HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use CNJ-016 safely and effectively. See full prescribing information for CNJ-016.

CNJ-016, Vaccinia Immune Globulin Intravenous (Human), sterile solution

Initial U.S. Approval: 2005

WARNING: INTERACTIONS WITH GLUCOSE MONITORING SYSTEMS

See full prescribing information for complete boxed warning.

Blood glucose measurement in patients receiving Vaccinia Immune Globulin Intravenous (Human) (VIGIV) must be done with a glucose-specific method (monitor and test strips) to avoid interference by maltose contained in VIGIV. Maltose in IGIV products may give falsely high blood glucose levels in certain types of blood glucose testing systems (for example those based on the GDH-PQQ or glucose-dye-oxidoreductase methods) resulting in inappropriate administration of insulin and life-threatening hypoglycemia. Cases of true hypoglycemia may go untreated if the hypoglycemic state is masked by falsely elevated glucose readings.

----------RECENT MAJOR CHANGES----------

----------INDICATIONS AND USAGE----------

CNJ-016 is an Immune Globulin Intravenous (Human), 5% Liquid, indicated for the treatment of complications due to vaccinia vaccination (1), including:

- Eczema vaccinatum
- Progressive vaccinia
- Severe generalized vaccinia
- Vaccinia infections in individuals who have skin conditions
- Aberrant infections induced by vaccinia virus (except in cases of isolated keratitis)

CNJ-016 is not indicated for isolated vaccinia keratitis or postvaccinial encephalitis (1).

----------DOSAGE AND ADMINISTRATION----------

- For intravenous use.
- CNJ-016 is administered at a dose of 6,000 Units per kg, as soon as symptoms for complication(s) due to vaccinia vaccination appear (2.1).
- Higher doses (e.g. 9,000 Units per kg or 24,000 Units per kg) may be considered in the event that the patient does not respond to the initial dose of 6,000 Units per kg (2.1).
- For patients with risk factors for thrombosis, the maximum daily dose of VIGIV should not exceed 12,000 Units per kg (2.3).

----------DOSAGE FORMS AND STRENGTHS----------

Sterile solution available as 20 mL single-use vial containing a dose of ≥50,000 Units per vial (3).

----------CONTRAINDICATIONS----------

- Isolated vaccinia keratitis (4)
- History of anaphylactic or severe systemic reaction to human globulins (4)
- IgA deficiency with antibodies against IgA and a history of IgA hypersensitivity (4)

----------WARNINGS AND PRECAUTIONS----------

- Hypersensitivity to human immune globulin (acute anaphylaxis) (5.1)
- Thrombosis may occur with immune globulin products, including VIGIV. For patients at risk of thrombosis, administer VIGIV 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. (5.3)
- Aseptic meningitis syndrome (AMS) (5.4)
- Hemolysis or hemolytic anemia (5.5)
- Noncardiogenic pulmonary edema [Transfusion-Related Acute Lung Injury (TRALI)] (5.6)
- Infusion rate precautions (5.7)
- Acute renal dysfunction/failure (5.8)
- Transmission of infectious agents from human plasma (5.9)
- Monitor renal function and urine output in patients at risk of renal failure; check baseline blood viscosity in patients at risk of hyperviscosity; and conduct confirmatory tests if hemolysis or TRALI is suspected (5.10)

----------ADVERSE REACTIONS----------

The most common adverse drug reactions to CNJ-016 (>10%) are headache, nausea, rigors and dizziness.

To report SUSPECTED ADVERSE REACTIONS, contact Cangene Corporation at 1-800-768-2304 or FDA at 1-800-FDA-1088 or *www.fda.gov/medwatch*.

----------DRUG INTERACTIONS----------

- Efficacy of live attenuated virus vaccines may be impaired by immune globulin administration; revaccination may be necessary (7.1)
- Antibodies in CNJ-016 may interfere with some serological tests (7.2)

----------USE IN SPECIFIC POPULATIONS----------

See 17 for PATIENT COUNSELING INFORMATION

Revised: [12/2015]

FULL PRESCRIBING INFORMATION: CONTENTS*

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

FULL PRESCRIBING INFORMATION

WARNING: INTERACTIONS WITH GLUCOSE MONITORING SYSTEMS

Blood glucose measurement in patients receiving VIGIV must be done with a glucose-specific method (monitor and test strips) to avoid interference by maltose contained in VIGIV. Glucose dehydrogenase pyrroloquinolinequinone (GDH-PQQ) or glucose-dye-oxidoreductase method (monitor and test strips) must not be used for blood glucose testing in patients receiving VIGIV, since maltose in IGIV products has been shown to give falsely high blood glucose levels in these testing systems. This could result in the inappropriate administration of insulin, resulting in life-threatening hypoglycemia. Cases of true hypoglycemia may go untreated if the hypoglycemic state is masked by falsely elevated glucose readings.

Carefully review the product information of the blood glucose testing system, including that of the test strips, to determine if the system is appropriate for use with maltose-containing parenteral products [see *5.2 Interference with Blood Glucose Testing*].

1 INDICATIONS AND USAGE

CNJ-016® [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.

Exercise caution when using VIGIV in the treatment of patients having complication due to vaccinia vaccination that include concomitant vaccinia keratitis, since a single study in rabbits has demonstrated increased corneal scarring upon intramuscular vaccinia immune globulin administration in vaccinia keratitis (1).

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

2 DOSAGE AND ADMINISTRATION

For intravenous use only.

2.1 Dosage for Treatment of Severe Complications of Vaccinia Vaccination

VIGIV should be administered at a dose of 6,000 Units per 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. 9,000 Units per kg) may be considered in the event that the patient does not respond to the initial 6,000 Units per kg dose. In clinical trials, doses of up to 24,000 Units per kg administered to healthy volunteers were well tolerated [see *14 CLINICAL STUDIES*].

2.2 Preparation

- Visually inspect parenteral products for particulate matter and discoloration prior to administration, whenever solution and container permit. Do not use CNJ-016 if the solution is turbid.
- DO NOT SHAKE VIAL. SHAKING VIAL MAY CAUSE FOAMING.
- Remove the entire contents of the vial to obtain the labeled dosage of CNJ-016. If partial vials are required for the dosage calculation, the entire contents of the vial should be withdrawn to ensure accurate calculation of the dosage requirement.
- CNJ-016 is compatible with 0.9% Sodium Chloride USP. No other drug interactions or compatibilities have been evaluated. If a pre-existing catheter must be used, the line should be flushed with 0.9% Sodium Chloride USP before use. Do not dilute more than 1:2 (v/v).
- CNJ-016 vial is for single use only. Do not reuse or save CNJ-016 for future use.
- CNJ-016 contains no preservatives. Discard partially used vials.

2.3 Administration

- Parenteral products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit. CNJ-016 should not be used if the solution is turbid.
- Administer CNJ-016 intravenously through a dedicated intravenous line with the rate of infusion of no greater than 2 mL/min.
- The maximum rate of infusion utilized for CNJ-016 is 4 mL/min [see *6.1 Clinical Trials Experience*].
- For patients weighing less than 50 kg, infuse the product at a rate no greater than 0.04 mL/kg/minute (133.3 Units per kg/minute).
- Slower infusion rate may be needed for patients who develop a minor adverse reaction (e.g. flushing) or for patients with risk factors for thrombosis/thromboembolism.
- For patients with pre-existing renal insufficiency, or at increased risk of acute kidney injury, thrombosis, or volume overload, do not exceed the recommended infusion rate and follow the infusion schedule closely.

- For patients with risk factors for thrombosis, the maximum daily dose of VIGIV should not exceed 12,000 Units per kg [see *5.3 Thrombotic Events*].

3 DOSAGE FORMS AND STRENGTHS

- Solution of gamma globulin (5% or 50 mg/mL)
- 20 mL single-dose vial containing antibodies to vaccinia virus at ≥50,000 Units per vial

4 CONTRAINDICATIONS

- VIGIV is contraindicated in *isolated* vaccinia keratitis.
- VIGIV is contraindicated in individuals with a history of anaphylaxis or prior severe systemic reaction associated with the parenteral administration of this or other human immune globulin preparations.
- VIGIV is contraindicated in IgA-deficient patients with antibodies against IgA and a history of IgA hypersensitivity, as it contains trace amounts of IgA (40 mcg/mL).

5 WARNINGS AND PRECAUTIONS

5.1 Hypersensitivity

Severe immediate hypersensitivity reactions to plasma-derived products may occur, for example, in patients with IgA deficiency or hypersensitivity to human globulin. Although acute systemic allergic reactions were not seen in clinical trials with VIGIV [see *6.1 Clinical Trials Experience*], administer the product only in a setting where appropriate equipment and personnel trained in the management of acute anaphylaxis are available. In case of hypotension, allergic or anaphylactic reaction, discontinue the administration of VIGIV immediately and give supportive care as needed. In case of shock, observe the current medical standards for shock treatment.

5.2 Interference with Blood Glucose Testing

Some types of blood glucose testing systems (for example those based on the glucose dehydrogenase pyrroloquinolinequinone (GDH-PQQ) or glucose-dye-oxidoreductase methods) could falsely interpret the maltose contained in VIGIV as glucose [see *BOXED WARNING*]. This could result in falsely elevated glucose readings and, consequently, in the inappropriate administration of insulin, resulting in life-threatening hypoglycemia. Also, cases of true hypoglycemia may go untreated if the hypoglycemic state is masked by falsely elevated glucose readings. Accordingly, when administering VIGIV or other parenteral maltose-containing products, measure blood glucose with a glucose-specific method.

Carefully review the product information of the blood glucose testing system, including that of the test strips, to determine if the system is appropriate for use with maltose-containing parenteral products. If any uncertainty exists, contact the manufacturer of the testing system to determine if the system is appropriate for use with maltose-containing parenteral products.

5.3 Thrombotic Events

Thrombotic events may occur in association with IGIV treatment. Patients at risk include those with a history of cardiovascular risk factors, advanced age, impaired cardiac output, hypercoagulable disorders, prolonged periods of immobilization, history of arterial or venous thrombosis, estrogen use, indwelling central vascular catheters, and/or known or suspected hyperviscosity. Weigh the potential risks and benefits of VIGIV against those of alternative therapies for all patients for whom VIGIV administration is being considered.

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

In patients where the benefits of VIGIV administration out-weigh the potential risks of thrombotic and thromboembolic events, administer VIGIV at the minimum concentration available and at the minimum rate of infusion practicable. While there are currently no prospective data in patients with thrombosis/thromboembolism to identify a maximum safe dose, concentration, and/or rate of infusion for VIGIV, the maximum daily dose of VIGIV should not exceed 12,000 Units per kg in patients with thrombotic risk factors.

5.4 Aseptic Meningitis Syndrome (AMS)

AMS may occur in association with IGIV administration. AMS usually begins within several hours to two days following IGIV treatment. Discontinuation of IGIV treatment has resulted in remission of AMS within several days without sequelae.

AMS is characterized by the following symptoms and signs: severe headache, nuchal rigidity, drowsiness, fever, photophobia, painful eye movements, and nausea and vomiting. Cerebrospinal fluid (CSF) 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, but negative culture results. Conduct a thorough neurological examination in patients exhibiting such symptoms and signs, including CSF studies, to rule out other causes of meningitis.

AMS may occur more frequently in association with high total doses (2 g/kg) of IGIV treatment. For VIGIV, at the recommended dosage of 6,000 Units per kg, a patient may be exposed to up to 0.12 g/kg protein after VIGIV administration.

5.5 Hemolysis

VIGIV may contain blood group antibodies which may act as hemolysins and induce *in vivo* coating of red blood cells with immune globulin, causing a positive direct antiglobulin reaction and hemolysis. Acute hemolysis, consistent with intravascular hemolysis, has been reported and hemolytic anemia can develop subsequent to IGIV therapy due to enhanced red blood cell sequestration.

The following risk factors may be associated with the development of hemolysis following Immune Globulin Intravenous (Human) (IGIV) products: high doses, given either as a single administration or divided over several days, and non-O blood group (2). Other individual

patient factors, such as an underlying inflammatory state (as may be reflected by, for example, elevated C-reactive protein or erythrocyte sedimentation rate), have been hypothesized to increase the risk of hemolysis following administration of IGIV (3), but their role is uncertain. Closely monitor VIGIV recipients for clinical signs and symptoms of hemolysis, particularly patients with risk factors noted above. Consider appropriate laboratory testing in higher risk patients, including measurement of hemoglobin or hematocrit prior to infusion and within approximately 36 to 96 hours post infusion. If signs and/or symptoms of hemolysis or a significant drop in hemoglobin or hematocrit have been observed after VIGIV infusion, perform additional confirmatory laboratory testing. If transfusion is indicated for patients who develop hemolysis with clinically compromising anemia after receiving VIGIV, perform adequate cross-matching to avoid exacerbating on-going hemolysis.

5.6 Transfusion-related Acute Lung Injury (TRALI)

Noncardiogenic pulmonary edema may occur in patients administered IGIV. 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.

Monitor VIGIV recipients for pulmonary adverse reactions. If TRALI is suspected, perform appropriate tests for the presence of anti-neutrophil antibodies in both the product and patient serum.

5.7 Infusion Rate Precautions

Adverse drug reactions may be related to the rate of infusion. Follow closely the recommended infusion rate given under *2.3 Administration*. Closely monitor and carefully observe patients and their vital signs for any symptoms throughout the infusion period and immediately following an infusion.

5.8 Acute Renal Dysfunction/Failure

Renal dysfunction, acute renal failure, osmotic nephropathy, proximal tubular nephropathy, and death may occur upon use of immune globulin intravenous (Human) (IGIV) products. Use VIGIV with caution in patients with pre-existing renal insufficiency and in patients at 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), and administer VIGIV at the minimum rate of infusion practicable. 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 *2.3 Administration*]. 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 VIGIV and at appropriate intervals thereafter. If renal function deteriorates, consider discontinuing VIGIV.

Most cases of renal insufficiency following administration of IGIV have occurred in patients receiving total doses containing 400 mg/kg of sucrose or greater. VIGIV does not contain sucrose. No prospective data are currently available in patients with risk factors for renal insufficiency to identify a maximum safe dose, concentration, and/or rate of infusion for VIGIV.

5.9 Transmission of Infectious Agents from Human Plasma

VIGIV is prepared from human plasma and carries the possibility 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 [see *11 DESCRIPTION*]. Despite these measures, VIGIV can still potentially transmit disease as some as yet unknown infectious agents may not be removed by the manufacturing process. Therefore VIGIV should be given only if a benefit is expected.

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 1-800-768-2304.

5.10 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 BUN and serum creatinine, before the initial infusion of VIGIV and at appropriate intervals thereafter.
- Because of the potentially increased risk of thrombosis, consider baseline assessment of blood viscosity in patients at risk for hyperviscosity, including those with cryoglobulins, fasting chylomicronemia/markedly high triacylglycerols (triglycerides), or monoclonal gammopathies.
- If signs and/or symptoms of hemolysis are present after an infusion of VIGIV, perform appropriate laboratory testing for confirmation.
- If TRALI is suspected, perform appropriate tests for the presence of anti-neutrophil antibodies in both the product and patient’s serum.

6 ADVERSE REACTIONS

Drug exposure to date has primarily been evaluated in healthy volunteers. The most common adverse reactions to VIGIV treatment (>10%) include headache, nausea, rigors and dizziness in clinical trials involving VIGIV. Although there were no serious adverse events reported in VIGIV clinical trials, there has been a post-marketing case of severe vaccinia infection that developed intravascular hemolysis, leukopenia and thrombocytopenia during VIGIV treatment.

6.1 Clinical Trials Experience

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.

In a safety/pharmacokinetics study, 60 healthy male and female volunteers received a single intravenous dose of either 6,000 Units per kg or 9,000 Units per kg VIGIV. 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 a pharmacodynamic study, 32 healthy male and female volunteers were randomized to receive vaccinia vaccination (n=10), VIGIV (9,000 Units per kg) 4 days prior to vaccinia vaccination (n=10), or VIGIV (9,000 Units per kg) concurrent with vaccinia vaccination (n=12). 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.

In an additional pharmacodynamic clinical study, 50 healthy male and female volunteers were randomized to receive VIGIV at 9,000 Units per kg (n=20) or at 24,000 Units per kg (n=20) or placebo (n=10) 4 days prior to vaccinia vaccination (n=30) or placebo (n=20). The population consisted of vaccinia vaccination-naïve male and female subjects, ages 18 to 33, in a 60:40 ratio. The ethnic background of patients included those of Caucasian, African American, and Hispanic descent, with the majority of them being African American.

The most frequently reported adverse reactions related to VIGIV administration in all three clinical studies were headache, nausea, rigors, and dizziness. Table 1 describes the adverse reactions that were temporally related to VIGIV or placebo administration that occurred during or within three days of product infusion with a frequency of 5% or higher in any one treatment group.

Table 1 Adverse Drug Reactions that Occurred Temporally* During or Following VIGIV Administration (≥5%)

SYSTEM ORGAN CLASS	PREFERRED TERM	CNJ-016 (%)				PLACEBO[a] N=32 (%)
		6,000 U/kg[b] N=31	9,000 U/kg[c] N=39	9,000 U/kg[d] N=20	24,000 U/kg[d] N=20	
All Body System	All Preferred Terms	19 (61.3)	30 (76.9)	2 (10.0)	5 (25.0)	4 (12.5)
Gastrointestinal Disorders	Nausea	4 (12.9)	11 (28.2)	0 (0.0)	0 (0.0)	1 (3.1)
	Vomiting NOS	1 (3.2)	3 (7.7)	0 (0.0)	0 (0.0)	0 (0.0)
General Disorders and Administration Site Conditions	Rigors	7 (22.6)	7 (17.9)	0 (0.0)	0 (0.0)	0 (0.0)
	Feeling cold	4 (12.9)	6 (15.4)	0 (0.0)	0 (0.0)	0 (0.0)
	Pain NOS	1 (3.2)	5 (12.8)	0 (0.0)	0 (0.0)	0 (0.0)
	Feeling hot	3 (9.7)	1 (2.6)	0 (0.0)	0 (0.0)	0 (0.0)
	Asthenia	2 (6.5)	2 (5.1)	0 (0.0)	0 (0.0)	1 (3.1)
	Pyrexia	2 (6.5)	1 (2.6)	0 (0.0)	0 (0.0)	0 (0.0)

SYSTEM ORGAN CLASS	PREFERRED TERM	CNJ-016 (%)				PLACEBO[a] N=32 (%)
		6,000 U/kg[b] N=31	9,000 U/kg[c] N=39	9,000 U/kg[d] N=20	24,000 U/kg[d] N=20	
	Fatigue	0 (0.0)	2 (5.1)	0 (0.0)	0 (0.0)	1 (3.1)
	Edema peripheral	0 (0.0)	0 (0.0)	0 (0.0)	1 (5.0)	0 (0.0)
Metabolism and Nutrition Disorders	Appetite decreased NOS	2 (6.5)	2 (5.1)	0 (0.0)	0 (0.0)	0 (0.0)
Musculoskeletal and Connective Tissue Disorders	Muscle spasm	2 (6.5)	2 (5.1)	0 (0.0)	1 (5.0)	0 (0.0)
	Back pain	2 (6.5)	2 (5.1)	0 (0.0)	0 (0.0)	0 (0.0)
Nervous System Disorders	Headache	17 (54.8)	23 (59.0)	1 (5.0)	4 (20.0)	3 (9.4)
	Dizziness	5 (16.1)	7 (17.9)	1 (5.0)	0 (0.0)	1 (3.1)
	Paraesthesia	2 (6.5)	1 (2.6)	0 (0.0)	0 (0.0)	0 (0.0)
	Tremor	1 (3.2)	2 (5.1)	0 (0.0)	0 (0.0)	0 (0.0)
Skin and Subcutaneous Tissue Disorders	Sweating increased	3 (9.7)	2 (5.1)	0 (0.0)	0 (0.0)	0 (0.0)
Vascular Disorders	Pallor	1 (3.2)	3 (7.7)	0 (0.0)	0 (0.0)	0 (0.0)

*Adverse events that occurred during or within 3 days of VIGIV or placebo administration.

[a] 0.9% NaCl infused at 2 mL/min.

[b] Infusion rate: 4 mL/min; subjects were fasted.

[c] Infusion rate: 4 mL/min or 2 mL/min; subjects were fasted.

[d] Infusion rate: 2 mL/min; subjects were not fasted.

Most adverse reactions were of mild intensity (defined in study protocols as awareness of a sign or symptom but subject can tolerate). One subject in the 9,000 Units per kg dosage group experienced syncope.

There was a lower incidence of adverse reactions when VIGIV (9,000 Units per kg) was infused at 2 mL/min than 4 mL/min. There was a higher incidence of adverse reactions after administration of VIGIV in fasted subjects compared to subjects that were not fasted overnight.

There were no serious adverse reactions or adverse reactions of severe intensity in the clinical studies. There were no instances of VIGIV discontinuation due to an adverse event, or reduction in dose or infusion rate.

6.2 Post-marketing Experience

Because post-marketing adverse reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to exposure to the product. This is also the case with literature reports authored independently.

There has been a case of severe vaccinia infection that developed intravascular hemolysis, leukopenia and thrombocytopenia while receiving VIGIV. However, the hemolysis did not reoccur with continued VIGIV dosing.

The following is a list of adverse reactions that have been identified and reported during the post-approval use of other IGIV products:

- *Infusion reactions*: Hypersensitivity (e.g., anaphylaxis), headache, diarrhea, tachycardia, fever, fatigue, dizziness, malaise, chills, flushing, urticaria or other skin reactions, wheezing or other chest discomfort, nausea, vomiting, rigors, back pain, myalgia, arthralgia, and changes in blood pressure
- *Renal*: Acute renal dysfunction/failure, osmotic nephropathy
- *Respiratory*: Apnea, Acute Respiratory Distress Syndrome (ARDS), TRALI, cyanosis, hypoxemia, pulmonary edema, dyspnea, bronchospasm
- *Cardiovascular*: Cardiac arrest, thromboembolism, vascular collapse, hypotension
- *Neurological*: Coma, loss of consciousness, seizures, tremor, aseptic meningitis syndrome
- *Integumentary*: Stevens-Johnson syndrome, epidermolysis, erythema multiforme, dermatitis (e.g., bullous dermatitis)
- *Hematologic*: Pancytopenia, leukopenia, hemolysis, positive direct antiglobulin (Coombs') test
- *Gastrointestinal*: Hepatic dysfunction, abdominal pain
- *General/Body as a Whole*: Pyrexia, rigors

7 DRUG INTERACTIONS

7.1 Live, Attenuated Vaccines

Immune globulin administration may impair the efficacy of live attenuated vaccines such as measles, rubella, mumps and varicella. Defer vaccination with live virus vaccines until approximately three months after administration of VIGIV. Revaccinate people who received VIGIV shortly after live virus vaccination three months after the administration of the VIGIV.

7.2 Drug/Laboratory Interactions

- VIGIV contains maltose, which can be misinterpreted as glucose by certain types of blood glucose testing systems (for example, those based on the GDH-PQQ or glucose-dye-oxidoreductase methods). Due to the potential for falsely elevated glucose readings, only testing systems that are glucose-specific should be used to test or monitor blood glucose levels in patients receiving VIGIV [see *BOXED WARNING* and *5.2 Interference with Blood Glucose Testing*].

- Antibodies present in VIGIV may interfere with some serological tests. After administration of immune globulins like VIGIV, a transitory increase of passively transferred antibodies in the patient's blood may result in positive results in serological testing (e.g. Coombs' test) [see *5.5 Hemolysis*].

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

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 (4). The risk/benefit of VIGIV administration should be assessed for each individual case.

8.3 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.

8.4 Pediatric Use

Safety and effectiveness in the pediatric population (<16 yrs of age) has not been established for VIGIV.

8.5 Geriatric Use

Safety and effectiveness in the geriatric population (>65 yrs of age) has not been established for VIGIV.

8.6 Renal Insufficiency

Use VIGIV with caution in patients with pre-existing renal insufficiency and in patients at increased risk of developing renal insufficiency [see *5.8 Acute Renal Dysfunction/Failure*].

11 DESCRIPTION

VIGIV is a solvent/detergent-treated, filtered 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. The product is a clear to opalescent liquid.

VIGIV is manufactured from plasma collected from healthy, screened donors with high titers of anti-vaccinia antibody (meeting minimum potency specifications) that is purified by an anion-exchange column chromatography method (5, 6). 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.

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. A 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. The Source Plasma has also been tested by NAT for hepatitis A virus (HAV) and parvovirus B19 and the limit for B19 in the manufacturing pool is set not to exceed 10^4 IU of B19 DNA per mL.

The manufacturing process contains two steps implemented specifically for virus clearance. The solvent and detergent step (using tri-n-butyl phosphate and Triton X-100) is effective in the inactivation of enveloped viruses, such as HBV, HCV and HIV (7). Virus filtration, using a Planova 20N virus filter, is effective for the removal of viruses based on their size, including some non-enveloped viruses (8). In addition to the two specific steps, the anion-exchange chromatography step contributes to the removal of small non–lipid enveloped viruses.

The inactivation and reduction of known enveloped and non-enveloped model viruses were validated in laboratory studies as summarized in Table 2.

Table 2 Virus Reduction Values (Log_{10}) Obtained through Validation Studies

Enveloped	**Enveloped**				**Non-Enveloped**			
Genome	**RNA**		**DNA**		**RNA**		**DNA**	
Virus	**HIV-1**	**BVDV**	**PRV**	**Vaccinia**	**HAV**	**EMC**	**MMV**	**PPV**
Family	retro	flavi	herpes	pox	picorna		parvo	
Size (nm)	80–100	50–70	120–200	220–450 long x 140–260 wide	25–30	30	20–25	18–24
Anion Exchange Chromatography (partitioning)	Not evaluated				2.3	n.e.	3.4	n.e.
20N Filtration (size exclusion)	≥4.7	≥3.5	≥5.6[a]	n.e.	n.e.	4.8	n.e.	4.1
Solvent/Detergent (inactivation)	≥4.7	≥7.3	≥5.5	≥3.7	Not evaluated			
Total Reduction (log_{10})	**≥9.4**	**≥10.8**	**≥11.1**	**≥3.7**	**7.1**		**7.5**	

[a]The PRV was retained by the 0.1 μm pre-filter during the virus validation. Since manufacturing employs a 0.1 μm pre-filter before the 20N filter, the claim of ≥5.6 reduction is considered applicable.

Abbreviations:

HIV-1: human immunodeficiency virus-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

HAV: human hepatitis A virus; relevant virus for HAV and model for small non-enveloped viruses in general
EMC: encephalomyocarditis virus; model for HAV and for small non-enveloped viruses in general
MMV: murine minute virus; model for human parvovirus B19 and for small non-enveloped viruses in general
PPV: porcine parvovirus; model for human parvovirus B19 and for small non-enveloped viruses in general
n.e.: not evaluated

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 to 70 mg/mL total protein and ≥50,000 units of vaccinia antibody neutralizing activity. The product contains ≤40 mcg/mL of Immune globulin A (IgA).

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

VIGIV provides passive immunity for individuals with complications to vaccinia virus vaccination. The exact mechanism of action is not known.

12.2 Pharmacodynamics

Two phase 2, double-blind pharmacodynamic studies were conducted in which 82 healthy volunteers were randomized to receive vaccinia vaccination with or without VIGIV.

In the first study, the efficacy of 9,000 Units per kg of VIGIV on the immunologic and local response to Dryvax was evaluated. A total of 32 healthy subjects were randomized to receive single IV infusions of either VIGIV (9,000 Units per kg) or Placebo (0.9% Sodium Chloride Injection USP) on Day 0, and either Placebo or VIGIV (9,000 Units per kg) concurrently with vaccinia (Dryvax) vaccination on Day 4.

In a second study, 50 healthy subjects were randomized to receive a single IV infusion of either VIGIV (9,000 Units per kg), VIGIV (24,000 Units per kg), or Placebo (0.9% Sodium Chloride Injection USP) on Day 0, and either placebo or vaccinia (Dryvax) vaccination on Day 4.

The effect of VIGIV on the immunologic response to Dryvax was determined by measuring vaccinia antibody titer (vaccinia IgG) in plasma and comparing titer levels across all three treatment arms. In addition, the effect of VIGIV on the local response (tissue) to Dryvax was assessed by evaluating the size of the pox reaction, as well as the area of erythema and induration following vaccination.

VIGIV (9,000 Units per kg and 24,000 Units per kg) reduced the local and immunological response to vaccinia vaccination when it was administered 4 days prior to vaccination compared to vaccination alone. This is consistent with the hypothesis that VIGIV can neutralize vaccinia virus *in vivo* [see *14 CLINICAL STUDIES*]. In addition, infusions of VIGIV of up to 24,000 Units per kg were well tolerated [see *6.1 Clinical Trials Experience*].

12.3 Pharmacokinetics

A phase 1, double-blind study was conducted in which 60 healthy subjects were randomized to receive either 6,000 Units per kg or 9,000 Units per kg VIGIV. After intravenous administration of 6,000 Units per kg to 31 healthy subjects, a mean peak plasma concentration of 161 Units per 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 mL. Pharmacokinetic parameters were calculated based on antibody levels determined by an ELISA.

The levels of vaccinia immune globulin remained in circulation for a prolonged period of time, with a mean half-life ranging from approximately 26 to 30 days. Maximum plasma concentrations (C_{max}) of VIGIV reached levels ranging from approximately 160 to 232 Units per mL in 1.8 to 2.6 hours. In addition, the drug had a large volume of distribution, as demonstrated by both non-compartmental and compartmental analyses.

Non-compartmental analyses demonstrated that at the two dose levels studied, the drug exhibited dose-proportionality (AUC and C_{max} values) (Table 3). The pharmacokinetic parameters estimated by compartmental analysis were similar to those calculated by non-compartmental methods.

Table 3 Non-compartmental Pharmacokinetic Parameters (mean (±SD)) of Vaccinia Immune Globulin Intravenous (Human)

VIGIV (6,000 U/kg or 9,000 U/kg) from Measured Data Arithmetic Mean (±SD)		
Parameter	**6,000 U/kg**	**9,000 U/kg**
$AUC_{0-\infty}$ (U*h/mL)	58521 (16079)	78401 (17502)
AUC_{0-t} (U*h/mL)	49405 (13246)	71541 (13173)
C_{MAX} (U/mL)	161 (40.0)	232 (40.9)
T_{MAX} (h)	1.84 (1.12)	2.61 (2.41)
$T_{½}$ (days)	30.0 (10.0)	26.2 (5.08)

The plasma concentration of circulating VIGIV was also compared to a theoretical value obtained from a model of previously licensed Baxter Vaccinia Immune Globulin (VIG) product at day 5 after IV administration of VIGIV. Since Baxter VIG was administered IM and VIGIV is to be administered IV, the comparison was made at approximately five days to account for equilibration between the extravascular and intravascular compartments following IM injection.

The binding capacity and neutralizing antibody activity of anti-vaccinia antibody in these subjects five days after intravenous administration of VIGIV (both 6,000 Units per kg and 9,000 Units per kg dosages) were at least as high as the theoretical values that would be achieved following the intramuscular administration of the comparator VIG (see Table 4). 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 VIG.

Table 4 Test of Non-inferiority

Dose VIGIV (U/kg)	Plasma Levels, U/mL (Range[a])		Ratio of Means % (97.5% Lower Confidence Interval Bound)[d]
	VIGIV[b]	VIGIM[c]	
6,000	60.1 (36.1–84.6)	66.2 (42.3–94.9)	90.82 (86.94)
9,000	90.3 (63.4–133.8)	64.8 (47.6–87.2)	139.40 (135.27)

[a] Geometric mean (range)

[b] Observed levels

[c] Simulated levels

[d] Expressed as a percentage relative to the geometric mean of the simulated concentrations at Day 5 after 6,000 U/kg intramuscular administration

13 NONCLINICAL TOXICOLOGY

Immune globulins are normal constituents of the human body. Toxicology studies have not been performed with VIGIV as the product has been formulated with ingredients that are known to be non-toxic at the levels present in the final product.

13.2 Animal Toxicology and/or Pharmacology

The efficacy of VIGIV against vaccinia virus in a mouse-tail lesion model was assessed. A range of doses of VIGIV and a previously licensed VIG were compared for their ability to reduce pox formation in this model.

Using this model, it was demonstrated that VIGIV exerted an *in vivo* protective effect against vaccinia infection when compared to a negative control. In addition, when using the mouse-tail lesion model with two different strains of vaccinia virus, it was observed that the protective effect of VIGIV appeared similar to that of the previously licensed VIG and a CBER reference standard.

Since VIGIV is a product of human origin, secondary pharmacodynamics, safety pharmacology and pharmacodynamic drug interactions were not investigated in animals.

14 CLINICAL STUDIES

The pharmacokinetic, pharmacodynamic and safety profiles of VIGIV were evaluated in three clinical trials. In these clinical studies, VIGIV was shown to have an acceptable safety profile when administered as single infusions of 6,000 Units per kg, 9,000 Units per kg or 24,000 Units per kg to healthy subjects. For the phase 1 safety/pharmacokinetics study, see *12.3 Pharmacokinetics*.

14.1 Pharmacodynamic Effect of VIGIV on Immune and Local Responses to Dryvax

- In a phase 2, randomized, single center, double-blind study with three parallel treatment arms, the efficacy of 9,000 Units per kg of VIGIV on the immunologic and local

response to the smallpox vaccine Dryvax was evaluated. Thirty-two healthy female and male subjects were randomized to receive single IV infusions of either VIGIV (9,000 Units per kg) or Placebo (0.9% Sodium Chloride Injection USP) on Day 0, and either Placebo or VIGIV (9,000 Units per kg) concurrently with vaccinia (Dryvax) vaccination on Day 4.

In this study, the curves for antibody titre vs. time were similar between administration of VIGIV four days prior to vaccination with Dryvax and concurrent administration of VIGIV with Dryvax.

Based on area under the effective time curve from Day 4 to 32 ($AUEC_{4-32}$) results, the administration of VIGIV four days prior to vaccination with Dryvax slightly reduced the pox reaction and erythema area by 4 to 9% and 8 to 12%, respectively, as compared to the concurrent administration of VIGIV with the Dryvax vaccine, or with Dryvax alone.

- In an additional phase 2, randomized, single center, double-blind, study with five parallel treatment arms, the efficacy of two different doses of VIGIV (9,000 Units per kg and 24,000 Units per kg) on the immunologic and local response to Dryvax was evaluated.

  Fifty healthy subjects were randomized to receive a single IV infusion of either VIGIV (9,000 Units per kg), VIGIV (24,000 Units per kg), or Placebo (0.9% Sodium Chloride Injection USP) on Day 0, and either placebo or vaccinia (Dryvax) vaccination on Day 4.

  The administration of VIGIV four days prior to vaccinia vaccination decreased the endogenous immune response to Dryvax in a dose-dependent manner. In addition, the mean pox reaction and erythema area diameters were smaller in size when 24,000 Units per kg of VIGIV was administered prior to vaccination with Dryvax compared to those when 9,000 Units per kg of VIGIV was administered prior to vaccination with Dryvax or to those from administration of Dryvax alone. These data are consistent with the hypothesis of vaccinia virus neutralization *in vivo* by VIGIV.

15 REFERENCES

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16 HOW SUPPLIED/STORAGE AND HANDLING

16.1 How Supplied

NDC 60492-0173-1

The product is supplied as a 20 mL single dose vial containing ≥50,000 Units per vial. It is packaged in a shelf carton with 24 vials and a package insert.

VIGIV does not contain latex.

16.2 Storage and Handling

Product may be stored frozen at or below 5°F (≤-15°C) or refrigerated at 36 to 46°F (2 to 8°C); refer to label for appropriate storage conditions. Do not use after expiration date.

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

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

17 PATIENT COUNSELING INFORMATION

Discuss the risks and benefits of VIGIV with the patient before prescribing or administration.

- Inform patients of the potential for hypersensitivity reactions, especially in individuals with previous reactions to human immune globulin and in individuals deficient in IgA [see 4 *CONTRAINDICATIONS* and *5.1 Hypersensitivity*]. Advise patients to be aware of the following symptoms associated with allergic reactions: hives, rash, chest tightness, wheezing, shortness of breath, or feeling light headed or dizzy when they stand. Patients should be cautioned to seek medical attention immediately should they experience any one or more of the above mentioned symptoms, as well as other side effects including injection site pain, chills, fever, headache, nausea, vomiting, and joint pain.
- Advise patients that the maltose contained in VIGIV can interfere with some types of blood glucose monitoring systems. They must use only testing systems that are glucose-specific for monitoring blood glucose levels as the interference of maltose could result in falsely elevated glucose readings. This could lead to untreated hypoglycemia or

to inappropriate insulin administration, resulting in life-threatening hypoglycemia [see *5.2 Interference with Blood Glucose Testing*].

- Advise patients that VIGIV may impair the effectiveness of certain live virus vaccines such as measles, rubella (i.e. German measles), mumps, and varicella (i.e. chickenpox). Should the patient have been recently vaccinated, they should notify their treating physician [see *7.1 Live, Attenuated Vaccines*].
- Inform patients that VIGIV is prepared from human plasma. Products made from human plasma may contain infectious agents such as viruses that can cause disease. The risk that such products 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 during manufacturing. Despite these measures, such products can still potentially transmit disease. There is also the possibility that unknown infectious agents may be present in such products [see *5.9 Transmission of Infectious Agents from Human Plasma*].

Manufactured by:

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