution since a single study in rabbits has demonstrated increased corneal scarring with

intramuscular VIG administration.[7] VIGIV is not considered to be effective in the treatment of postvaccinial encephalitis.

CLINICAL STUDIES

The effectiveness of VIGIV was evaluated on the basis of the serum antibody concentrations in healthy volunteers 5 days after administration of VIGIV and a comparison with the estimated (modeled) serum antibody concentration 5 days after administration of the previously licensed product [Vaccinia Immune Globulin Intramuscular (VIGIM)]. There are no controlled trials demonstrating a clinical benefit, such as a reduction in mortality or in the severity of smallpox complications.

Two clinical trials were conducted. The first study was an open-label, dose-ascending study using lyophilized VIGIV in 78 healthy adult volunteers. Subjects received 100 mg/kg (2 mL/kg), 200 mg/kg (4 mL/kg), or 500 mg/kg (10 mL/kg) VIGIV. No serious adverse events (SAEs) or deaths were reported, and no subjects withdrew because of adverse events (AEs). In this study it was shown that serum neutralizing antibody levels for vaccinia five days after administration of VIGIV were not less than those expected following a similar dose of VIGIM. The AE profile was comparable among doses.

The second study was an open-label, Phase 1, safety and tolerability study conducted using a 100 mg/kg (2 mL/kg) dose of the liquid formulation of VIGIV in 33 healthy volunteers. No SAEs or deaths were reported, and no subjects withdrew because of AEs.

CONTRAINDICATIONS

While VIGIV should be considered in treatment of severe ocular complications due to vaccinia virus, VIGIV is contraindicated for use in the presence of isolated vaccinia keratitis.

VIGIV should not be used in individuals with a history of prior severe reaction associated with the parenteral administration of this or other human immunoglobulin preparations.[5,6,8]

VIGIV contains trace amounts of IgA. Persons with selective IgA deficiency can develop

antibodies to IgA and therefore could have anaphylactic reactions to subsequent administration of blood products that contain IgA, including VIGIV.

WARNINGS

Immune globulin intravenous (Human) (IGIV) products have been reported to be associated with renal dysfunction, acute renal failure, osmotic nephrosis, proximal tubular nephropathy, and death.[9,10] Although these reports of renal dysfunction and acute renal failure have been associated with the use of many licensed IGIV products, those that contained sucrose as a stabilizer and were administered at daily doses of 400 mg/kg or greater have accounted for a disproportionate share of the total number.[11] VIGIV contains sucrose (5%) as a stabilizer, and the recommended dose is 100 mg/kg. Patients predisposed to acute renal failure include the following: patients with any degree of pre-existing renal insufficiency, diabetes mellitus, volume depletion, sepsis, or paraproteinemia, patients who are at least 65 years of age, or patients who are receiving known nephrotoxic drugs. Especially in such patients, VIGIV should be administered at the minimum concentration available and at the minimum rate of infusion practical.[8]

VIGIV is derived from human plasma. Few experimental or epidemiological studies of variant CJD (vCJD) transmissibility by blood components or plasma derivatives have been published. It is not known whether plasma-derived products can transmit the vCJD agent. No such transmissions have been reported to date. Source Plasma donors for VIGIV may have lived in areas where there is a known risk of exposure to the vCJD agent (e.g., military bases for 6 months or more between 1980 and 1990 or at bases elsewhere in Europe for 6 months between 1980 and 1996). To date, no donors of any Source Plasma have been diagnosed with vCJD. The risk of transmission of recognized blood-borne viruses has been reduced by the viral inactivation and/or removal properties of the procedures used in the

manufacturing of VIGIV (see DESCRIPTION section) including cold ethanol precipitation, nanofiltration, and solvent/detergent treatment with C18 column chromatography. The ability of these procedures to reduce infectivity of the causative agent of vCJD has not been evaluated for VIGIV. Despite these measures, some as yet unrecognized blood-borne viruses or other infectious agents may not be inactivated or removed by the manufacturing process; therefore, VIGIV, like any other blood product, should be given only if a benefit is expected. Epinephrine and diphenhydramine should be available for the treatment of acute allergic symptoms (see PRECAUTIONS section).

PRECAUTIONS

General

VIGIV should only be administered as an intravenous infusion, since other routes of administration have not been evaluated. VIGIV should not be used if the solution is turbid. During administration, the patient's vital signs should be monitored continuously, and the patient should be carefully observed for any symptoms throughout the infusion. Although acute systemic allergic reactions were not seen in clinical trials with VIGIV (see ADVERSE REACTIONS section), epinephrine and diphenhydramine should be available for treatment of acute allergic symptoms. If hypotension or anaphylaxis occurs, the administration of VIGIV should be discontinued immediately and supportive care given as needed.

VIGIV 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 years, volume depletion, paraproteinemia, sepsis, and patients receiving known nephrotoxic drugs). In these cases, it is important to ensure that patients are not volume depleted before VIGIV infusion. Do not exceed the recommended infusion rate, and follow the infusion schedule closely (see

DOSAGE AND ADMINISTRATION section). Most cases of renal insufficiency have occurred in patients receiving total doses of IGIV containing 400 mg/kg of sucrose or greater. Doses of VIGIV higher than 400 mg/kg will exceed this level of sucrose, and are thus not recommended in patients with potential renal problems. However, no prospective data are currently available to identify a maximum safe dose, concentration, or rate of infusion in patients at increased risk of acute renal failure.[8]

Aseptic meningitis syndrome (AMS) has been reported to occur infrequently in association with IGIV administration.[12-15] The syndrome usually begins within several hours to 2 days after IGIV treatment. It is characterized by symptoms and signs including the following: 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 per cubic millimeter, predominately from the granulocytic series, and with elevated protein concentrations up to several hundred mg/dL. Patients exhibiting such symptoms and signs should receive a thorough neurological examination to rule out other causes of meningitis.[12-15] AMS may occur more frequently in association with high total doses (2 g/kg) of IGIV treatment. Discontinuation of IGIV treatment has resulted in remission of AMS within several days without sequelae.[8]

Hemolysis

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.[16-18] Hemolytic anemia can develop subsequent to IGIV therapy due to enhanced red blood cell sequestration.[19] VIGIV 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[20]. TRALI is characterized by severe respiratory distress, pulmonary edema, hypoxemia, normal left ventricular function, and fever and typically occurs within 1 to 6 hours after transfusion. Patients with TRALI may be managed using oxygen therapy with adequate ventilatory support.

VIGIV 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.[21-23] 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 VIGIV should be weighed against those of alternative therapies for all patients for whom VIGIV 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 VIGIV infusion, appropriate confirmatory laboratory testing should be done.

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

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.

Drug Interactions

Antibodies present in immune globulin preparations may interfere with the immune response to live virus vaccines such as polio, measles, mumps, and rubella; THEREFORE, VACCINATION WITH LIVE VIRUS VACCINES SHOULD BE DEFERRED UNTIL APPROXIMATELY 6 MONTHS AFTER ADMINISTRATION OF VIGIV. If such vaccinations were given shortly before or after VIGIV administration, a revaccination may be necessary. Admixtures of VIGIV with other drugs have not been evaluated. It is recommended that VIGIV be administered separately from other drugs or medications that the patient may be receiving (see ADMINISTRATION section).

Pregnancy Category C

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

Nursing Mothers

It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when VIGIV is administered to a nursing woman.

Pediatric Use

VIGIV has not been tested for safety or efficacy in pediatric populations.

Geriatric Use

VIGIV has not been tested for safety or efficacy in geriatric populations.

ADVERSE REACTIONS

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared with rates in the clinical trials of another drug in the same therapeutic class and may not reflect the rates observed in practice. However, the adverse reaction information from clinical trials does provide a basis for identifying the adverse events (AEs) that appear to be related to drug use and for approximating rates of AE occurrence. Table 2 summarizes the most frequently reported (5% or greater) AEs and treatment-related AEs in two clinical trials.

In the first study where 78 healthy adult volunteers received 100 mg/kg (2 mL/kg), 200 mg/kg (4 mL/kg), or 500 mg/kg (10 mL/kg) VIGIV (lyophilized formulation), all three doses of VIGIV were well tolerated. There were no marked differences among the three doses of VIGIV for any reported AEs or with respect to clinical laboratory evaluations, vital signs, and physical examination findings. A total of 62 subjects reported AEs, the majority of which were mild or moderate. Headache was the most common AE. Urticaria was reported to be of mild to moderate severity and was experienced in 4 cases (5%) of

VIGIV-treated subjects during or after infusion. No cases of urticaria were associated with shortness of breath or with other signs or symptoms of anaphylaxis.

In the second study, 33 healthy adult volunteers received a 100 mg/kg (2 mL/kg) dose of liquid VIGIV.

The most common AE for both studies was headache, occurring in 32% of subjects. Other common AEs that occurred across doses and studies included upper respiratory infection not otherwise specified (NOS) (9%), back pain (7%), nausea (6%), injection site reaction NOS (7%), and dizziness (5%) (Table 2).

Table 2. Most Frequently Reported (≥ 5%) Adverse Events and Treatment-Related Adverse Events*

Body System Preferred Term	VIGIV-lyophilized						VIGIV-liquid	
	500 mg/kg (N = 26)		200 mg/kg (N = 26)		100 mg/kg (N = 26)		100 mg/kg (N = 33)	
	All (%)	*Rel. (%)*	*All (%)*	*Rel. (%)*	*All (%)*	*Rel. (%)*	*All (%)*	*Rel. (%)*
Any adverse event	22 (85)	6 (23)	16 (62)	5 (19)	24 (92)	5 (19)	24 (73)	7 (21)
Nervous system disorders								
Headache	10 (39)	1 (4)	6 (23)	0 (0)	10 (39)	1 (4)	10 (30)	2 (6)
Dizziness	1 (4)	0 (0)	1 (4)	0 (0)	1 (4)	1 (4)	3 (9)	2 (6)
Somnolence	0 (0)	0 (0)	1 (4)	0 (0)	0 (0)	0 (0)	3 (9)	0 (0)
General disorders and administration site conditions								
Injection site reaction	2 (8)	0 (0)	1 (4)	0 (0)	3 (12)	3 (12)	2 (6)	0 (0)
Musculoskeletal, connective tissue, and bone disorders								
Back pain	4 (15)	1 (4)	1 (4)	0 (0)	3 (12)	0 (0)	0 (0)	0 (0)
Arthralgia	1 (4)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	3 (9)	1 (3)
Gastrointestinal disorders								
Nausea	1 (4)	1 (4)	1 (4)	0 (0)	3 (12)	0 (0)	2 (6)	1 (3)
Abdominal pain	0 (0)	0 (0)	1 (4)	1 (4)	0 (0)	0 (0)	3 (9)	1 (3)
Toothache	1 (4)	0 (0)	0 (0)	0 (0)	2 (8)	0 (0)	1 (3)	0 (0)
Sore throat	2 (8)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Infections and infestations								
Upper respiratory tract infection NOS	3 (12)	0 (0)	2 (8)	0 (0)	2 (8)	0 (0)	3 (9)	0 (0)
Skin and subcutaneous tissue disorders								
Erythema	0 (0)	0 (0)	0 (0)	0 (0)	3 (12)	1 (4)	0 (0)	0 (0)
Dermatitis contact	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	3 (9)	0 (0)
Urticaria	2 (8)	2 (8)	1 (4)	1 (4)	1 (4)	1 (4)	0 (0)	0 (0)
Respiratory, thoracic, and mediastinal disorders								
Nasal congestion	2 (8)	0 (0)	0 (0)	0 (0)	1 (4)	0 (0)	1 (3)	0 (0)
Dyspnea	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	2 (6)	0 (0)
Injury, poisoning and procedural complications								
Skin lacerations	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	2 (6)	0 (0)
Vascular disorders								
Flushing	2 (8)	2 (8)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)

*Incidence of adverse events is calculated for each study independently (VIGIV-lyophilized, N=78; VIGIV-liquid, N=33). Adverse events reported here include all events observed from the start of infusion through day 42 after infusion; two baseline adverse events were reported in the VIGIV-liquid study (headache and lightheadedness) but are not included in this table. Treatment-related adverse events are those considered definitely, probably, or possibly related to VIGIV treatment.

Systemic reactions such as chills, muscle cramps, back pain, fever, nausea, vomiting, and wheezing were the most frequent adverse reactions observed during the clinical trials of other similarly prepared human IGIVs.[24] These reactions were most often related to infusion rates greater than that recommended for VIGIV.[11] If a patient develops any infusion-related adverse reaction, slow the rate of infusion immediately or temporarily interrupt the infusion.

Severe adverse reactions (e.g., angioneurotic edema and anaphylactic shock), although not observed during clinical trials with VIGIV, are possible.[25,26] Clinical anaphylaxis may occur even when a patient does not have a history of sensitivity to immunoglobulin products. A reaction may be related to the rate of infusion; therefore, carefully adhere to the infusion rates as outlined in the DOSAGE AND ADMINISTRATION section. If anaphylaxis or hypotension occurs, discontinue the infusion immediately and administer epinephrine with or without diphenhydramine for acute allergic symptoms.[6,8]

Increases in serum creatinine and blood urea nitrogen have been observed as soon as 1 to 2 days after treatment with other IGIVs. Other severe renal AEs seen after IGIV therapy include acute renal failure, acute tubular necrosis, proximal tubular nephropathy, and osmotic nephrosis.[9-11,24]

Postmarketing Experience with Other IGIV Products

The following adverse reactions have been identified and reported during the post-approval use of other IGIV products:[16-23,27]

Respiratory

Apnea, Acute Respiratory Distress Syndrome (ARDS), Transfusion Associated Lung Injury (TRALI), cyanosis, hypoxemia, pulmonary edema, dyspnea, bronchospam

Cardiovascular

Cardiac arrest, thromboembolism, vascular collapse, hypotension

Neurological

Coma, loss of consciousness, seizures, tremor

Integumentary

Stevens-Johnson syndrome, epidermolysis, erythema multiforme, bullous dermatitis

Hematologic

Pancytopenia, leukopenia, hemolysis, positive direct antiglobulin (Coombs) test

General/Body as a Whole

Pyrexia, rigors

Musculoskeletal

Back pain

Gastrointestinal

Hepatic dysfunction, abdominal pain

Because post-marketing 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 a reaction or establish a causal relationship to exposure to the product. Such is also the case with literature reports authored independently.

OVERDOSAGE

Although limited data are available, clinical experience with other immunoglobulin preparations suggests that the major manifestations would be those related to volume overload.[8]

DOSAGE AND ADMINISTRATION

The recommended total dosage of VIGIV is 2 mL/kg (100 mg/kg), given as an intravenous infusion, when the clinical diagnosis of a severe vaccinia-related complication is established. This dose may be repeated, depending on the severity of the symptoms and response to treatment.

The administration of higher doses (200 mg/kg or 500 mg/kg) may be considered in the event that the patient does not respond to the initial 100-mg/kg dose.

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

VIGIV should be inspected visually for particulate matter and discoloration before administration. Infuse the solution only if it is colorless, free of particulate matter, and not turbid.

Infusion: Intravenous 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 monitored continuously. VIGIV should be administered through an intravenous catheter with an administration set that contains an in-line filter (pore size: 0.22 μm) and a constant infusion pump (i.e., an IVAC pump or equivalent). Predilution of VIGIV before infusion is not recommended. VIGIV should be administered through a dedicated intravenous

catheter. Otherwise, VIGIV may be "piggybacked" into a pre-existing catheter if the catheter contains either 0.9% Sodium Chloride for 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, and 20% dextrose in water. If a pre-existing access must be used, the line should be flushed before use and the VIGIV should not be diluted more than 1:2 (v/v) with any of these solutions. Admixtures of VIGIV with any other solutions have not been evaluated.

Infusion Rate: VIGIV should be infused at a rate of 1.0 mL/kg/h for the first 30 minutes, increased to 2.0 mL/kg/h for the next 30 minutes and then to 3.0 mL/kg/h for the remainder of the infusion, as tolerated. DO NOT EXCEED THESE RATES OF ADMINISTRATION.

The patient should be monitored closely during and after each infusion rate change. At the recommended rates, infusion at the indicated dose (100 mg/kg [2 mL/kg]) should take approximately 70 minutes.

Adverse reactions related to the infusion rate have been experienced by patients treated with immune globulin intravenous (IGIV) products; most infusion rate-related adverse reactions reported for other IGIV products have been minor (including flushing, chills, muscle cramps, back pain, fever, nausea, vomiting, arthralgia, and wheezing), however, major adverse events are possible. Patients should be observed for increase in heart rate, respiratory rate, retractions, and rales. If the patient develops a minor adverse reaction (e.g., flushing), slow the rate of infusion or temporarily interrupt the infusion. For serious adverse reactions such as anaphylaxis or a significant drop in blood pressure,

discontinue the infusion and administer epinephrine with or without diphenhydramine. A loop diuretic should be available for management of fluid overload during administration. To prevent the transmission of hepatitis viruses or other infectious agents, sterile, disposable syringes and needles should be used. The syringes and needles should never be reused.

VIGIV 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 years, volume depletion, paraproteinemia, sepsis, and patients receiving known nephrotoxic drugs). In such patients who do not respond to the 100 mg/kg dose, the concentration and infusion rate selected should be the minimum practicable. Most cases of renal insufficiency have occurred in patients receiving total doses of IGIV containing 400 mg/kg of sucrose or greater. Doses of VIGIV higher than 400 mg/kg will exceed this level of sucrose, and are thus not recommended in patients with potential renal problems.

HOW SUPPLIED

VIGIV is supplied in a sterile vial; each vial contains 50 mL of solution with VIGIV at a concentration of 50 mg/mL (2,500 mg immunoglobulin per vial).

STORAGE

VIGIV should be stored between 2^{o} and 8^{o}C (35.6^{o} to 46.4^{o}F), and intravenous infusion should begin within 6 hours after entering the vial.

REFERENCES

1. Wells MA, Wittek AE, Epstein JS, et al. Inactivation and partition of human T-cell lymphotrophic virus, type III, during ethanol fractionation of plasma. Trans 1986;26:210-213.

2. Bossell J, et al. Safety of therapeutic immune globulin preparations with respect to transmission of human T-lymphotropic virus type III/lymphadenopathy-associated virus infection. Morb Mortal Wkly Rep 1986;35:231-233.

3. Horowitz B, Wiebe ME, Lippin A, Stryker MH. Inactivation of viruses in labile blood derivatives. Transfusion 1985;25:516-522.

4. Edwards CA, Piet MPJ, Chin S, Horowitz B. Tri(n-butyl) phosphate/detergent treatment of licensed therapeutic and experimental blood derivatives. Vox Sang 1987;52:53-59.

5. Immune globulin intravenous (human) Iveegam En IGIV. In: eds. Physician's Desk Reference. 55th Ed. Montvale, New Jersey: Medical Economics Company, Inc.;2001:816-820.

6. Immune globulin intravenous (human) (IGIV) Gammagard® S/D. In: Physician's Desk Reference. 58th ed. Montvale, New Jersey: Medical Economics Company, Inc.; 2004:816-819.

7. Fulginiti VA, Winograd LA, Jackson M, Ellis P. Therapy of experimental vaccinal keratitis Effect of idoxuridine and VIG. Arch Ophthal 1965;74:539-544.

8. Cytogam®, cytomegalovirus immune globulin intravenous (human) (CMV-IGIV). In: Physician's Desk Reference. 58th ed. Montvale, New Jersey: Medical Economics Company, Inc.; 2004:1907-1909.

9. Perazella MA, Cayco AV. Acute renal failure and intravenous immune globulin: sucrose nephropathy in disguise? Am J Ther 1998;5:399-403.

10. Cayco AV, Perazella MA, Hayslett JP. Renal insufficiency after intravenous immune globulin therapy: a report of two cases and an analysis of the literature. J Am Soc Nephrol 1997;8:1788-1793.

11. Important Drug Warning ("Dear Doctor") letter. Center for Biologics Evaluation and Research, Food and Drug Administration;1998.

12. Sekul EA, Cupler EJ, Dalakas MC. Aseptic meningitis associated with high-dose intravenous immunoglobulin therapy: frequency and risk factors. Ann Intern Med 1994;121:259-262.

13. Kato E, Shindo S, Eto Y, et al. Administration of immune globulin associated with aseptic meningitis. JAMA 1988;259:3269-3270.

14. Casteels-Van Daele M, Wijndaele L, Hunninck K. Intravenous immunoglobulin and acute aseptic meningitis. N Engl J Med 1990;323:614-615.

15. Scribner C, Kapit R, Philips E, Rickels N. Aseptic meningitis and intravenous immunoglobulin therapy. Ann Intern Med 1994;121:305-306.

16. Copelan EA, Strohm PL, Kennedy MS, Tutschka PJ. Hemolysis following intravenous immune globulin therapy. Transfusion 1986;26(5):410-412.

17. Thomas MJ, Misbah SA, Chapel HM, Jones M, Elrington G, Newsom-Davis J. Hemolysis after high-dose intravenous Ig. Blood 1993;82(12):3789.

18. Reinhart WH, Berchtold PE. Effect of high-dose intravenous immunoglobulin therapy on blood rheology. Lancet 1992;339(8794):662-664.

19. 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 Autoimmunity 1999;13:129-135.

20. Rizk A, Gorson KC, Kenney L, Weinstein R. Transfusion-related acute lung injury after the infusion of IVIG. Transfusion 2001;41(2):264-268.

21. Dalakas MC. High-dose intravenous immunoglobulin and serum viscosity: risk of precipitating thromboembolic events. Neurology 1994;44(2):223-226.

22. Woodruff RK, Grigg AP, Firkin FC, Smith IL. Fatal thrombotic events during treatment of autoimmune thrombocytopenia with intravenous immunoglobulin in elderly patients. Lancet 1986;2(8500):217-218.

23. Wolberg AS, Kon RH, Monroe DM, Hoffman M. Coagulation factor XI is a contaminant in intravenous immunoglobulin preparations. Am J Hematol 2000;65(1):30-34.

24. Snydman DR, Werner BG, Tilney NL, et al. Final analysis of primary cytomegalovirus disease prevention in renal transplant recipients with cytomegalovirus immune globulin: comparison of the randomized and open-label trials. Transplant Proc 1991;23:1357-1360.

25. Denepoux S, et al. Molecular characterization of human IgG monoclonal antibodies specific for major birch pollen allergen Bet v 1. Anti-allergen IgG can enhance the anaphylactic reaction. FEBS Lett 2000;465:36-46.

26. Burks AW, Sampson HA, Buckley RH. Anaphylactic reactions after gamma globulin administration in patients with hypogammaglobulinemia. Detection of IgE antibodies to IgA. N Engl J Med 1986;314:560.

27. Pierce LR, Jain N. Risks associated with the use of intravenous immunoglobulin. Transfus Med Rev 2003;17(4):241-251.

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NDC 00000-0000-0
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Revised February 2005