

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use CNJ-016 (vaccinia immune globulin intravenous, human), VIGIV safely and effectively. See full prescribing information for VIGIV.

VIGIV (vaccinia immune globulin, human), 5% solution for intravenous use

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 VIGIV (vaccinia immune globulin intravenous, human) 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

| | |
|---|---------|
| DOSAGE AND ADMINISTRATION, Preparation (2.2) | 11/2018 |
| DOSAGE AND ADMINISTRATION, Administration (2.3) | 11/2018 |
| WARNINGS AND PRECAUTIONS, Thrombosis (5.4) | 11/2018 |
| WARNINGS AND PRECAUTIONS, Aseptic Meningitis Syndrome (5.6) | 11/2018 |

INDICATIONS AND USAGE

VIGIV is an Immune Globulin (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)

VIGIV is not indicated for postvaccinal encephalitis (1).

DOSAGE AND ADMINISTRATION

- For intravenous use only.
- VIGIV is administered at a dose of 6000 Units per kg, as soon as symptoms for complication(s) due to vaccinia vaccination appear (2.1).
- Higher doses (e.g. 9000 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 6000 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 $\geq 50,000$ 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)
- Acute renal dysfunction/failure (5.2)
- 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 (5.4).
- Hemolysis or hemolytic anemia (5.5)
- Aseptic meningitis syndrome (AMS) (5.6)
- Noncardiogenic pulmonary edema [Transfusion-Related Acute Lung Injury (TRALI)] (5.7)
- Transmission of infectious agents from human plasma (5.8)
- 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 (5.9)

ADVERSE REACTIONS

The adverse drug reactions to VIGIV treatment in clinical trials (>10%) include headache, nausea, rigors and dizziness. (6)

To report SUSPECTED ADVERSE REACTIONS, contact Emergent BioSolutions Canada Inc. 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 VIGIV may interfere with some serological tests (7.2)

See 17 for PATIENT COUNSELING INFORMATION

Revised: [11/2018]

FULL PRESCRIBING INFORMATION: CONTENTS*

BOXED WARNING

| | |
|-----|--|
| 1 | INDICATIONS AND USAGE |
| 2 | DOSAGE AND ADMINISTRATION |
| 2.1 | Dosage for Treatment of Severe Complications of Vaccinia Vaccination |
| 2.2 | Preparation |
| 2.3 | Administration |
| 3 | DOSAGE FORMS AND STRENGTHS |
| 4 | CONTRAINDICATIONS |
| 5 | WARNINGS AND PRECAUTIONS |
| 5.1 | Hypersensitivity |
| 5.2 | Acute Renal Dysfunction/Failure |
| 5.3 | Blood Glucose Monitoring |
| 5.4 | Thrombosis |
| 5.5 | Hemolysis |
| 5.6 | Aseptic Meningitis Syndrome (AMS) |
| 5.7 | Transfusion-related Acute Lung Injury (TRALI) |
| 5.8 | Transmissible Infectious Agents |
| 5.9 | Monitoring: Laboratory Tests |
| 6 | ADVERSE REACTIONS |
| 6.1 | Clinical Trials Experience |
| 6.2 | Post-marketing Experience |
| 7 | DRUG INTERACTIONS |
| 7.1 | Live, Attenuated Vaccines |
| 7.2 | Drug/Laboratory Interactions |

| | |
|------|---|
| 8 | USE IN SPECIFIC POPULATIONS |
| 8.1 | Pregnancy |
| 8.2 | Lactation |
| 8.4 | Pediatric Use |
| 8.5 | Geriatric Use |
| 11 | DESCRIPTION |
| 12 | CLINICAL PHARMACOLOGY |
| 12.1 | Mechanism of Action |
| 12.2 | Pharmacodynamics |
| 12.3 | Pharmacokinetics |
| 13 | NONCLINICAL TOXICOLOGY |
| 13.1 | Carcinogenesis, Mutagenesis, Impairment of Fertility |
| 13.2 | Animal Toxicology and/or Pharmacology |
| 14 | CLINICAL STUDIES |
| 14.1 | Pharmacodynamic Effect of VIGIV on Immune and Local Responses to Dryvax |
| 15 | REFERENCES |
| 16 | HOW SUPPLIED/STORAGE AND HANDLING |
| 16.1 | How Supplied |
| 16.2 | Storage and Handling |
| 17 | PATIENT COUNSELING INFORMATION |

*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 5.3 *Blood Glucose Monitoring*].

1 INDICATIONS AND USAGE

VIGIV (vaccinia immune globulin intravenous, human) 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.

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

Administer VIGIV at a dose of 6000 Units per kg, as soon as symptoms appear and are judged to be due to severe vaccinia-related complication. Consider repeat dosing, depending on the severity of the symptoms and response to treatment; however, clinical data on repeat doses are lacking. Consider higher doses (e.g. 9000 Units per kg) if the patient does not

respond to the initial 6000 Units per kg dose. Doses up to 24,000 Units per kg administered to healthy volunteers were well tolerated in clinical trials [see *14 CLINICAL STUDIES*].

2.2 Preparation

- Bring VIGIV vials to room temperature prior to dosing.
 - If frozen, thaw vial by placing in a refrigerator at 36 to 46°F (2 to 8°C) until the contents are thawed for approximately 14 hours. Product can be thawed rapidly by placing at room temperature for one hour followed by a water bath at 98.6°F (37°C) until thawed.
 - Do not thaw this product in a microwave oven.
 - Do not refreeze the vial.
- DO NOT SHAKE VIAL. SHAKING VIAL MAY CAUSE FOAMING.
- Remove the entire contents of the vial to obtain the labeled dosage of VIGIV. If partial vials are required for the dosage calculation, withdraw the entire contents of the vial to ensure accurate calculation of the dosage requirement.
- VIGIV 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, flush the line with 0.9% Sodium Chloride USP before use. VIGIV may be administered either undiluted or diluted no more than 1:2 (v/v).
- VIGIV vial is for single use only. Do not reuse or save VIGIV for future use.
- VIGIV contains no preservatives. Discard partially used vials.

2.3 Administration

- Inspect the product prior to use and do not use if solution is cloudy, discolored or contains particulates.
- Administer VIGIV intravenously through a dedicated intravenous line with the rate of infusion of no greater than 2 mL/min.
- 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).
- Adverse drug reactions may be related to the rate of infusion. 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.
- Closely monitor and carefully observe patients and their vital signs for any symptoms throughout the infusion period and immediately following an infusion.
- 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 5.4 *Thrombosis*].

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 $\geq 50,000$ Units per vial

4 CONTRAINDICATIONS

VIGIV is contraindicated in:

- *Isolated* vaccinia keratitis.
- Individuals with a history of anaphylaxis or prior severe systemic reaction associated with the parenteral administration of this or other human immune globulin preparations.
- 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 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.

5.3 Blood Glucose Monitoring

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.

5.4 Thrombosis

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. Ensure adequate hydration in patients before administration. Monitor for signs and symptoms of thrombosis and assess blood viscosity in patients at risk for hyperviscosity. 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.

5.5 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 (1). 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 (2), 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 ongoing hemolysis.

5.6 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 6000 Units per kg, a patient may be exposed to up to 0.18 g/kg protein after VIGIV administration.

5.7 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 one to six 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.

5.8 Transmissible Infectious Agents

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

All infections thought to have been possibly transmitted by this product should be reported by the physician or other health care provider to Emergent BioSolutions Canada Inc. at 1-800-768-2304.

5.9 Monitoring: Laboratory Tests

- Periodic monitoring of renal function and urine output is particularly important in patients judged to be at increased risk of developing acute renal failure. Assess renal function, including measurement of 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

The adverse drug reactions to VIGIV treatment in clinical trials (>10%) include headache, nausea, rigors and dizziness.

6.1 Clinical Trials Experience

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

In a safety/pharmacokinetics study, 60 healthy male and female volunteers received a single intravenous dose of either 6000 Units per kg or 9000 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 (9000 Units per kg) 4 days prior to vaccinia vaccination (n=10), or VIGIV (9000 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 9000 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 | VIGIV (%) | | | | PLACEBO ^a N=32 (%) |
|--|------------------------|--------------------------------|--------------------------------|--------------------------------|----------------------------------|----------------------------------|
| | | 6000 U/kg ^b N=31 | 9000 U/kg ^c N=39 | 9000 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) |
| | 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) |

| SYSTEM ORGAN CLASS | PREFERRED TERM | VIGIV (%) | | | | PLACEBO ^a N=32 (%) |
|---|--------------------|--------------------------------|--------------------------------|--------------------------------|----------------------------------|----------------------------------|
| | | 6000 U/kg ^b N=31 | 9000 U/kg ^c N=39 | 9000 U/kg ^d N=20 | 24,000 U/kg ^d N=20 | |
| 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 9000 Units per kg dosage group experienced syncope.

There was a lower incidence of adverse reactions when VIGIV (9000 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.

Severe vaccinia infection that developed possible intravascular hemolysis and transient renal injury has been reported. As VIGIV may contain blood group antigens that may have hemolysins, VIGIV doses may have contributed to the hemolysis. However, the hemolysis did not reoccur with continued VIGIV dosing. Mild and transient chest pain that occurred the same day of VIGIV infusion has been reported.

The following are adverse reactions listed by body system that have been identified and reported during the post-approval use of other IGIV products:

- *Cardiovascular*: Cardiac arrest, tachycardia
- *Hematologic and Lymphatic*: Neutropenia, leukopenia, anemia, lymphadenopathy
- *Integumentary*: Stevens-Johnson syndrome, epidermolysis, erythema multiforme, dermatitis (e.g., bullous dermatitis), urticaria or other skin reactions
- *Gastrointestinal*: Hepatic dysfunction, abdominal pain, diarrhea
- *Muscular*: Myalgia, arthralgia
- *Neurological*: Coma, loss of consciousness, seizures
- *Renal*: Acute kidney injury, osmotic nephropathy
- *Respiratory*: Apnea, Acute Respiratory Distress Syndrome (ARDS), cyanosis, hypoxemia, pulmonary edema, dyspnea, bronchospasm, wheezing
- *General/Body as a Whole*: Malaise, chest discomfort

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 use testing systems that are glucose-specific to test or monitor blood glucose levels in patients receiving VIGIV [see *BOXED WARNING* and *5.3 Blood Glucose Monitoring*].
- 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

Risk Summary

There are no data on the use of VIGIV in pregnant women to inform on drug-associated risk. Animal reproduction studies have not been conducted with VIGIV.

8.2 Lactation

Risk Summary

There are no data to assess the presence or absence of VIGIV in human milk, the effects on the breastfed child or the effects on milk production/excretion.

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.

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 (3, 4). 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 (5). Virus filtration, using a Planova 20N virus filter, is effective for the removal of viruses based on their size, including some non-enveloped viruses (6). 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 (Log₁₀) 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 (log₁₀) | ≥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 80 mg/mL total protein and $\geq 50,000$ 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 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 9000 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 (9000 Units per kg) or Placebo (0.9% Sodium Chloride Injection USP) on Day 0, and either Placebo or VIGIV (9000 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 (9000 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 (9000 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 double-blind study was conducted in which 60 healthy subjects were randomized to receive either 6000 Units per kg or 9000 Units per kg VIGIV. After intravenous administration of 6000 Units per kg to 31 healthy subjects, a mean peak plasma concentration of 161 Units per mL was achieved within two 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 (\pm SD)) of VIGIV

| VIGIV (6000 U/kg or 9000 U/kg) from Measured Data | | |
|--|------------------|------------------|
| Arithmetic Mean (\pmSD) | | |
| Parameter | 6000 U/kg | 9000 U/kg |
| AUC _{0-∞} (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 intramuscularly (IM) and VIGIV is 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 6000 Units per kg and 9000 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 | |
| 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) |

^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 6000 U/kg intramuscular administration

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenicity, genotoxicity and fertility studies have not been conducted with VIGIV.

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.

A single study in rabbits has demonstrated increased corneal scarring upon intramuscular vaccinia immune globulin administration in vaccinia keratitis (7).

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 6000 Units per kg, 9000 Units per kg or 24,000 Units per kg to healthy subjects. For the safety/pharmacokinetics study, see *12.3 Pharmacokinetics*.

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

In a randomized, single center, double-blind study with three parallel treatment arms, the efficacy of 9000 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 (9000 Units per kg) or Placebo (0.9% Sodium Chloride Injection USP) on Day 0, and either Placebo or VIGIV (9000 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 (AUEC₄₋₃₂) 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 randomized, single center, double-blind, study with five parallel treatment arms, the efficacy of two different doses of VIGIV (9000 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 (9000 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 9000 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

1. Kahwaji J et al., Acute Hemolysis after High-Dose Intravenous Immunoglobulin Therapy in Highly HLA Sensitized Patients. Clin J Am Soc Nephrol. 2009 December 4;1993-97.
2. Daw Z, Padmore R, Neurath D, et al. Hemolytic transfusion reactions after administration of intravenous immune (gamma) globulin: A case series analysis. Transfusion 2008;48:1598-601.
3. Bowman JM, Friesen AD, Pollock JM, Taylor WE. WinRho: Rh immune globulin prepared by ion exchange for intravenous use. Canadian Med Assoc J. 1980;123:1121-5.
4. Friesen AD, Bowman JM, Price HW. Column ion-exchange preparation and characterization of an Rh immune globulin (WinRho) for intravenous use. Journal Appl Biochem. 1981;3:164-75.

5. Horowitz B. Investigations into the application of tri(n-butyl)phosphate/detergent mixtures to blood derivatives. *Curr Stud Hematol Blood Transfus.* 1989;56:83-96.
6. Burnouf T. Value of virus filtration as method for improving the safety of plasma products. *Vox Sang.* 1996;70:235-6.
7. Fulginiti VA, Winograd LA, Jackson M, Ellis P. Therapy of experimental vaccinal keratitis: Effect of idoxuridine and VIG. *Arch Ophthal.* 1965;74:539-44.

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 $\geq 50,000$ Units per vial. It is packaged in a shelf carton with 24 vials and four package inserts.

VIGIV does not contain natural rubber latex.

16.2 Storage and Handling

Product may be stored frozen at or below 5°F ($\leq -15^{\circ}\text{C}$) 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. Begin intravenous infusion within 4 hours after entering the vial.

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

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. Caution patients 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. Patients must use testing systems that are glucose-specific for monitoring blood glucose levels as the interference of maltose could result in falsely elevated glucose readings, which could lead to untreated hypoglycemia

or to inappropriate insulin administration, resulting in life-threatening hypoglycemia [see *5.3 Blood Glucose Monitoring*].

- 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). Patients recently vaccinated must 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 *5.8 Transmissible Infectious Agents*].

Manufactured by:

Emergent BioSolutions Canada Inc.

155 Innovation Drive

Winnipeg, Manitoba

Canada, R3T 5Y3

U.S. License No. 2084