

****Obtain informed consent prior to VIGIV initiation****

**Expanded Access IND Protocol: Use of Vaccinia Immune Globulin
Intravenous (VIGIV, CNJ-016) for Treatment of Human Orthopoxvirus
Infection in Adults and Children**

BB-IND No. 10788

CDC IRB No. 3744

**Version 8.0
October 13, 2022**

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Centers for Disease Control and Prevention

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1.0 INTRODUCTION AND BACKGROUND

Orthopoxviruses (OPXVs) belonging to the *Poxviridae* family that infect humans are variola virus (smallpox), *vaccinia virus* (the virus in smallpox vaccine ACAM2000 and smallpox/monkeypox vaccine Jynneos), *monkeypox virus*, *cowpox virus*, *Akhmeta virus* and *Alaskapox virus*. Variola virus, the etiologic cause of smallpox, is the only one that affects humans exclusively, while the others are zoonotic infections that can also be transmitted person-to-person. Poxvirus infections may be localized to the skin or disseminated. The initial site of infection may be the skin, a mucosal surface, or the respiratory tract. Orthopoxviruses, such as monkeypox, can also cause serious clinical illness including, but not limited to encephalitis, severe inflammatory response syndrome, respiratory failure, painful head and neck lymph node swelling with or without associated airway and/or swallowing compromise, extensive dermal disruption during rash phase, and/or other septic syndromes.

With the eradication of smallpox in the late 1970s, the use of vaccinia vaccine was nearly eliminated. Certain U.S. military personnel and persons at occupational risk for exposure to orthopoxvirus infections are recommended to receive smallpox and/or monkeypox vaccine per Advisory Committee on Immunization Practices (ACIP).

<https://www.cdc.gov/vaccines/hcp/acip-recs/vacc-specific/smallpox.html>. Replication-competent vaccinia virus vaccine carries a risk for serious adverse events (e.g., progressive vaccinia and eczema vaccinatum), for which treatment with vaccinia immune globulin intravenous (VIGIV) and antivirals may be used. For more information, see <https://www.cdc.gov/smallpox/clinicians/vaccine-adverse-events5.html> and <https://www.cdc.gov/smallpox/clinicians/vaccine-medical-management6.html>.

Since May 2022, a global outbreak of monkeypox has been occurring involving approximately 90 countries. Currently, there are no Food and Drug Administration (FDA)–approved treatments for human monkeypox available. However, antivirals and other medical countermeasures developed for use in patients with smallpox may prove beneficial against monkeypox. Medical countermeasures available from the Strategic National Stockpile (SNS) as therapeutic options for the treatment of monkeypox include tecovirimat (TPOXX), VIGIV, and brincidofovir (anticipated availability in early November 2022). Data are not available on the effectiveness of VIGIV in treatment of monkeypox virus infection. However, VIGIV may potentially provide clinical benefit in some patients based on the existence of shared serologic cross-reactivity between the orthopoxviruses and the ability of neutralizing antibodies to one orthopoxvirus to partially neutralize the infectivity of other members of the genus orthopoxvirus. Genetic comparison of genome sequences of monkeypox virus (MPXV) in the current outbreak and vaccinia virus suggests immune responses induced by vaccinia virus-based vaccines remain highly cross-reactive against MPXV [1]. Use of VIGIV for treatment of orthopoxvirus infection, especially in severe manifestations of disease, including MPX, may be clinically necessary. Please refer to CDC’s clinical guidance for current recommendations on use of VIGIV: <https://www.cdc.gov/poxvirus/monkeypox/clinicians/clinical-guidance.html>.

1.1 Unmet Medical Need and Rationale for Use of VIGIV under Expanded Access IND

Currently, there is no treatment approved by the Food and Drug Administration (FDA) for non-variola orthopoxviruses (NV-OPXV), including MPX. Although vaccinia immune globulin intravenous (VIGIV, CNJ-016) is FDA-approved for vaccinia virus in adults and children, the approved indications are limited to the treatment and/or modification of the following complications due to replication-competent vaccinia vaccine:

- 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

Therefore, this intermediate-size patient population expanded access Investigational New Drug (IND), sponsored by CDC and authorized by FDA, is to allow access to and use of stockpiled VIGIV for post-exposure prophylaxis (PEP) or treatment of OPXV infection, including MPX in adults and children, and vaccinia vaccine complications not covered by its FDA-approved indications based on clinical judgment and individual risk-benefit assessment given the potential clinical benefit from the cross-reactive neutralizing antibodies of VIGIV. See **Section 2.1** VIGIV Eligibility.

While the effectiveness of VIGIV for PEP or treatment of human OPXV infection other than vaccinia infection has not been evaluated, it may be reasonable to anticipate potential treatment benefit based on the existence of shared serologic cross-reactivity between orthopoxviruses.

2.0 PROGRAM OBJECTIVES

The purpose of this expanded access IND (compassionate use) program is to provide stockpiled VIGIV for PEP or treatment of orthopoxvirus infections (e.g., monkeypox), including complications resulting from replication-competent vaccinia vaccination in adults and children not covered under its [FDA-approved indication](#) [2].

Under this EA-IND program, patients treated with VIGIV will be monitored, including for any occurrence of serious adverse events (SAE), clinical progress, and outcomes information are also intended to be collected to the extent feasible (e.g., baseline clinical conditions, progression/improvement post treatment, recovered or not recovered from OPXV infection). Please refer to **Section 8.0** Clinical Assessment and Monitoring of Patients.

2.1 VIGIV Eligibility

All patient populations, who meet eligibility criteria, can receive VIGIV under this IND program (e.g., children and all adults including pregnant and nursing individuals, and prisoners). Clinical considerations of VIGIV during an outbreak may evolve depending on the duration and nature of the outbreak and event-based information that may become available during the outbreak. For up-to-date interim clinical guidance for treatment of monkeypox during the current 2022 monkeypox outbreak, please refer to CDC's website at:

<https://www.cdc.gov/poxvirus/monkeypox/clinicians/treatment.html>

2.1.1 Treatment

VIGIV treatment may be administered to patients with laboratory confirmed orthopoxvirus infection or suspected infection based on known exposure(s) and/or clinical manifestations of disease. Patients with an initial negative OPXV test, but for whom both epidemiologic and

clinical evidence suggests OPXV disease (particularly if clinically worsening or severe disease manifestations), should be re-tested but be treated with VIGIV while results are pending.

VIGIV may be used if a patient is ineligible for antiviral treatment, including tecovirimat, after antiviral treatment has been exhausted, or in conjunction with antivirals and/or other therapies for severe manifestations of OPXV infection based on the treating physician's clinical judgment.

2.1.2 Post-exposure prophylaxis (PEP)

VIGIV may be considered for post-exposure prophylaxis on an **individual case-by-case basis** in consultation with CDC by contacting eocevent482@cdc.gov or after hours, CDC Emergency Operations Center (770) 488-7100 for the following:

- individuals with known high-risk exposure to a confirmed or probable case of OPXV infection (as defined on <https://www.cdc.gov/poxvirus>) and clinical conditions that necessitate an alternative or complementary option to PEP vaccination based on clinical judgment (e.g., severe allergic reaction to vaccine or vaccine components, immunocompromising conditions).
- prevention of serious complications in individuals with major contraindications to non-emergency vaccination who have been inadvertently vaccinated or inoculated with replication-competent vaccinia vaccine; or
- Use of VIGIV in neonates: VIGIV may be considered given lack of safety and effectiveness data for use of Jynneos and tecovirimat as PEP in neonates given potential concern of live attenuated vaccine of Jynneos and concern for ability to accurately dose oral tecovirimat in a neonate.

Additional considerations for use of VIGIV for treatment or PEP

- For OPXV infections:
VIGIV may be considered for persons who –
 - Have serious illness resulting from exposure to vaccinia virus or related OPXVs (e.g., development of ocular complications or severe generalized skin rash, or other serious illness manifestations that can be associated with a specific OPXV such as painful head and neck lymph node swelling with airway and/or swallowing compromise, encephalitis, sepsis syndrome that can be associated with MPX infection), that is suspected of being the result of continued virus proliferation and may therefore respond to the cross-reactive neutralizing antibodies of VIG.
 - Are at high risk for severe disease including persons with severe immunocompromise (e.g., HIV, AIDS, leukemia, lymphoma), pediatric populations particularly patients younger than 8 years of age, pregnant or breastfeeding people, and people with a condition affecting skin integrity as described on CDC's webpage:
<https://www.cdc.gov/poxvirus/monkeypox/clinicians/treatment.html>
- For replication-competent vaccinia vaccine complications:
VIGIV may be considered for persons who –
 - Have an immunosuppressive condition (e.g., HIV, AIDS, leukemia, hypogammaglobulinemia) or on immunosuppressive therapy identified within the 14-

- day period following replication-competent vaccinia vaccination before the expected appearance of vaccine-induced neutralizing antibodies. Vaccination sites in an immunosuppressed individual that do not appear to be progressing through normal healing stages (i.e., drying of lesion with beginning formation of scab) after day 14 should be evaluated as possible progressive vaccinia. If progressive vaccinia is suspected, these individuals should receive appropriate VIGIV treatment.
- Have serious skin-integrity compromising conditions (e.g., extensive burns) occur within the 10-day period following vaccination before the expected appearance of vaccination-induced neutralizing antibodies.
 - Have high-risk occupational exposures (e.g., eye splash or mucosal membrane exposure or high-dose exposure) to vaccinia virus or related OPXV that has a high likelihood of resulting in a serious clinical infection such as ocular infection or severe generalized skin rash, or other illness associated with the specific OPXV to which the laboratory or other worker was exposed.
 - Have serious clinical illness manifestations that are not covered by the FDA-approved indication (e.g., vaccinia keratitis, post-vaccinial encephalitis) following vaccination or exposure to vaccinia virus that is suspected of being the result of continued virus proliferation and would therefore be expected to respond to VIGIV treatment for viral neutralization in the estimation of the treating physician. For detailed information about medical management of smallpox vaccine (vaccinia) complications, please refer to: <https://www.cdc.gov/smallpox/clinicians/vaccine-medical-management6.html>.
 - Caution needs to be exercised 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 demonstrated increased corneal scarring upon VIGIM administration in vaccinia keratitis [3]. Individuals with vaccinia keratitis should not be excluded from treatment with VIGIV because of this condition if other serious vaccine complications or sight threatening manifestations of ocular vaccinia are present and the treating physician feels that the benefit of VIGIV treatment outweighs the potential risk of corneal scarring. Antiviral ophthalmic solutions are other treatments recommended in the treatment of ocular vaccinia and keratitis.
 - Postvaccinial encephalitis (PVE) is considered to be most often the result of an immune reaction following vaccination, similar to other post-infectious encephalitis and not usually secondary to proliferation of vaccinia virus in the Central Nervous System (CNS). VIGIV may be considered if an individual case of PVE, or serious neurologic manifestation due to a related orthopoxvirus infection, is believed to be a direct result of viral proliferation in the CNS.
 - Persons who have a positive serum or urine pregnancy test within the 10-day period following smallpox vaccination (replication-competent vaccinia virus vaccine) before the expected appearance of vaccination-induced neutralizing antibodies, where the possibility of viremia resulting in infection of the fetus is at its greatest. After 10 days, neutralizing antibodies would be expected to have appeared in response to vaccination in a pregnant primary or revaccinee with an otherwise normal immune system and additional VIGIV would not be expected to provide any additional theoretical benefit.

2.2 VIGIV Ineligibility

VIGIV should not be administered in the following individuals:

1. Persons with a history of anaphylactic or severe systemic reaction to human globulins or any ingredient contained in VIGIV.*
2. Persons with selective immunoglobulin A (IgA) deficiency. These individuals have the potential for developing antibodies to IgA and could have anaphylactic reactions to subsequent administration of blood products that contain IgA.*

*Note: The above precaution criteria are valid except in cases of patients with serious or imminently lethal vaccinia or other orthopoxvirus disease unresponsive to all other treatment. The treating physician may make a risk-benefit assessment and administer VIGIV if they determine that the potential benefits outweigh the risks and closely monitor and carefully observe patients and their vital signs before, during, and immediately after VIGIV infusion.

3.0 PROGRAM DESIGN AND PROCEDURE

If an individual requires VIGIV for PEP or treatment of orthopoxvirus infection or complications from vaccinia virus vaccination, the individual's treating physician will contact CDC's clinical consultations team (eocevent482@cdc.gov) or after hours, CDC's Emergency Operations Center (EOC) at 770-488-7100 to request product. The decision to release VIGIV from SNS for clinical use will be made by CDC once VIGIV therapy is determined to be clinically appropriate upon consultation with the requesting physician. The decision to administer VIGIV will be made solely by the requesting/treating physician and upon patient/guardian consent. Serology testing at CDC may be available on a case-by-case basis as determined during consultation with CDC.

For requests of VIGIV as PEP in laboratory and other workers following exposure to an orthopoxvirus, each case will be evaluated in terms of virus involved, route of exposure, and concentration of virus at time of exposure. VIGIV preventive therapy for laboratory and other workers with known high-risk exposures would be initiated in anticipation of the probable development of an orthopox-type infection or recombinant vaccinia-vectored virus infection of the skin epithelium or of the eye that may be expected to clinically manifest similar to eczema vaccinatum, progressive vaccinia, ocular vaccinia, generalized vaccinia, or other serious orthopoxvirus infection (e.g., monkeypox).

4.0 PRODUCT DESCRIPTION

4.1 VIGIV Composition

VIGIV contains human vaccinia virus immune globulin and inactive ingredients maltose and polysorbate 80. 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. The plasma donors were boosted with vaccinia vaccine prior to donating plasma used in the production of the product. Each plasma donation used for the manufacture of VIGIV is tested for the presence of hepatitis B virus (HBV) surface antigen (HBsAg) and antibodies to human immunodeficiency viruses (HIV) 1/2, and hepatitis C virus (HCV) using FDA-licensed serological tests.

In addition, mini-pool testing of plasma used in the manufacture of this product was tested by FDA licensed Nucleic Acid Testing (NAT) for HIV-1 and HCV and found to be negative. An investigational NAT for HBV was also performed on all Source Plasma used, and found to be negative; however, the significance of a negative result has not been established. 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 104 IU of B19 DNA per mL

4.2 VIGIV Formulation and Storage

VIGIV is supplied in a 20 mL single-dose vial containing $\geq 50,000$ Units (U) per vial of neutralizing vaccinia immune globulin antibodies. 20 mL refers to the vial size, not the fill volume, which varies by lot. Each VIGIV vial is filled to contain $\geq 50,000$ U regardless of fill volume. The exact volume or concentration (U/mL) is NOT indicated on the vial label itself. VIGIV does not contain natural rubber latex.

VIGIV may be stored frozen at or below 5°F ($\leq -15^{\circ}\text{C}$) or refrigerated at 36°F to 46°F (2°C to 8°C) until used. Do not use after the expiration date. If product is received frozen, use within 60 days of thawing at 36°F to 46°F (2°C –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, discard partially used vials.

5.0 DOSAGE AND ADMINISTRATION OF VIGIV

5.1 VIGIV Dose

- **For intravenous use only.**
- VIGIV dose is based on actual body weight: 6,000 U/kg is administered, as soon as symptoms appear and are judged to be due to orthopoxvirus or severe vaccinia virus vaccination complications. Initial higher dose (e.g., 9,000 U/kg) may be considered for patients with severe disease based on clinical judgment.
- Higher doses (e.g., 9,000 U/kg, 24,000 Units/kg) may be considered in the event that the patient does not respond to the initial 6,000 or 9,000 U/kg dose. In clinical trials, administration of higher doses of up to 24,000 U/kg was well tolerated and showed to be safe and to decrease the endogenous immune response to vaccinia vaccine along with a concomitant decrease in vaccination lesions.
- Consideration may be given to repeat dosing, depending on the severity of the symptoms and response to treatment based on clinical judgment of the treating physician in consultation with CDC.
- To request clinical consultation regarding redosing or dosing adjustments, contact the CDC on-call clinical consultations team at eoevent482@cdc.gov or after hours, CDC Emergency Operations Center (770) 488-7100.

Instructions on How to Calculate the Weight-Based VIGIV Dose by Units and Corresponding Volume for Dosing Preparation

VIGIV vial does not have fill volume printed on the vial label. The extractable volume of VIGIV vial varies per lot and ranges from about 8–12 mL. The vial size is 20 mL. **Please do not mistake the vial size as the volume of VIGIV liquid contained in the vial.** Regardless of fill volume, each vial contains $\geq 50,000$ U/vial. It is not necessary to calculate the concentration (U/mL) to determine the volume corresponding to the dose. The following describes the instructions for calculating the number of VIGIV vials needed to prepare a dose.

Calculate the Number of VIGIV vials Needed to Prepare a Dose*	Example
Obtain patient's weight (actual body weight)	45.5 kg
Select a dose (e.g., 6,000 U/kg, 9,000 U/kg)	6,000 U/kg
Multiple the weight and dose (U/kg) to get the total units (U) of VIGIV needed	$45.5 \text{ kg} \times 6,000 \text{ U/kg} = 273,000 \text{ U}$
Divide the total Units (U) of VIGIV needed for the dose by 50,000 (U/vial)	$273,000 \text{ U} \div 50,000 \text{ U/vial} = 5.5 \text{ vials}$
<p>For the number of whole vials: pool the entire volume of the vials. Then add the volume needed for the partial vial if needed (described below).</p> <p>For a partial vial, if needed: If a partial vial is needed: extract the entire contents of the vial to measure the total volume (mL) contained in the vial. Use the measured volume (mL) of the vial to calculate the amount (mL) from the vial needed</p>	<p>Using the above example of VIGIV dose that requires 5.5 vials, see below:</p> <p>A. Extract the entire volume of 5 vials. Add the volume needed for the 6th vial (steps below).</p> <p>For volume needed from the 6th vial:</p> <p>B. Extract the entire contents of the 6th vial and measure it (example: 10 mL).</p> <p>C. Multiply the portion of the vial needed by the measured volume: $0.5 \text{ vial} \times 10 \text{ mL/vial} = 5 \text{ mL}$</p> <p>D. The total volume of the VIGIV dose (5.5 vials) = Contents of 5 vials (A) + 5 mL (C).</p>

* The volume of a vial only needs to be measured if the dose involves a partial vial.

5.2 Preparation of VIGIV

- Bring VIGIV vials to room temperature prior to preparing the dose.
- If frozen, thaw vial by placing in a refrigerator at 36°F to 46°F (2°C to 8°C) until the contents are thawed completely (may take approximately 14 hours). Frozen VIGIV vials may 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 refreeze the vial.
- DO NOT SHAKE VIAL. SHAKING VIAL MAY CAUSE FOAMING.
- 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.

5.3 Administration of VIGIV

- Inspect the VIGIV vial 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/minute.
- For patients weighing less than 50 kg, infuse the product at a rate no greater than 0.04 mL/kg/minute (133.3 U/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. For instance,
 - VIGIV administration should be initiated at an infusion rate of 0.01-0.02 mL/kg/minute for the first 30 minutes then increased by 0.01-0.02 mL/kg/minute from the initial infusion rate for the next 30 minutes. The remaining infusion may be administered at an infusion rate of 2 mL/minute.
- Closely monitor and carefully observe patients and their vital signs before, during, and immediately after VIGIV infusion:
 - For instance, monitor vital signs before infusion, then every 30 minutes during infusion and 1 hour following completion of 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.

Appropriate equipment, oxygen, medication (including epinephrine, diphenhydramine, and corticosteroids) and personnel trained in the management of infusion or hypersensitivity reaction must be available.

VIGIV infusion stopping rules:

- If hypotension, anaphylaxis, or severe allergic reaction (e.g., angioneurotic edema or respiratory distress) occurs, discontinue the infusion of VIGIV immediately and administer epinephrine (1:1000) as needed. Administer corticosteroids, diphenhydramine, assist respiration, and provide other resuscitative measures as appropriate. If hypotension occurs, stop the infusion of VIGIV, and stabilize blood pressure with pressors, if necessary.
- If mild or moderate non-anaphylactoid reactions (e.g., headache, chills, nausea), closely observe patient. If the reaction is causing substantial discomfort, but is not otherwise serious, the rate of infusion can be reduced by half and the patient monitored closely. If the reaction worsens or the patient develops additional symptoms, the infusion should be further reduced or discontinued if the patient is experiencing a serious reaction to VIGIV.

Discontinuation of VIGIV:

At any time during VIGIV treatment, a patient may voluntarily discontinue or refuse VIGIV for any reason, or treatment may be stopped or paused due to serious adverse events (SAEs), clinically significant abnormalities in laboratory values, or per the clinical judgment of the treating clinician and/or appropriate health authority.

Drug-Drug Interactions:

- Efficacy of live attenuated virus vaccines (e.g., measles, rubella, mumps, and varicella) may be impaired by immune globulin administration; revaccination may be necessary. Vaccination with live virus vaccines should be deferred until approximately three months after administration of VIGIV. People who received VIGIV shortly after live virus vaccination should be revaccinated 3 months after the administration of the immune globulin.

- Admixtures or VIGIV with other drugs have not been evaluated. It is recommended that VIGIV be administered separately from other drugs or medications that the patient may be receiving. If a pre-existing catheter must be used, the line should be flushed with 0.9% Sodium Chloride USP and not with other solutions such as dextrose in water.

Laboratory Test 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 that can lead to untreated hypoglycemia or inappropriate insulin administration, only testing systems that are glucose-specific should be used to test or monitor blood glucose levels in patients receiving VIGIV.
- 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).

6.0 POSSIBLE RISKS OF VIGIV TREATMENT

6.1 Adverse Reactions

The adverse drug reactions to VIGIV treatment in clinical trials (>10%) include headache, nausea, rigors and dizziness. Other adverse events associated with infusion of immunoglobulins include hypotension, pallor, diarrhea, joint pain, dizziness, hyperkinesia, drowsiness, pruritis, rash, renal dysfunction, perspiration, and vasodilation.

Although there were no serious adverse drug reactions reported following administration of VIGIV in clinical trials, there has been a post-marketing case of severe vaccinia infection that developed intravascular hemolysis, leucopenia and thrombocytopenia during VIGIV treatment.

6.2 Contraindications

VIGIV should not be administered in individuals with a history of anaphylaxis or prior severe systemic reaction associated with the parenteral administration of this or other human immune globulins or any ingredient contained in VIGIV. VIGIV contains trace amounts of IgA. While VIGIV contains less than 40 µg/mL of IgA, persons with selective IgA deficiency can develop antibodies to IgA and therefore could have anaphylactic reactions to subsequent administration of blood products that contain IgA, including VIGIV. See **Section 2.2** VIGIV Ineligibility for exceptions.

6.3 Warnings and Precautions

Isolated vaccinia keratitis

While VIGIV should be considered in treatment of severe ocular complication due to vaccinia virus, it is contraindicated for use in the presence of isolated vaccinia keratitis per FDA labeling [2]. However, patients having other complications due to vaccinia vaccination that include vaccinia keratitis, may still be treated with VIGIV in addition to trifluridine, and ophthalmologic consultation.

Hypersensitivity to human immune globulin (acute anaphylaxis)

Anaphylactic reactions to injections of immune globulin products such as VIGIV are rare. The symptoms of classic anaphylactic reactions are: flushing, facial swelling, dyspnea, cyanosis,

anxiety, nausea, vomiting, malaise, hypotension, loss of consciousness, and in some cases, death. They appear within seconds to several hours after infusion.

Although acute systemic allergic reactions were not seen in clinical trials with VIGIV, 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.

During administration of VIGIV, vital signs should be monitored closely, and careful observation made for any symptoms throughout the infusion. Epinephrine and other standard drugs (e.g., antihistamines, intravenous steroids) and devices should be available for the treatment of an acute anaphylactic reaction. Clinical anaphylaxis may occur even when the patient is not known to be sensitized to IG products. A reaction may be related to the rate of infusion; therefore, careful adherence to the infusion rates as outlined is important. If anaphylaxis or drop in blood pressure occurs, discontinue infusion and treat appropriately.

Infusion-related reactions

Non-anaphylactic reactions are the most common type of reaction to immune globulin injections. These reactions include back or abdominal pain, nausea, and vomiting within the first 10 minutes of injection. Usually there is no dyspnea or other change in vital signs. Chills, fever, headache, myalgia, and fatigue may begin at the end of infusion and continue for several hours. More severe reactions of this type may require pretreatment with corticosteroids or acetaminophen.

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.

Blood Glucose Monitoring

Per black boxed warning, some types of blood glucose testing systems (for example those based on the glucose dehydrogenase pyrroloquinoline quinone (GDH-PQQ) or glucose-dye-oxidoreductase methods) could falsely interpret the maltose contained in VIGIV as glucose. 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. 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.

Thrombosis

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

Aseptic Meningitis Syndrome (AMS)

AMS has been reported to occur infrequently in association with IGIV treatment. AMS usually begins within several hours to 2 days following IGIV treatment, and is characterized by a range of signs and symptoms including severe headache, nuchal rigidity, drowsiness, fever, photophobia, painful eye movements, nausea, and vomiting. In these patients, a thorough neurological examination, including cerebrospinal fluid (CSF) studies, should be done to rule out other causes of meningitis. CSF studies frequently show a pleocytosis of several thousand cells per cu mm, predominantly granulocytes, and elevated protein levels up to several hundred mg/dL. AMS may occur more frequently in association with high dose (2 g/kg) IGIV treatment. Discontinuation of IGIV treatment has resulted in remission of AMS within several days without sequelae.

Hemolysis or Hemolytic Anemia

IGIV products can 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. Hemolytic anemia can develop subsequent to IGIV therapy due to enhanced red blood cell sequestration and acute hemolysis, consistent with intravascular hemolysis, has been reported.

Transfusion-related Acute Lung Injury (TRALI)/Noncardiogenic pulmonary edema

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.

Transmissible Infectious Agents from Human Plasma

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

7.0 SPECIAL POPULATIONS

7.1 Pregnancy

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 person 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. The risk/benefit of VIGIV administration should be assessed for each individual case.

7.2 Lactation

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 person who is nursing.

7.3 Pediatric and Geriatric Populations

Safety and effectiveness in the pediatric population (< 16 years of age) and geriatric population (>65 years of age) has not been established for VIGIV.

7.4 Patients with Renal Insufficiency

Use VIGIV with caution in patients with pre-existing renal insufficiency and in patients at increased risk of developing renal insufficiency. 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.

8.0 CLINICAL ASSESSMENT AND MONITORING OF PATIENTS

Upon presentation, the patient should be thoroughly assessed per clinician's judgement to determine if VIGIV treatment is appropriate. This may include a medical history, review of concomitant medications, clinical laboratory testing (e.g., hematology, chemistry, liver function tests, urinalysis, pregnancy), determination of immunocompromise (e.g., through evaluation of CD4 count and HIV viral load as well as awareness of other immunocompromising conditions), and a physical examination with vital signs (e.g., weight, blood pressure, pulse, respiratory rate, temperature, and height).

Patients should be monitored for clinical response and any occurrence of adverse events after VIGIV administration through discharge. For patients who receive VIGIV for PEP, monitor through 3 weeks after VIGIV administration. For patients pregnant at the time of VIGIV administration, follow-up if feasible within 1 month of pregnancy outcome (defined as full-term or premature delivery of live or non-viable infant, or spontaneous abortion). Follow-up will be conducted by phone, telemedicine visits, or in person to assess for any serious adverse events, medically attended adverse events and adverse events of special interest (e.g. symptoms consistent with vaccinia vaccine complications or orthopoxvirus infections, including monkeypox). The patient will be advised to report any suspected adverse reactions to their treating physician for reporting to CDC.

Treating clinicians or their designees will be responsible for patient assessment, monitoring, and reporting information to CDC. The following report forms are required to be completed, retained, and/or returned to CDC:

- Obtain Informed Consent (**Attachment 2**) – prior to VIGIV administration; provide a copy to the patient and retain a copy at the treating facility/institution. A copy does NOT need to be returned to CDC. Only if the signed informed consent forms cannot be maintained at the treating facility/institution, then they can be sent to CDC within 7 calendar days of VIGIV administration.
- Complete Form FDA 1572 and return to CDC prior to VIGIV administration to the extent feasible but no later than within 7 calendar days of VIGIV administration.
- Patient Intake Form (**Attachment 3 – Form A**). Please return to CDC within 7 calendar days of VIGIV administration. The required fields on the form are noted with an asterisk (*). The relevant information at the time of VIGIV treatment include:
 - Medical history, baseline signs/symptoms, vital signs, concomitant medications
 - For clinical laboratory parameters tested, attach a copy of the results (e.g., hematology, chemistry, renal and liver function tests, urinalysis).
- Clinical Outcome Form (**Attachment 3 – Form B**). Complete upon discharge. For patients who receive VIGIV for PEP, complete 3 weeks after VIGIV administration.

Return the completed Clinical Outcome Form to CDC within 7 calendar days of last patient follow-up. The relevant information includes:

- Progress of VIGIV therapy and clinical outcomes, clinical labs, and lesion/scab and serum samples (if collected).
- If any serious or life-threatening AEs and/or medication errors occur, report to CDC by completing the Serious Adverse Event/Medication Error Form (**Attachment 3 – Form C**) and returning to CDC via email (regaffairs@cdc.gov). SAEs must be reported within 72 hours of awareness or sooner if possible. All SAEs, whether or not the treating clinician considers the event to be drug-related, must be reported.
 - SAE defined as death, life-threatening AE, inpatient hospitalization or prolongation of existing hospitalization, persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions; congenital anomaly/birth defect; an important medical event that based on appropriate medical judgement may jeopardize the patient and may require medical or surgical intervention to prevent one of the aforementioned outcomes.
- Pregnancy Outcome Form (**Attachment 3 – Form D**). Report outcome of pregnancy within 1 month of outcome for individuals pregnant at the time of VIGIV treatment.

Methods of returning the above information

- Please return completed forms to CDC via encrypted email (regaffairs@cdc.gov) or uploading to secure [ShareFile](#) (enter your name and email address before uploading; please zip multiple files and use filenames with patient identifier [e.g., name, initials], patient age, hospital/facility name, state, date/time of VIGIV infusion, and file contents [e.g., 1572, CV, Patient Intake Form]). Personally identifiable information should not be emailed without encryption.

Considerations for Clinical Laboratory Monitoring:

- Monitor hematology, chemistry, urinalysis, renal and hepatic function before and after administration of VIGIV as appropriate based on clinical judgment of the treating physician. 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.

Table 1 Summary of Clinical Assessment and Monitoring Parameters

Days	Pre-VIGIV Treatment	Post Completion VIGIV Treatment
	Prior to VIGIV Treatment	Upon discharge or for patients who receive VIGIV for PEP, 3 weeks after last dose of VIGIV

Parameters*	Patient Intake Form (Attachment 3-A)	Clinical Outcome Form (Attachment 3-B)
Signed Informed Consent	X	N/A
Inclusion/Exclusion Criteria	X	N/A
Baseline clinical assessment	X	N/A
Hematology, chemistry, urinalysis, renal and liver function tests	X	Monitor based on clinical judgment of treating physician
Clinical progress	N/A	Report clinical outcomes following VIGIV therapy (Attachment 3-B)
Serious Adverse Events/Medication Errors*	N/A	Report if SAEs or medication errors occur (Attachment 3-C)
Pregnancy outcome, if applicable	N/A	Report pregnancy outcome within 1 month of pregnancy outcome (Attachment 3-D)
Lesion samples	Optional	Optional (for any new lesions post-treatment)

* Additional information regarding patient monitoring:

- SAEs must be reported by emailing a completed Serious Adverse Event/Medication Error Form (Attachment 3-C) to CDC (regaffairs@cdc.gov) within 72 hours of awareness or sooner if possible.
- Serology testing at CDC may be available on a case-by-case basis as determined during consultation with CDC.

For patients pregnant at the time of VIGIV administration, the Pregnancy Outcome Form is to be completed within 1 month of pregnancy outcome (defined as full-term or premature delivery of live or non-viable infant, or spontaneous abortion)

Inadvertent Vaccination or Inoculation of Individuals with Major Contraindications to Replication-Competent Vaccinia Virus Vaccine.

In the cases of patients who receive VIGIV due to inadvertent vaccination or inoculation with replication-competent vaccinia virus vaccine, the treating physicians should be advised to immediately report any of the following during their observation periods for vaccine-related adverse events:

- Development of rash before primary vaccine site has completely healed (scab has separated with healed skin underneath)
- Failure of primary vaccine site to heal or development of other similar lesions on other areas of body
- For pregnancy, development of any of the following complications during the pregnancy
 - Spontaneous abortion or intrauterine fetal death
 - Pre-term delivery
 - Low birth weight infant
 - Infant death occurring in the perinatal period
 - Congenital malformations
 - Delivery of an infant with evidence of intrauterine vaccinia infection manifested by the presence of vaccinal type skin lesions or scarring (Fetal Vaccinia)

9.0 ALTERNATIVES TO VIGIV

At this time, no FDA-approved therapy is available to treat non-variola OPXV infections. Furthermore, there are no proven alternatives to VIGIV for PEP of serious complications in laboratory and other workers with high-risk accidental exposures to vaccinia virus, treating and preventing serious complications from the infection, or preventing serious complications in individuals with major contraindications to non-emergency vaccination who have been

inadvertently vaccinated or inoculated with replication-competent vaccinia vaccine. Refer to CDC's website for additional information:

<https://www.cdc.gov/poxvirus/monkeypox/clinicians/treatment.html> and <https://www.cdc.gov/smallpox/prevention-treatment/index.html>.

Tecovirimat (TPOXX)

Tecovirimat is available under a separate CDC-sponsored [EA-IND protocol](#) (IND 116,039, CDC IRB #6402). Tecovirimat is an FDA-approved antiviral drug; however, this proposed use is investigational and has not been studied in humans; therefore, the benefit of tecovirimat therapy in vaccinia-vaccine related complications is uncertain. The efficacy of tecovirimat for the treatment of other related OPXV infections is also unknown. VIGIV is considered the primary treatment for replication-competent vaccinia vaccine (e.g., ACAM2000) related complications. However, tecovirimat may be considered as a possible secondary treatment for complications from vaccinia vaccination in individuals who are non-responsive to VIGIV therapy and who are seriously ill from vaccinia vaccine-related adverse events (e.g., clinical progression with possibility of death or permanent impairment such as loss of sight). Tecovirimat should only be used for the treatment of vaccinia-related complications if VIGIV treatment is unavailable (i.e., supplies are exhausted) or in conjunction with VIGIV or other therapies based on the treating physician's clinical judgment.

Cidofovir (VISTIDE®)

Cidofovir is an FDA-approved antiviral drug; however, its use for orthopoxvirus infection is investigational and has not been studied in humans; therefore, the benefit of cidofovir therapy in vaccinia-vaccine related complications is uncertain. The efficacy of cidofovir for the treatment of non-vaccinia orthopoxvirus infections is also unknown. VIGIV is considered the primary treatment for vaccinia-vaccine related complications. However, cidofovir may be considered as a possible secondary treatment for complications from vaccinia vaccination in individuals who are non-responsive to VIGIV therapy and who are seriously ill from vaccinia vaccine-related adverse events (e.g., clinical progression with possibility of death or permanent impairment such as loss of sight). Cidofovir should only be used for the treatment of vaccinia-related complications if VIGIV treatment is unavailable (i.e., supplies are exhausted) or in conjunction with VIGIV or other therapies based on the treating physician's clinical judgment.

Cidofovir is commercially available and can be used under practice of medicine for treatment of orthopoxvirus infection by treating clinicians. Use of stockpiled cidofovir for the treatment of orthopoxvirus infection and vaccinia-vaccine related complications is under a separate EA-IND protocol (IND 63,488).

Brincidofovir (Tembexa; anticipated availability from the SNS in early November 2022)

Brincidofovir, a prodrug of cidofovir, is FDA-approved for the treatment of human smallpox disease in adult and pediatric patients, including neonates. Data are not available on the effectiveness of brincidofovir in treatment of cases of monkeypox virus infection in people. However, it has shown to be effective against orthopoxviruses in *in vitro* and animal studies. Brincidofovir should not be used simultaneously with cidofovir.

For additional alternative therapies, please see: <https://www.cdc.gov/smallpox/prevention-treatment/index.html>

10.0 RECORDING AND REPORTING SERIOUS ADVERSE EVENTS

10.1 Definitions (21 CFR 312.32)

An **ADVERSE EVENT** (AE) is any untoward medical occurrence associated with the use of VIGIV in humans, whether or not considered related to VIGIV. It can be any unfavorable and unintended sign (e.g., an abnormal laboratory finding), symptom, or disease temporally associated with the use of VIGIV, without any judgment about causality.

A **SUSPECTED ADVERSE REACTION** is any AE for which there is a reasonable possibility that VIGIV caused the AE. It is a subset of all AEs for which there is a reasonable possibility that VIGIV caused the event. “Reasonable possibility” means there is evidence to suggest a causal relationship between VIGIV and the AE. “Suspected adverse reaction” implies a lesser degree of certainty about causality than “adverse reaction.”

An **ADVERSE REACTION** is any AE caused by VIGIV. Adverse reactions are a subset of all suspected adverse reactions for which there is a reason to conclude that VIGIV caused the event.

SERIOUS: An AE or suspected adverse reaction is considered “serious” if in the view of either the treating clinician or CDC, it results in any of the following outcomes:

- Death
- a life-threatening AE
- inpatient hospitalization or prolongation of existing hospitalization
- a persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions
- a congenital anomaly/birth defect

NOTE: Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered serious when, based upon appropriate medical judgment, they may jeopardize the patient and may require medical or surgical intervention to prevent one of the outcomes previously listed.

LIFE-THREATENING: An AE or suspected adverse reaction is considered “life-threatening” if, in the view of either the treating clinician or CDC, its occurrence places the patient at immediate risk of death. It does not include an AE or suspected adverse reaction that, had it occurred in a more severe form, might have caused a death.

10.2 Treating Clinician Reporting Requirements to CDC

All SAEs must be reported. These include all SAEs that the patient reports spontaneously, those the clinician observes, and those the clinician elicits in response to open-ended questions. All SAEs, whether or not the treating clinician considers the event to be drug-related, must be reported by emailing a completed Serious Adverse Event/Medication Error Form (**Attachment 3-C**) to CDC (regaffairs@cdc.gov) within 72 hours of awareness or sooner if possible.

10.3 CDC Reporting Requirements to FDA and CDC Institutional Review Board (IRB)

CDC will review all SAEs and report serious, unexpected suspected adverse reactions to FDA within 15 calendar days of initial receipt or after determining that the information qualifies for reporting under 21 CFR 312.32I(1).

In cases of unexpected suspected adverse reactions that are fatal or life-threatening (serious), CDC will report to FDA as soon as possible, but no later than 7 calendar days after initial receipt of the information (21 CFR 312.32(c)(2)).

All three (3) of the definitions contained in the requirement must be met for expedited reporting to FDA:

1. Serious,
2. Unexpected, and
3. Suspected Adverse Reaction.

CDC will report all serious and unexpected suspected adverse reactions and incidents to CDC IRB according to CDC IRB's policy and procedures.

AEs that are voluntarily reported by providers to CDC that do not meet the requirements for expedited reporting to FDA will be submitted under the IND in Annual Reports.

11.0 REGULATORY AND ADMINISTRATIVE REQUIREMENTS

CDC, the sponsor of the IND, and all licensed healthcare providers who request and receive VIGIV under this IND protocol will abide by the Code of Federal Regulations (in particular, 21 CFR Parts 50, 56, and 312). The IND protocol is subject to FDA's review and authorization as well as review and approval by an Institutional Review Board (IRB). CDC IRB serves as the central IRB for review and approval of this VIGIV IND protocol, and has determined it non-research (i.e., does not constitute human subjects research per 45 CFR 46.102(l)). Therefore, participating sites may use CDC IRB's approval of this protocol that meets FDA's requirements regarding IRB review per 21 CFR Parts 50 and 56.

Any change or modification to the IND protocol that affects purpose, procedures, or significant data or administrative aspects of the program will require a formal amendment. Such amendments will be submitted to FDA for review and approved by the CDC IRB prior to implementation. Revised IND protocol and/or procedural modifications will be communicated by CDC to the clinicians and medical facilities participating in the VIGIV treatment.

Data Management and Handling:

IND case report forms (**Attachment 3**), laboratory results, visit summaries, hospital discharge summaries, medical records, etc., may be used as source documents. The information obtained through the case report forms of this IND protocol and additional supplemental information provided by treating clinicians to CDC will be maintained by the CDC. Any analysis of data contents will be conducted without individual identifiers. The information gathered under this expanded access IND program and any analysis generated will be reported to the FDA as part of the annual report for this IND. Data from case report forms and other related information collected under this IND may also be provided to Emergent BioSolutions Canada, Inc and the Department of Health and Human Services/Biomedical Advanced Research and Development Authority (HHS/BARDA). Information about specific treating clinicians (i.e., names, CVs, or Form FDA 1572) and/or hospitals/sites may be shared with FDA, and local public health jurisdictions, and the manufacturer. Any information pertaining to treating clinicians and/or participating sites that are provided to the manufacturer is limited to use in the manufacturer's discussions with health authorities concerning this CDC-sponsored IND program.

Informed Consent:

Informed consent in compliance with 21 CFR 50 must be obtained via the enclosed informed consent/permission form (**Attachment 2**) from the patient, including adolescents, deemed as mature or emancipated minors by state and/or local law who can consent for themselves, before VIGIV is administered. If the patient is unable to give consent, consent can be obtained from a legally authorized representative (LAR).

A single consent form (**Attachment 2**) will be used to obtain informed consent/parental permission. Waiver of assent for children (7–11 years of age) under 21 CFR 50.55(c)(1) and for children (12–17 years of age) under 21 CFR 50.55(c)(2) was approved by the CDC IRB for all patients under this IND program. Parental permission will be sought in accordance with 21 CFR 50.55 for children aged 12–17 years (permission of only one parent is required) with exceptions for adolescents, deemed as mature or emancipated minors by state and/or local law who can consent for themselves for medical care. The ultimate responsibility for decision-making regarding treatment with VIGIV in minors should lie with the parent or guardian, or by the adolescents, deemed as mature or emancipated minors by state and/or local law who can consent for themselves for medical care.

For patients with limited English proficiency, if a version of the informed consent form is not available in the patient's (LAR's) language, the form must be translated orally by a certified interpreter. If a certified interpreter is not available, another adult who is fluent in both English and the language needed may interpret, provided the patient (parent/LAR) is comfortable sharing medical information (i.e., the reason treatment is being offered) with that person. If a facility wishes to create a written translation of the informed consent form, the CDC IRB-approved informed consent form must be translated by a certified translator and the translation must be submitted to and approved by the CDC IRB prior to use. A short form for obtaining informed consent from patients with limited English proficiency, along with a written summary of the information in the informed consent form for use with the short form will be available online on CDC's website. The same requirements for interpretation or translation additionally apply to the short form.

In the situation that a patient is unable to respond and make wishes known about VIGIV treatment, no next-of-kin or legal representative is available, and the patient's illness is life-threatening, obtaining informed consent may be deemed not feasible per 21 CFR 50.23 "Exception from general requirements." In such situations that necessitate VIGIV treatment, the patient's treating clinician and a clinician who is not otherwise participating in this expanded access IND program will document the clinical determination on the last page of the informed consent form (**Attachment 2**). The information in the consent form should be provided to the patient or LAR at the first available opportunity. Notify CDC via email (regaffairs@cdc.gov) within 3 working days of VIGIV initiation when the treatment determination was made based on the mentioned certification by the treating and an independent clinician.

12.0 SUMMARY OF AVAILABE SAFETY AND EFFICACY DATA OF VIGIV

12.1 Human Safety Data of VIGIV

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. The safety of VIGIV has not been studied in patients with smallpox or non-vaccinia orthopoxvirus disease.

Clinical Trials

In the following three clinical trials, the most frequently reported adverse reactions related to VIGIV administration in all three clinical studies were headache, nausea, rigors, and dizziness:

- (1) safety/pharmacokinetics study: 60 healthy volunteers received a single intravenous dose of either 6000 U/kg or 9000 U/kg VIGIV;
- (2) pharmacodynamic study: 32 healthy male and female volunteers were randomized to receive vaccinia vaccination (n=10), VIGIV (9000 U/kg) 4 days prior to vaccinia vaccination (n=10), or VIGIV (9000 U/kg) concurrent with vaccinia vaccination (n=12); and
- (3) pharmacodynamic study, 50 healthy volunteers received VIGIV at 9000 U/kg (n=20) or at 24,000 U/kg (n=20) or placebo (n=10) 4 days prior to vaccinia vaccination (n=30) or placebo (n=20).

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.

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

12.2 Human Effects Data

Eighty-two healthy volunteers were randomized to receive vaccinia vaccination with or without VIGIV in the following two double-blind pharmacodynamic studies: 1) A pilot phase 1 double-blind pharmacodynamic study was conducted in which 32 healthy volunteers were randomized to receive single IV infusion of either VIGIV (9000 U/kg) or placebo (0.9% Sodium Chloride Injection USP) on Day 0, and either placebo or vaccinia (Dryvax[®]), and either placebo or VIGIV (9000 U/kg) concurrently with vaccinia (Dryvax[®]) vaccination on Day 4. The objectives of the study were to assess the effects of VIGIV upon the local and immunological response to vaccinia vaccination and to further characterize the safety of VIGIV. The curves for antibody titer vs. time were similar between administration of VIGIV 4 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 results, VIGIV administration 4 days prior to Dryvax vaccination 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 Dryvax, or with Dryvax alone. When VIGIV was administered prior to or concurrently with vaccinia vaccination, the safety profile of VIGIV was consistent with the pharmacokinetic study.

2) A phase 2, double-blind pilot study of the immunological response in vaccinia vaccine naïve subjects following administration of prior to Dryvax[®] vaccination was conducted in 50 subjects. Following randomization, subjects were administered a single intravenous infusion of either VIGIV (9,000 U/kg), VIGIV (24,000 U/kg) or 0.9% Sodium Chloride USP Injection on Day 0, and either vaccinia (Dryvax[®]) vaccination or placebo vaccination on Day 4. All subjects were healthy volunteers of either sex between the ages of 18 and 33 years. Results from this study showed that VIGIV administered at 9,000 U/kg and 24,000 U/kg, 4 days prior to the administration of Dryvax[®], significantly attenuated the production of endogenous vaccinia-specific antibodies compared to subjects administered Dryvax[®] alone. However, only when 24,000 U/kg of VIGIV was administered, a concomitant reduction in size of the mean pox reaction and erythema area diameters were observed, suggesting that the higher the VIGIV dose level, the lower the local response.

12.3 Clinical VIGIV Use

During the current 2022 monkeypox outbreak, an infant aged <2 months was treated with oral tecovirimat and VIGIV under EA-IND for confirmed monkeypox infection [4]. The infant also received trifluridine drops to prevent ocular complications from the eyelid lesion. The infant was afebrile and stable throughout the illness. The infant tolerated tecovirimat and VIGIV, and fully recovered. <https://www.cdc.gov/mmwr/volumes/71/wr/mm7138e3.htm>. A neonate, whose mother was initially tested positive for non-variola orthopoxvirus, was administered VIGIV because of concern for congenital or perinatal transmission under a single patient emergency IND [5]. The neonate tolerated VIGIV administration well and was reported to have been doing well at last follow-up 5.5 weeks after administration. <https://www.cdc.gov/mmwr/volumes/71/wr/mm7136e1.htm>.

There are published VIGIV clinical use data for vaccinia-related infections [6-8]. The existence of shared serologic cross-reactivity between the orthopoxviruses (which led to their grouping as a genus), and the ability of neutralizing antibodies to one orthopoxvirus to partially neutralize the infectivity of other members of the genus orthopoxvirus [9], permit speculation that some clinical benefit may be achieved by the use of VIGIV for viral neutralization in instances where active replication of an orthopoxvirus other than variola and vaccinia is occurring. The fact that VIGIV may provide any amount of protection following variola exposure may indicate that

VIGIV could have a more clinically beneficial effect against an orthopoxvirus less virulent to humans, including monkeypox virus.

Kempe, et al. reviewed this immune globulin generalized protection. In his 1956 paper, "Hyper immune Vaccinial Gamma Globulin - Source, Evaluation, and Use in Prophylaxis and Therapy," it showed hyper-immune vaccinial immune globulin would neutralize the smallpox virus and suppress or diminish viremia, thereby suppressing or diminishing infection of skin epithelium [10]. The clinical expression of the disease would thus be modified or aborted, even though infection might still occur.

12.3 Pharmacokinetics Data

A phase 1, randomized, double-blind study was conducted in which 60 healthy volunteers received either 6,000 U/kg or 9,000 U/kg VIGIV. After IV administration of 6,000 U/kg to 31 male and female volunteers, a mean peak plasma concentration of 161 U/mL was achieved within 2 hours. The half-life of VIGIV was 30 days (range of 13–67 days) and the volume of distribution was 6630 mL. Pharmacokinetics parameters were calculated based on antibody levels determined by an ELISA.

The levels of VIGIV 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 U/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.

For additional information on VIGIV, please refer to the approved VIGIV package insert (available at [DailyMed \(nih.gov\)](https://www.accessdata.fda.gov/drugsatfda_docs/nda/2019/141051Orig1s010.pdf)).

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