Vaccinia Immune Globulin Intravenous (Human) (VIGIV)

DESCRIPTION

CNJ-016, Vaccinia Immune Globulin Intravenous (Human) (VIGIV), is a solvent/detergent-treated sterile solution of purified gamma globulin (IgG) fraction of human plasma containing antibodies to vaccinia virus. It is stabilized with 10% maltose and 0.03% polysorbate 80 (pH is between 5.0 and 6.5) and contains no preservative. This agent is manufactured from plasma collected from healthy, screened donors with high titres of anti-vaccinia antibody (meeting minimum potency specifications) that is purified by an anion-exchange column chromatography method.[1, 2] The plasma donors were boosted with vaccinia vaccine prior to donating plasma used in the production of the product. Each plasma donation used for the manufacture of VIGIV is tested for the presence of hepatitis B virus (HBV) surface antigen (HBsAg) and antibodies to human immunodeficiency viruses (HIV) 1/2, and hepatitis C virus (HCV) using FDA-licensed serological tests. In addition mini-pool testing of plasma used in the manufacture of this product was tested by FDA licensed Nucleic Acid testing (NAT) for HIV-1 and HCV and found to be negative. An investigational NAT for HBV was also performed on all Source Plasma used, and found to be negative; however, the significance of a negative result has not been established.

Several steps in the manufacturing process have been validated for their ability to remove/inactivate viruses that may not have been detected in the Source Plasma. The manufacturing process includes both a Planova 35 N virus filtration step and a solvent/detergent treatment step (using tri-n-butyl phosphate and Triton X-100®) that have been validated for their capacity to remove and/or inactivate lipid-enveloped and non-enveloped viruses.[3] Table 1 summarizes the viral reduction values obtained through validation studies. The viruses employed for the spiking studies were selected to represent those viruses that are potential contaminants for the product, and to represent a wide range of physio-chemical properties, in order to challenge the manufacturing process's ability for viral clearance in general.

Table 1 Virus reduction values obtained through validation studies.

Virus Used for Validation	**HIV-1**	**BVDV**	**PRV**
Genome Envelope Size	RNA Yes 80-100 nm	RNA Yes 50-70 nm	DNA Yes 120-200 nm
35N Nanofiltration Step	≥ 6.0	4.4 to ≥ 6.4 [1]	≥ 6.8
S/D Step	≥ 4.7	≥ 6.6	≥ 5.0
Total Reduction (log_{10})	**> 10.7**	**≥ 11.0**	**≥ 11.8**

[1] The lower value was used for calculation of the total reduction factor. The range obtained was for the validation of the process robustness.
HIV-1: relevant virus for human immunodeficiency virus-1 and model for HIV-2
BVDV: bovine viral diarrhea virus; model virus for hepatitis C virus (HCV) and West Nile virus (WNV)
PRV: pseudorabies virus; model for large enveloped DNA viruses, including herpes and hepatitis B virus

In addition to the validated reduction values for lipid-enveloped viruses, two steps were identified as contributing to the overall viral clearance capacity for small, non-lipid enveloped viruses: 1) The anion-exchange chromatographic step yielded a clearance of 3.4 log_{10} of murine minute virus (MMV), which is a model for parvovirus B-19, and a clearance of 2.3 log_{10} for the relevant virus, hepatitis A virus (HAV). 2) The nanofiltration step yielded a clearance of 4.25 log_{10} of poliovirus, a model for hepatitis A virus.

The 35N nanofiltration step is expected to remove the vaccinia virus, based on the size of the virus (200-450 nm long x 140-460 nm wide), and on the results obtained for BVDV (50-70 nm). However, no validation studies were performed for the 35N nanofiltration step specifically using vaccinia virus. Further clearance is obtained by the solvent and detergent step, which was validated for the inactivation, and resulted in a 3.7 log_{10} reduction of the vaccinia virus. In addition, the presence of anti-vaccinia antibodies in the product is also predicted to inactivate the vaccinia virus. [3]

The product potency (as determined by a plaque reduction neutralization test) is expressed in arbitrary units (U) by comparison to the FDA reference standard. Each vial contains approximately 40-70 mg/mL total protein and greater than 50,000 units of vaccinia

antibody neutralizing activity. The product contains ≤ 40 µg/mL of Immunoglobulin A (IgA).

CLINICAL PHARMACOLOGY

A phase 1, randomized, double-blind study was conducted in which 60 healthy volunteers received either 6000 U/kg or 9000 U/kg VIGIV. [4] After intravenous administration of 6000 U/kg to 31 healthy male and female volunteers, a mean peak plasma concentration of 161 U/mL was achieved within 2 hours. The half-life of VIGIV was 30 days (range of 13 to 67 days) and the volume of distribution was 6630 L. Pharmacokinetic parameters were calculated based on antibody levels determined by an ELISA.

The binding capacity and neutralizing antibody activity of anti-vaccinia antibody in these subjects 5 days after intravenous administration of VIGIV [4] (both 6000 U/kg and 9000 U/kg dosages) were at least as high as the theoretical values that would be achieved following the administration of the comparator Vaccinia Immune Globulin (VIG) (see Table 2). Five days represents the approximate time of peak serum anti-vaccinia antibody concentration following intramuscular administration of other Immune Globulin (Human) products. No historical pharmacokinetic data are available for the theoretical intramuscular comparator, Vaccinia Immune Globulin (VIG). [5] Nor are there any pharmacodynamic or efficacy data from controlled trials available for any VIG IM/IV product.

Table 2 Test of Non-inferiority [5]

Dose VIGIV, U/kg	**Plasma levels, U/mL (Range*)**		**Ratio of Means % (97.5% Lower Confidence Interval Bound)****
	VIGIV**	**VIGIM*****	
6000	60.1 (36.1-84.6)	66.2 (42.3-94.9)	90.82 (86.94)
9000	90.3 (63.4-133.8)	64.8 (47.6-87.2)	139.40 (135.27)

*geometric mean (range) **observed levels *** simulated levels **** expressed as a percentage relative to the geometric mean of the simulated concentrations at Day 5 after 6000 U/kg intramuscular administration

A pilot phase 1 double blind pharmacodynamic study was conducted in which 32 healthy volunteers were randomized to receive vaccinia vaccination with or without VIGIV. The objectives of the study were to assess the effects of VIGIV upon the local and immunological response to vaccinia vaccination and to further characterize the safety of VIGIV. When VIGIV was administered prior to or concurrently with vaccinia vaccination, the safety profile of VIGIV was consistent with the pharmacokinetic study.

Ongoing clinical studies are further evaluating the effects of concurrent administration of VIGIV with vaccinia vaccine on the pharmacokinetics of the vaccine-induced antibody response, on local vaccination site reaction, and on safety.

INDICATIONS AND USAGE

Vaccinia Immune Globulin Intravenous (Human) (VIGIV) is indicated for the treatment and/or modification of the following conditions:

- **Eczema vaccinatum**
- **Progressive vaccinia**
- **Severe generalized vaccinia**
- **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**
- **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.**

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. [6] VIGIV is not considered to be effective in the treatment of postvaccinial encephalitis.

Prospective clinical studies to evaluate the efficacy and safety of any VIG IM/IV product in patients suffering complications of vaccinica vaccination have not been conducted.

CONTRAINDICATIONS

While Vaccinia Immune Globulin Intravenous (Human) (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 anaphylaxis or prior severe systemic reaction associated with the parenteral administration of this or other human immunoglobulin preparations. [7, 8, 9] VIGIV contains trace amounts of IgA. While CNJ-016™ contains less than 40 µg/mL 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

Vaccinia Immune Globulin Intravenous (Human) (VIGIV) is prepared from human plasma and, like other plasma products, carries the possibility for transmission of blood-borne viral agents and, theoretically, the Creutzfeld Jakob disease agent. The risk of transmission of recognized blood-borne viruses has been reduced by screening plasma donors for prior exposure to certain viruses, by testing for the presence of certain current viral infections, and by implementing process steps for the inactivation and/or removal of certain potential viruses during manufacturing. Despite these measures, some as yet unrecognized blood-borne viruses may not be removed by the manufacturing process; therefore VIGIV, like any other blood product, should be given only if a benefit is expected (see **PRECAUTIONS – General**).

Severe immediate hypersensitivity reactions to plasma-derived products are generally rare. These reactions can occur in very rare cases of IgA deficiency or hypersensitivity to human globulin. In case of allergic or anaphylactic reaction, the infusion should be stopped immediately. The product should be administered only in a setting where appropriate equipment and personnel trained in the management of acute anaphylaxis are available (see **PRECAUTIONS** section). In case of shock, the current medical standards for treatment of shock should be observed.

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. [10, 11] 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 Ig/kg or greater have accounted for a disproportionate share of the total number. [12] CNJ-016™ does not contain sucrose (5%) as a stabilizer, and the recommended dose is less than 400mg Ig/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, as well as in patients judged to be at risk of thrombotic and thromboembolic events, CNJ-016™ should be administered at the minimum concentration available and at the minimum rate of infusion practicable. [9]

The physician should discuss the risks and benefits of this product with the patient, before prescribing or administering it (see **PRECAUTIONS – General**).

PRECAUTIONS

General

VIGIV should only be administered intravenously. VIGIV should not be used if the solution is turbid.

Certain adverse drug reactions may be related to the rate of infusion. The recommended infusion rate given under **DOSAGE AND ADMINISTRATION** must be closely followed. Patients and their vital signs must be closely monitored and carefully observed for any symptoms throughout the infusion period and immediately following an infusion.

Although acute systemic allergic reactions were not seen in clinical trials with VIGIV (see **ADVERSE REACTIONS**), the product should be administered only in a setting where appropriate equipment and personnel trained in the management of acute anaphylaxis are available. 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 following administration of IGIV have occurred in patients receiving total doses containing 400 mg/kg of sucrose or greater. CNJ-016™ does not contain sucrose. No prospective data are currently available in patients with risk factors for renal insufficiency and/or thrombois/thromboembolism to identify a maximum safe dose, concentration, and/or rate of infusion for CNJ-016™.

Vaccinia Immune Globulin Intravenous (Human) (VIGIV), like other products made from human plasma, may contain infectious agents, such as viruses, that can cause disease. The risk that VIGIV will transmit an infectious agent has been reduced by screening plasma donors for prior exposure to certain viruses, by testing for the presence of certain current virus infections, and by inactivating and/or removing certain viruses (see **DESCRIPTION** section). However, despite these measures, VIGIV can still potentially transmit disease. There is also the possibility that unknown infectious agents may be present. All infections thought to have been possibly transmitted by this product should be reported by the physician or other health care provider to Cangene Corporation at 1-877-CANGENE (226-4363).

An aseptic meningitis syndrome (AMS) has been reported to occur infrequently in association with IGIV administration. [13, 14, 15, 16] The syndrome usually begins within several hours to two days following 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 levels 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. [13, 14, 15, 16] AMS may occur more frequently in association with high total doses (2 g/kg) of IGIV treatment (in comparison, at the recommended dosage of 6000 U/kg, a patient may be exposed to up to 0.12 g/kg protein after VIGIV administration). Discontinuation of IGIV treatment has resulted in remission of AMS within several days without sequelae. [9]

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. [17, 18, 19] Hemolytic anemia can develop subsequent to IGIV therapy due to enhanced red blood cell sequestration. [20] 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. [21] 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. [22, 23, 24] Patients at risk may include those with a history of atherosclerosis, multiple cardiovascular risk factors, advanced age, impaired cardiac output, hypercoagulable disorders, prolonged periods of immobilization, 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

Immune globulin administration may impair the efficacy of live attenuated vaccines such as measles, rubella, mumps and varicella. [25, 26] Vaccination with live virus vaccines should be deferred until approximately three months after administration of VIGIV. People who received VIGIV shortly after live virus vaccination, should be revaccinated 3 months after the administration of the immune globulin.

There are no available data on concomitant use of Vaccinia Immune Globulin Intravenous (Human) (VIGIV) and other medications. 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 **DOSAGE AND ADMINISTRATION** section). If a pre-existing catheter must be used, the line should be flushed with 0.9% Sodium Chloride for injection USP before administering the product. Compatibility of VIGIV was only assessed with 0.9% Sodium Chloride USP and not with other solutions such as dextrose in water.

Drug/Laboratory Test Interactions

After administration of VIGIV, a transitory increase of passively transferred antibodies in the patient's blood may result in misleading positive results in serological testing (e.g. anti-HBs).

Pregnancy Category C

Animal reproduction studies have not been conducted with VIGIV; therefore it is not known whether VIGIV can cause fetal harm when administered to a pregnant woman or whether it can affect reproduction capacity. However, immune globulins have been widely used during pregnancy for many years without any apparent negative reproductive effects. [27] The risk/benefit of VIGIV administration should be assessed for each individual case.

Nursing Mothers

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

Pediatric and Geriatric Use

Safety and effectiveness in the pediatric or geriatric populations have not been established for VIGIV.

ADVERSE REACTIONS

Overview

No serious adverse drug reactions have been reported following the administration of Vaccinia Immune Globulin Intravenous (Human) (VIGIV). However, drug exposure to date has been in healthy volunteers. The majority of adverse events reported in a clinical trial evaluating the pharmacokinetics of VIGIV in healthy volunteers were mild and were similar to those regarded as causally related to infusion of other protein products, such as

headache, nausea, dizziness, feeling hot, feeling cold and rigors (see **ADVERSE REACTIONS - General**).

General Adverse Reactions

Because clinical trials are conducted under very specific conditions the adverse reaction rates observed in the clinical trials may not reflect the rates observed in practice and should not be compared to the rates in the clinical trials of another drug. Adverse reaction information from clinical trials is useful for identifying drug-related adverse events and for approximating rates.

In a clinical study, 60 healthy male and female volunteers received a single intravenous dose of either 6000 U/kg or 9000 U/kg VIGIV in a pharmacokinetics trial. [4] The population consisted of vaccinia vaccination-naïve subjects, ages 18 to 32, with both males and females enrolled in an approximate 50:50 ratio.

In another clinical study, 32 healthy male and female volunteers were randomized to receive vaccinia vaccination (n=10), VIGIV (9000 u/kg) four days prior to vaccinia vaccination (n=10), or VIGIV (9000 U/kg) concurrent with vaccinia vaccination (n=12). [28] The population consisted of vaccinia vaccination-naïve subjects, ages 18 to 32, with both male and female enrolled in a 75:25 ratio. The ethnic background of patients included those of Caucasian, African American, Asian and Hispanic descent, with the majority of them being Caucasian.

The most frequently reported adverse events related to VIGIV administration in both studies were headache, rigors, nausea, dizziness, feeling cold, sweating increased and feeling hot. Table 3 describes all adverse events that were temporally related (overall and related) to VIGIV or placebo administration (within 3 days).

Table 3 Adverse events that occurred temporally† following VIGIV administration (≥5%)

Body System Preferred Term	VIGIV						PLACEBO[3] (N=22)	
	6000 U/kg[1] (N=31)		9000 U/kg[1] (N=29)		9000 U/kg[2] (N=10)			
	All (%)	Rel. (%)	All (%)	Rel. (%)	All (%)	Rel. (%)	All (%)	Rel. (%)
All body systems	21 (67.7)	19 (61.3)	25 (86.2)	24 (82.8)	6 (60)	6 (60)	7 (31.8)	4 (18.2)
Eye disorders	2 (6.5)	2 (6.5)	1 (3.4)	1 (3.4)	0 (0)	0 (0)	0 (0)	0 (0)
Gastrointestinal disorders	5 (16.1)	5 (16.1)	8 (27.6)	8 (27.6)	5 (50)	3 (30)	1 (4.5)	1 (4.5)
Nausea	4 (12.9)	4 (12.9)	8 (27.6)	8 (27.6)	4 (40)	3 (30)	1 (4.5)	1 (4.5)
Vomiting NOS	1 (3.2)	1 (3.2)	2 (6.9)	2 (6.9)	2 (20)	1 (10)	0 (0)	0 (0)
Lip dry	0 (0)	0 (0)	0 (0)	0 (0)	1 (10)	0 (0)	0 (0)	0 (0)
General disorders and administration site conditions	10 (32.3)	10 (32.3)	16 (55.2)	15 (51.7)	4 (40)	4 (40)	2 (9.1)	1 (4.5)
Rigors	7 (22.6)	7 (22.6)	6 (20.7)	6 (20.7)	3 (30)	1 (10)	0 (0)	0 (0)
Feeling cold	4 (12.9)	4 (12.9)	7 (24.1)	6 (20.7)	0 (0)	0 (0)	0 (0)	0 (0)
Pain NOS	1 (3.2)	1 (3.2)	2 (6.9)	2 (6.9)	3 (30)	3 (30)	0 (0)	0 (0)
Asthenia	2 (6.5)	2 (6.5)	2 (6.9)	2 (6.9)	0 (0)	0 (0)	1 (4.5)	1 (4.5)
Feeling hot	3 (9.7)	3 (9.7)	1 (3.4)	1 (3.4)	0 (0)	0 (0)	0 (0)	0 (0)
Pyrexia	2 (6.5)	2 (6.5)	0 (0)	0 (0)	1 (10)	1 (10)	0 (0)	0 (0)
Fatigue	0 (0)	0 (0)	2 (6.9)	2 (6.9)	0 (0)	0 (0)	1 (4.5)	1 (4.5)
Energy increased	0 (0)	0 (0)	0 (0)	0 (0)	1 (10)	1 (10)	1 (4.5)	0 (0)
Metabolism and nutrition disorders	2 (6.5)	2 (6.5)	2 (6.9)	2 (6.9)	0 (0)	0 (0)	0 (0)	0 (0)
Appetite decreased NOS	2 (6.5)	2 (6.5)	2 (6.9)	2 (6.9)	0 (0)	0 (0)	0 (0)	0 (0)
Musculoskeletal and connective tissue disorders	6 (19.4)	5 (16.1)	7 (24.1)	7 (24.1)	0 (0)	0 (0)	0 (0)	0 (0)

Body System Preferred Term	VIGIV						PLACEBO[3] (N=22)	
	6000 U/kg[1] (N=31)		9000 U/kg[1] (N=29)		9000 U/kg[2] (N=10)			
	All (%)	Rel. (%)	All (%)	Rel. (%)	All (%)	Rel. (%)	All (%)	Rel. (%)
Back pain	2 (6.5)	2 (6.5)	2 (6.9)	2 (6.9)	0 (0)	0 (0)	0 (0)	0 (0)
Muscle cramp	2 (6.5)	2 (6.5)	2 (6.9)	2 (6.9)	0 (0)	0 (0)	0 (0)	0 (0)
Nervous system disorders	19 (61.3)	18 (58.1)	21 (72.4)	20 (69)	6 (60)	6 (60)	5 (22.7)	4 (18.2)
Headache	17 (54.8)	17 (54.8)	19 (65.5)	18 (62.1)	5 (50)	5 (50)	4 (18.2)	3 (13.6)
Dizziness	5 (16.1)	5 (16.1)	6 (20.7)	6 (20.7)	1 (10)	1 (10)	1 (4.5)	1 (4.5)
Paraesthesia	2 (6.5)	2 (6.5)	1 (3.4)	1 (3.4)	0 (0)	0 (0)	0 (0)	0 (0)
Tremor	1 (3.2)	1 (3.2)	2 (6.9)	2 (6.9)	0 (0)	0 (0)	0 (0)	0 (0)
Respiratory, thoracic and mediastinal disorders	2 (6.5)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Skin and subcutaneous tissue disorders	3 (9.7)	3 (9.7)	2 (6.9)	2 (6.9)	0 (0)	0 (0)	0 (0)	0 (0)
Sweating increased	3 (9.7)	3 (9.7)	2 (6.9)	2 (6.9)	0 (0)	0 (0)	0 (0)	0 (0)
Vascular disorders	2 (6.5)	1 (3.2)	2 (6.9)	2 (6.9)	3 (30)	1 (10)	1 (4.5)	1 (4.5)
Pallor	1 (3.2)	1 (3.2)	2 (6.9)	2 (6.9)	3 (30)	1 (10)	0 (0)	0 (0)

[1] Infusion rate: 4 mL/min. [2] Infusion rate: 2 mL/min. [3] 0.9% NaCl infused at 2 mL/min.

† Adverse events that occurred within 3 days of VIGIV administration.

These adverse events were mostly mild and expected, and are related to intravenous infusion of immune globulins. VIGIV had no effect on blood pressure or heart rate during a clinical trial of 90 days duration. Other less frequently reported adverse events related to VIGIV included back pain, nonspecific pain, pyrexia, vomiting, muscle cramps, muscle tightness and muscle spasms. One subject in the 9000 U/kg dosage group experienced syncope. These less frequently reported adverse events are also expected with intravenous infusion of immune globulins. There was a lower incidence of adverse events when

VIGIV (9000 U/kg) was infused at 2 mL/min (60%) than 4 mL/min (86%). It is important to note that all subjects were fasted overnight prior to infusion of VIGIV or placebo.

There were no serious adverse events or adverse events of severe intensity in this clinical trial. There were no instances where VIGIV was either discontinued due to an adverse event, or where a reduction in either the dose administered or the infusion rate was required.

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 adverse events seen after IGIV therapy include acute renal failure, acute tubular necrosis, proximal tubular nephropathy, and osmotic nephrosis. [10, 11, 12, 29]

Post-marketing Experience with Other IGIV Products

The following is a list of adverse reactions that have been identified and reported during the post-approval use of IGIV: [17, 18, 19, 20, 21, 22, 23, 24, 30]

- **Respiratory:** Cyanosis, hypoxemia, pulmonary edema, dyspnea, bronchospasm
- **Cardiovascular:** Thromboembolism, hypotension
- **Neurological:** Seizures, tremor
- **Hematologic:** Hemolysis, positive direct antiglobulin (Coombs) test
- **General/Body as a Whole:** Pyrexia, rigors
- **Musculoskeletal:** Back pain
- **Gastrointestinal:** Hepatic dysfunction, abdominal pain
- **Rare and Uncommon Adverse Events:**
    - **Respiratory:** Apnea, Acute Respiratory Distress Syndrome (ARDS), Transfusion Associated Lung Injury (TRALI)
    - **Integumentary:** Bullous dermatitis, epidermolysis, erythema multiforme, Stevens-Johnson syndrome

- **Cardiovascular:** Cardiac arrest, vascular collapse
- **Neurological:** Coma, loss of consciousness
- **Hematologic:** Pancytopenia, leukopenia

Because post-marketing reporting of these reactions is voluntary and the at-risk populations are 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. This is also the case with literature reports authored independently.

OVERDOSAGE

Consequences of an overdose are not known.

DOSAGE AND ADMINISTRATION

For the treatment of severe complications of vaccinia vaccination (see **INDICATIONS AND USAGE** section), Vaccinia Immune Globulin Intravenous (Human) (VIGIV) should be administered at a dose of 6000 U/kg, as soon as symptoms appear and are judged to be due to severe vaccinia-related complication. Consideration may be given to repeat dosing, depending on the severity of the symptoms and response to treatment; however, clinical data on repeat doses are lacking. The administration of higher doses (e.g. 9000 U/kg) may be considered in the event that the patient does not respond to the initial 6000 U/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.** Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration.

VIGIV should be administered directly through a dedicated intravenous line with a rate of injection of no greater than 2 mL/min. For subjects weighing less than 50 kg, it is

recommended to infuse the product at a rate no greater than 0.04 mL/kg/minute (133.3 U/kg/minute). The maximum assessed rate of infusion of VIGIV has been 4 mL/min (see **ADVERSE REACTIONS** section). The dosage and the rate of infusion have not been evaluated in pediatric or geriatric patients (see **PRECAUTIONS** section). It may be prudent to infuse the product more slowly if the patient develops a minor adverse (e.g. flushing) reaction or in patients with risk factors for thrombosis/thromboembolism, and/or renal insufficiency.

Compatibility of VIGIV was only assessed with 0.9% Sodium Chloride USP and not with other solutions such as dextrose in water. If a pre-existing catheter must be used, the line should be flushed with 0.9% Sodium Chloride USP before use and VIGIV should not be diluted more than 1:2 (v/v).

Do not reuse or save VIGIV for future use. This product contains no preservative; therefore partially used vials should be discarded.

HOW SUPPLIED

VIGIV is supplied as a 15 mL single dose vial containing ≥ 50,000 U/vial. NDC Number to be determined.

STORAGE

Store at 36 to 46°F (2 to 8°C). Do not use after expiration date.

If product is received frozen, use within 60 days of thawing at 2-8°C. Intravenous infusion should begin within 4 hours after entering the vial.

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