

PRODUCT MONOGRAPH

VariZIG[®]

Varicella Zoster Immune Globulin (Human) Sterile Solution for Injection

Sterile Liquid 125 IU/vial

World Health Organization (WHO) Anti-Varicella Zoster
Immune Globulin, International Reference Standard

Passive Immunizing Agent

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VariZIG®

Varicella Zoster Immune Globulin (Human) Sterile Solution for Injection

PART I: HEALTH PROFESSIONAL INFORMATION

SUMMARY PRODUCT INFORMATION

| Route of Administration | Dosage Form / Strength | Nonmedicinal Ingredients |
|------------------------------|---------------------------------------|-------------------------------------|
| Intravenous or Intramuscular | Sterile Liquid for Injection / 125 IU | 10% maltose 0.03% polysorbate 80 |

DESCRIPTION

VariZIG® (Varicella Zoster Immune Globulin (Human) Injection) is a sterile solution of gamma immune globulin (IgG) fraction of human plasma containing antibodies to varicella zoster virus (anti-VZV). Varicella zoster virus (VZV) is the causative agent of chickenpox. VariZIG, is manufactured from plasma collected from healthy, screened donors with high titres of anti-VZV which is purified by an anion exchange column chromatography method.

VariZIG is prepared from pools of human plasma that may contain the causative agents of hepatitis and other viral diseases. The manufacturing process includes both a 20 nm virus filter that effectively removes lipid-enveloped and non-enveloped viruses based on size and a solvent/detergent treatment step that effectively inactivate lipid-enveloped viruses. These two processes are designed to increase product safety by reducing the risk of viral transmission of several viruses including human immunodeficiency virus (HIV), hepatitis B virus (HBV) and hepatitis C virus (HCV). However, 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 **WARNINGS AND PRECAUTIONS**).

The product potency is expressed in international units (IU) by comparison to the World Health Organization (WHO) international anti-varicella zoster immune globulin reference preparation. Each vial contains approximately 125 IU of anti-VZV. The final product is formulated with 10% maltose and 0.03% polysorbate 80. VariZIG has a pH range of 5.0 – 6.5 and contains no preservative.

INDICATIONS AND CLINICAL USE

VariZIG is indicated for:

Prevention or reduction in severity of maternal infections within 4 days of exposure to the varicella zoster virus.

Administration of VariZIG is recommended for prevention or reduction of severity of maternal infections within 4 days of exposure to the varicella zoster virus. Greatest effectiveness of treatment is expected when it is begun within 4 days of exposure; treatment after 4 days is of uncertain value.

Pregnant women may be at a higher risk of complications from chickenpox than healthy adults. The decision to administer VariZIG to a pregnant woman should be evaluated on an individual basis. The clinician should consider the patient's health status, type of exposure, and likelihood of previous unrecognized varicella infections before deciding whether to administer VariZIG. If, after careful evaluation of all available information, which may include the use of reliable and sensitive tests for varicella antibody, a normal pregnant woman with significant exposure to varicella is believed susceptible, VariZIG may be administered (For more information, see **PART II: SCIENTIFIC INFORMATION - CLINICAL TRIALS**).

Geriatrics: *No data is available*

Pediatrics: Based on the efficacy of other varicella zoster immune globulins in at-risk pediatric populations, similar efficacy can be expected for VariZIG. However, no specific pediatric clinical data is available for VariZIG.

CONTRAINDICATIONS

VariZIG should **not** be administered to patients:

- With known immunity to varicella zoster virus; i.e. with previous varicella infections or varicella vaccination.
- Who are deficient in IgA. While VariZIG contains less than 40 µg/mL IgA, individuals who are deficient in IgA may have the potential to develop IgA antibodies and have an anaphylactoid reaction.
- With a history of anaphylactic or other severe systemic reaction to immune globulins.
- Who are hypersensitive to this drug or to any ingredient in the formulation or component

of the container. For a complete listing, see the **Dosage Forms, Composition and Packaging**.

WARNINGS AND PRECAUTIONS

Serious Warnings and Precautions

VariZIG is prepared from pools of human plasma, which may contain the causative agents of hepatitis and other viral diseases. 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.

True hypersensitivity reactions are rare. These reactions can occur in very rare cases of IgA deficiency or hypersensitivity to human globulin. In case of allergic or anaphylactic reaction, the infusion should be stopped immediately. In case of shock, the current medical standards for treatment of shock should be observed.

The physician or health care professional should discuss the risks and benefits of this product with the patient, before prescribing or administering to the patient (see **WARNINGS AND PRECAUTIONS-General**)

General

Following intramuscular (IM) or intravenous (IV) administration of VariZIG, patients should be kept under observation for at least 20 minutes for monitoring of potential adverse effects. This product should be administered under the supervision of a qualified health professional that is experienced in the use of passive immunizing agents and in the management of pregnant women exposed to varicella zoster virus. Appropriate management of therapy and complications is only possible when adequate diagnostic and treatment facilities are readily available.

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. The manufacturing process includes both a 20 nm virus filter that effectively removes lipid-

enveloped and non-enveloped viruses based on size and a solvent/detergent treatment step that effectively inactivates lipid-enveloped viruses by irreversibly destroying the lipid coat. These two processes are designed to increase product safety by reducing the risk of viral transmission of several viruses including human immunodeficiency virus (HIV), hepatitis B and hepatitis C. However, 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. Individuals who receive infusions of blood or plasma products may develop signs and/or symptoms of some viral infections. All infections thought to have been possibly transmitted by this product should be reported by the physician or other health care professional to Saol Therapeutics Research Limited at 1-877-443-0224.

Cardiovascular

Rare thrombotic events have been reported in association with immune globulin intravenous (Human) (IGIV). Patients at risk may include those with a history of atherosclerosis, multiple cardiovascular risk factors, advanced age, impaired cardiac output, hypercoagulable disorders, prolonged periods of immobilization, and/or known or suspected hyperviscosity. The potential risks of VariZIG to produce thrombotic events is significantly lower than IGIV due to the differences in amount of protein infused, the volume of product infused and the relative health of the patient populations. Although the risk of thrombotic adverse events following VariZIG is extremely low, care should be taken in patients at risk for hyperviscosity, including those with cryoglobulins, fasting chylomicronemia/markedly high triacylglycerols (triglycerides), or monoclonal gammopathies. In such patients, it may be preferable to administer VariZIG IM as thrombotic adverse events have been reported following IV administration of immune globulins. 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 (see **ADVERSE REACTIONS**).

Renal

IGIV products have been reported to be associated with renal dysfunction, acute renal failure, osmotic nephrosis, proximal tubular nephropathy, and death. Although these reports of renal dysfunction and acute renal failure have been associated with the use of many licensed IGIV products, those that contained sucrose as a stabilizer and were administered at daily doses of 400 mg of sucrose (or greater) have accounted for a disproportionate share of the total number. VariZIG contains low levels of maltose (i.e., a maximum dose of 6 mL or 5 vials constitutes 0.72 g maltose/dose). Furthermore, the recommended dose of VariZIG contains considerably lower amounts of protein than IGIV products (i.e., <0.780 g/dose versus >20 g/dose, respectively). Patients predisposed to acute renal failure include the following: patients with any degree of pre-existing renal insufficiency, diabetes mellitus, volume depletion, sepsis, or paraproteinemia, or patients who are receiving known nephrotoxic drugs.

Respiratory

There have been rare reports of noncardiogenic pulmonary edema [Transfusion-Related Acute Lung Injury (TRALI)] 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. The potential risks of VariZIG to produce severe respiratory complications is significantly lower than IGIV due to the differences in amount of protein infused, the volume of product infused and the relative health of the patient populations. Although the risk of severe respiratory complications following VariZIG is extremely low, care should be taken in patients with pre-existing respiratory conditions. In such patients, it may be preferable to administer VariZIG IM as severe respiratory adverse events have been reported following IV administration of immune globulins.

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

Sensitivity/Resistance

Although allergic reactions have not been reported following VariZIG administration (see **Adverse Drug Reaction Overview**), epinephrine and diphenhydramine should be available for the treatment of any allergic reactions.

VariZIG contains trace quantities of IgA. The physician must weigh the potential benefit of treatment with VariZIG against the potential for hypersensitivity reactions. Individuals deficient in IgA have a potential for development of IgA antibodies and anaphylactic reactions after administration of blood components containing IgA. It has been reported that as little as 15 µg IgA/mL of blood product may elicit an anaphylactic reaction in IgA deficient individuals.

Special Populations

Pregnant Women: Animal reproduction studies have not been conducted with VariZIG. VariZIG should be given to pregnant women only if clearly needed. No new risk in pregnancy was identified in a randomized trial of VariZIG to prevent or modify the course of varicella zoster virus infection in 60 pregnant women. Clinical use of other immune globulins, such as Rh₀(D) immune globulin, administered during pregnancy suggests that there are no known adverse effects on the fetus from the immune globulin itself.

Nursing Women:

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

Pediatrics (< 18 years of age):

Safety and effectiveness in the pediatric population have not been established for VariZIG.

Geriatrics (> 65 years of age):

Safety and effectiveness in the geriatric population have not been adequately established for VariZIG.

Monitoring and Laboratory Tests

In the prevention of varicella zoster infections, the presence of passively administered varicella zoster antibody in the blood can lead to false-positive tests for immunity to VZV for 3 months after receiving VariZIG. Therefore, serodiagnostic tests to determine immunity to VZV should not be performed within 3 months of VariZIG administration.

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

ADVERSE REACTIONS**Adverse Drug Reaction Overview**

Reactions to VariZIG are rare and mild in intensity. In the intended patient population in clinical trials, the most frequent treatment related adverse events were pain at the injection site (17%), headache (7%), and rash (5%). Other less frequent adverse reactions were myalgia, rigors, fatigue, nausea and flushing. The adverse event profile of VariZIG is expected to be comparable to other commercially available varicella zoster immune globulin (human) and IV immune globulin (human) products. The most common expected adverse drug reactions are chills, fever, headaches, vomiting, allergic reactions, nausea, arthralgia and moderate low back pain.

As is the case with all drugs of this nature, there is a remote chance of an anaphylactic/anaphylactoid reaction with VariZIG in individuals with hypersensitivity to blood products. In the event of an immediate reaction (anaphylaxis) characterized by collapse, rapid pulse, wheezing, difficulty breathing, pallor, cyanosis, edema or generalized urticaria, epinephrine should be instituted followed by administration of hydrocortisone, if necessary.

Clinical Trial Adverse Drug Reactions

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

A randomized, active controlled clinical trial was conducted in 60 pregnant women without immunity to varicella zoster virus confirmed by a latex agglutination test. Patients were stratified on the basis of time from first exposure to varicella (1-4 days and 5-14 days) and randomized to receive 125 IU/10 kg body weight to a maximum dose of 625 IU of VariZIG (IV or IM) or another commercially available varicella zoster immune globulin, VZIG (IM). The patients were followed for 42 days after administration of VariZIG or active VZIG control for adverse events. A total of 94 adverse events were reported by 31 of the 41 patients (76%) treated with either IM or IV VariZIG; 24 of the adverse events were considered related to the administration of VariZIG. The most frequent adverse drug reactions were pain at injection site (17%), headache (7%), and rash (5%). Similar incidences of adverse drug reactions were reported in the reference product arm of the study.

Table 1 Adverse drug reactions reported by pregnant women following VariZIG or VZIG administration

| | | VariZIG [IV (N=22) or IM (N= 19)]; N=41 | | | VZIG (IM; N=19) | | |
|--|---------------------------|--|-----------|-----------|-----------------|-----------|-----------|
| System Organ Class | Preferred Term | # of events | # of subj | % of subj | # of events | # of subj | % of subj |
| All body systems | All preferred Terms | 24 | 14 | 34.1 | 16 | 12 | 63.2 |
| Gastrointestinal disorders | | | | | | | |
| | Nausea | 1 | 1 | 2.4 | 1 | 1 | 5.3 |
| General disorders and administration site conditions | | | | | | | |
| | Fatigue | 1 | 1 | 2.4 | 0 | 0 | 0.0 |
| | Injection site bruising | 1 | 1 | 2.4 | 0 | 0 | 0.0 |
| | Injection site pain | 7 | 7 | 17.1 | 9 | 9 | 47.4 |
| | Injection site pruritus | 1 | 1 | 2.4 | 0 | 0 | 0.0 |
| | Injection site tenderness | 1 | 1 | 2.4 | 0 | 0 | 0.0 |
| | Pain | 0 | 0 | 0.0 | 1 | 1 | 5.3 |
| Pyrexia | 0 | 0 | 0.0 | 1 | 1 | 5.3 | |

Table 1 Adverse drug reactions reported by pregnant women following VariZIG or VZIG administration

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|---|-------------------|--|-----------|-----------|-----------------|-----------|-----------|
| System Organ Class | Preferred Term | # of events | # of subj | % of subj | # of events | # of subj | % of subj |
| | Chills | 1 | 1 | 2.4 | 0 | 0 | 0.0 |
| Musculoskeletal and connective tissue disorders | Myalgia | 1 | 1 | 2.4 | 0 | 0 | 0.0 |
| | Neck pain | 0 | 0 | 0.0 | 1 | 1 | 5.3 |
| Nervous system disorders | Dizziness | 0 | 0 | 0.0 | 1 | 1 | 5.3 |
| | Dysgeusia | 1 | 1 | 2.4 | 0 | 0 | 0.0 |
| | Headache | 3 | 3 | 7.3 | 2 | 2 | 10.5 |
| Psychiatric disorders | Insomnia | 1 | 1 | 2.4 | 0 | 0 | 0.0 |
| Skin and subcutaneous tissue disorders | Dermatitis | 1 | 1 | 2.4 | 0 | 0 | 0.0 |
| | Rash erythematous | 1 | 1 | 2.4 | 0 | 0 | 0.0 |
| | Rash | 2 | 2 | 4.9 | 0 | 0 | 0.0 |
| Vascular disorders | Flushing | 1 | 1 | 2.4 | 0 | 0 | 0.0 |

In addition to the VZ-006 clinical study described above, VariZIG safety data was also collected from two other clinical studies conducted in either normal healthy subjects (VZ-001) or geriatric patients with post-herpetic neuralgia (VZ-003). Similar incidences and types of adverse events were reported in these patient populations following administration of VariZIG.

Post-Market Adverse Drug Reactions

Adverse events have been reported minimally in the post-marketing setting with VariZIG. No cases, due to their nature or frequency impacts the safety profile of VariZIG further than that described in the clinical trial section above.

DRUG INTERACTIONS

Overview

Serious Drug Interactions

- Live attenuated virus vaccines: immune globulin administration may impair the efficacy of live attenuated virus vaccines for a period of 3 months or more (see **DRUG INTERACTIONS - Overview**).

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

Administration of VariZIG with other drugs has not been evaluated. It is recommended that VariZIG be administered separately from other drugs. Refer to the **DOSAGE AND ADMINISTRATION** section for information on drug compatibility.

Drug-Drug Interactions

Table 2 - Established or Potential Drug-Drug Interactions

| Varicella Zoster Immune Globulin (Human) | Reference | Effect | Clinical comment |
|---|------------------|-------------------------------------|--|
| Live attenuated virus vaccines (e.g., measles, rubella, mumps, varicella) | T | Immune globulin may impair efficacy | If VariZIG is given less than 14 days after vaccination, revaccination should be considered. |

Legend: C = Case Study; CT = Clinical Trial; T = Theoretical

Interactions with other drugs have not been established.

Drug-Food Interactions

Interactions with foods have not been established.

Drug-Herb Interactions

Interactions with herbs have not been established.

Drug-Laboratory Interactions

After administration of VariZIG, a transitory increase of passively transferred antibodies in the

patient's blood may result in misleading positive results in serological testing (e.g. Coomb's test).

DOSAGE AND ADMINISTRATION

Recommended Dose and Dosage Adjustment

Dosing of VariZIG is based on body weight. The recommended adult dose is 125 IU/10 kg body weight up to a maximum of 625 IU. VariZIG should be given by intravenous (IV) or intramuscular (IM) administration. The minimum dose is 125 IU and the maximum dose of 625 IU should be sufficient to prevent or modify infection in at-risk patients. VariZIG should be administered within 96 hours of varicella exposure, preferably as soon as possible. The efficacy of varicella immune globulins in the reduction of incidence or severity of varicella infections in at-risk patients has not been demonstrated when administered more than 96 hours after exposure.

Preparation and Handling

Each vial of VariZIG contains a minimum potency of 125 IU in 1.2 mL.

Bring VariZIG to room temperature prior to use.

Inspect VariZIG for particulate matter and discoloration prior to administration. Do not use if the solution is cloudy or contains particulates.

VariZIG is for single use only. Discard any unused portion.

The solution is ready to use, no reconstitution or further dilution required.

Dosing of VariZIG is based on body weight. Administer a single dose of VariZIG IM or IV as recommended in

Table-3.

The standard dose of VariZIG is 125 IU/10 kg of body weight up to a maximum of 625 IU per patient. The maximum dose of 625 IU should be administered for all patients greater than 40 kilograms in weight.

Table 3 VariZIG Dose and Volume of Administration

| Weight of Patient | | VariZIG Dose | | Volume to Administer (milliliters)* |
|-------------------|--------|--------------|-----------------|-------------------------------------|
| Kilograms | Pounds | IU | Number of Vials | |
| ≥ 40.1 | ≥ 88.1 | 625 | 5 | 6.0 |

*Extractable volumes are confirmed using a 21 gauge needle as per USP General Chapters <1> Injections.

Parenteral products such as VariZIG should be inspected for particulate matter and discoloration prior to administration. VariZIG should be stored at 2-8°C prior to use. Do not freeze. Do not use after expiration date.

Administration:

If VariZIG is administered by an IV route, then drug should be infused into a suitable vein over 3-5 minutes.

If VariZIG is administered by an IM route, it should be given as an injection into the deltoid muscle or the anterolateral aspects of the upper thigh. Due to the risk of sciatic nerve injury, the gluteal region should not be used as a routine injection site. If the gluteal region is used, use only the upper, outer quadrant. Depending on the dose volume, the dose may be divided and administered IM in two or more injection sites.

To prevent the transmission of infectious agents from one person to another, a separate sterile disposable syringe and needle should be used for each individual patient.

There are no available data on concomitant use of VariZIG and other medications. Admixtures of VariZIG with other drugs have not been evaluated. It is recommended that VariZIG be administered separately from other drugs or medications that the patient may be receiving. If a pre-existing catheter must be used for IV administration, the line should be flushed with 0.9% Sodium Chloride for injection USP before administering the product.

OVERDOSAGE

In clinical studies, 15 patients were administered a VariZIG dose of 50 IU/kg of body weight (IV). This dose is approximately four times greater than the recommended dose for the immunoprophylaxis of varicella. Related adverse events were mostly mild in nature. All of the related adverse events of chills, nausea, pain at the injection site, rash, urticaria, asthenia, headache, back pain, arthralgia, dizziness and twitch have previously been reported with the use

of immune globulins and are expected adverse events. No clinically significant changes in laboratory test results or vital signs were associated with VariZIG infusion.

ACTION AND CLINICAL PHARMACOLOGY

Mechanism of Action

VariZIG is used for the passive immunization of pregnant women in the event of contact with varicella zoster virus. Administration of VariZIG prevents or reduces the severity of maternal infections with varicella zoster virus when administered within 4 days of initial contact. It is hypothesized that anti-VZV antibodies in VariZIG bind to proteins on the varicella virus; thereby, preventing or reducing the severity of varicella infections.

Upon absorption into the circulation, varicella zoster antibodies persist for 6 weeks or longer. The precise concentration of antibodies that must be achieved or maintained in order to attenuate varicella is not known. In a clinical study of pregnant women without immunity to varicella, the overall infection frequency of 29% observed in patients administered VariZIG was significantly lower than the expected rate of 89% in at-risk pregnant women exposed to varicella. In addition to decreasing the incidence of varicella infections, VariZIG decreased the severity of varicella infections compared to historical cases of varicella infections in at-risk patients.

Pharmacodynamics

No pharmacodynamic studies have been conducted with VariZIG.

Pharmacokinetics

The pharmacokinetic properties of immune globulin preparations manufactured by anion exchange chromatography and having the same formulation as VariZIG have been determined. Peak levels (C_{max}) following IV were reached in less than three hours while C_{max} was reached 2 to 7 days after IM administration.

In the VariZIG clinical development program, higher levels of varicella zoster antibodies were detected in patients 2 days after IV administration than compared to patients receiving VariZIG IM. Based on non-compartmental analysis, the area under the curve (AUC) was similar in these studies regardless of the route of administration of the drug. The half-life of hyperimmune products is approximately 18-24 or 24-30 days following IV or IM administration, respectively. Upon absorption into the circulation, varicella zoster antibodies are expected to persist for at least 6 weeks. Thus, an IV administration is expected to lead to a higher peak passive antibody level that is achieved earlier than with an IM route of administration. However, the levels of circulating antibodies over time are expected to be similar regardless of route of administration.

Absorption: Following IM administration of varicella immune globulin products, varicella antibodies are detectable within 2-3 days. The maximum concentration of varicella antibodies is

expected to occur within 3-7 days of VariZIG administration.

Distribution: The bioavailability following IV administration of VariZIG is expected to be immediate and complete, with passive antibodies quickly distributed between plasma and extravascular spaces. Based on AUC comparisons from pharmacokinetic studies of other hyperimmune products, IM administration is expected to be nearly 100% bioavailable.

Metabolism: Immune globulins and immune complexes are metabolized in the reticuloendothelial system.

Excretion: Based on the studies with other immune globulin products, an elimination half-life of 18-24 or 24-30 days for VariZIG is expected following IV or IM administration, respectively. The half-life is expected to vary from patient to patient.

STORAGE AND STABILITY

Store VariZIG under refrigeration at 2-8°C. **Do not freeze. Do not use after expiration date.**

SPECIAL HANDLING INSTRUCTIONS

The product should be brought to room or body temperature immediately prior to use. The product should be clear or slightly opalescent. Do not use product that appears cloudy or contains deposits.

DOSAGE FORMS, COMPOSITION AND PACKAGING

Dosage Forms and Packaging: VariZIG is supplied as a sterile liquid containing approximately 125 IU of anti-VZV antibodies in a 3 mL type 1 glass tubing vial fitted with a 13 mm rubber stopper (latex free) and a 13 mm flip-off seal, and a package insert.

Composition: VariZIG is a sterile solution for injection. It is a gamma globulin (IgG) fraction of human plasma containing antibodies to varicella zoster virus. Non-medicinal ingredients include 10% maltose and 0.03% (w/w) polysorbate 80. Each 125 IU vial contains less than 156 mg human IgG. It contains no preservative and is intended for single use only. VariZIG does not contain mercury and the stopper is latex free.

PART II: SCIENTIFIC INFORMATION

PHARMACEUTICAL INFORMATION

Drug Substance

| | |
|--|--|
| Proper name: | Varicella Zoster Immune Globulin (Human) |
| Chemical name: | Varicella Zoster Immune Globulin (Human) |
| Molecular formula & molecular mass: | Glycoprotein of approximately 160 kDa |
| Structural formula: | Gamma Immune Globulin (IgG) |
| Physicochemical properties: | IgG is a monomeric protein with a sedimentation coefficient of 7S and a molecular weight ranging from 146 to 170 kDa. Carbohydrate content of IgG is approximately 2-3%. |

Product Characteristics

VariZIG is a sterile solution for injection. It is an IgG fraction of human plasma containing antibodies to varicella zoster virus, prepared by an anionexchange column chromatography method.

Viral Inactivation

The manufacturing steps are designed to reduce the risk of transmission of viral disease. The solvent/detergent treatment step, is effective in inactivating known enveloped viruses such as hepatitis B virus (HBV), hepatitis C virus (HCV), and human immunodeficiency virus (HIV). Virus filtration using a 20 nm Virus Filter, is effective in reducing some known enveloped and non-enveloped model viruses. The inactivation and reduction of known enveloped and non-enveloped model viruses were validated in laboratory studies as summarized in Table 5 below:

Table 5 Viral validation of model viruses in laboratory studies

| Genome | Enveloped | | | Non-Enveloped | | | |
|--|---------------|---------------|---------------|---------------|------------|------------|------------|
| | RNA | | DNA | RNA | | DNA | |
| Virus | HIV-1 | BVDV | PRV | HAV | EMC | MMV | PPV |
| Family | retro | flavi | herpes | picorna | | parvo | |
| Size (nm) | 80–100 | 50–70 | 120–200 | 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* | n.e. | 4.8 | n.e. | 4.1 |
| Solvent/Detergent (inactivation) | ≥ 4.7 | ≥ 7.3 | ≥ 5.5 | Not evaluated | | | |
| Total Reduction (log₁₀) | ≥ 9.4 | ≥ 10.8 | ≥ 11.1 | 2.3 | 4.8 | 3.4 | 4.1 |

*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

n.e.: not evaluated

CLINICAL TRIALS

The safety and efficacy of VariZIG was evaluated in 3 clinical trials. Study VZ-001 was a phase 1 study that evaluated the safety of VariZIG in normal healthy volunteers. Study VZ-003 was a phase 2 study that evaluated the safety and efficacy of VariZIG in the treatment of post-herpetic neuralgia. This study is unrelated to the licensed indications and has been used as supporting safety data. Study VZ-006 was the pivotal phase 3 study that evaluated the safety and efficacy of VariZIG compared to the licensed VZIG in the prevention or reduction of severity of varicella infections in at-risk pregnant women.

Study demographics and trial design

Table 6 Summary of patient demographics for VariZIG clinical trials

| Study # | Trial design | Dosage, route of administration and duration | Study subjects (n=number) | Mean age (\pm SD) | Gender |
|---------|---|--|--|---|---|
| VZ-001 | Phase 1, single centre, randomized, double blind safety study in normal healthy volunteers. | Single dose of VariZIG at either 625 IU/ subject IM or 50 IU/kg IV. | Healthy Adults, 10 subjects (5 in each arm) | 27 \pm 6 years | 9 M: 1 F |
| VZ-003 | Phase 2, multi-centre, randomized, double blind, placebo-controlled study in patients with post-herpetic neuralgia. | Single dose of saline placebo or VariZIG at either 10 IU/kg IV or 50 IU/kg IV. | Patients with post-herpetic neuralgia, Placebo n=8 VariZIG (10 IU/kg) n=6 VariZIG (50 IU/kg) n=10 | 66 \pm 11 years 76 \pm 10 years 71 \pm 10 years | 4 M: 4 F 3 M: 3 F 2 M: 8 F |
| VZ-006 | Phase 3, multi-centre, randomized, active controlled study in at-risk pregnant women exposed to varicella virus. | Single dose of VZIG (125 IU/10 kg IM) or VariZIG at either 125 IU/ 10 kg IM or 125 IU/ 10 kg IV. | Pregnant women, VZIG(IM) n= 19 VariZIG (IM) n=17 VariZIG (IV) n=21 | 29 \pm 4 years 29 \pm 6 years 31 \pm 6 years | 0 M: 19 F 0 M: 17 F 0 M: 21 F |

The pivotal VZ-006 recruited 60 pregnant women, who were randomized to receive either VariZIG or the licensed VZIG. Ten patients did not complete all assessments, and three did not meet the entry criteria (2 IV VariZIG and 1 IM VariZIG). All of the patients enrolled were included in the intent-to-treat analysis of safety; of these, 57 were included in the per-protocol analysis of efficacy. The patients had comparable demographic characteristics between the 3 arms of the study (see Table 7). In addition, the patients that received VariZIG or VZIG had comparable varicella contact with respect to duration of exposure, time since exposure and type of varicella exposure.

Study results

Table 7 Results of study VZ-006 in prevention of or reduction of severity of varicella infections in at-risk pregnant women.

| Primary Endpoints | VariZIG | | VZIG |
|--|-----------|-----------|---------|
| | IM (n=17) | IV (n=21) | IM n=19 |
| Incidence of Varicella Infections | 5 (29%) | 6 (29%) | 8 (42%) |
| Severity of varicella infection (mean constitutional illness score*) | 1.35 | 0.90 | 1.42 |

*Constitutional Illness Score (CIS) is a subjective measure that assesses pruritus, anorexia, pyrexia and lethargy (Wallace et al. 358-63).

The efficacy of VariZIG and licensed VZIG was evaluated through a comparison of the numbers of patients contracting varicella, the CIS for each treatment group and stratum. Fewer patients treated with VariZIG developed clinical varicella (IM: 5 (29%); IV: 6 (29%)) compared to those treated with commercial IM VZIG (8 patients, 42%). However, the differences between the VariZIG groups and commercial group were not statistically significant ($p=0.643$). Overall, the infection frequency of 29% (11 of 38) observed with VariZIG was significantly lower than the expected rate of 89% in at-risk pregnant women exposed to varicella. The distribution of CIS at the time of onset of clinical varicella indicates a wide variability in the individual scores. When averaged across all patients, the mean weighted CIS scores were similar for the VariZIG IM group (1.35) and IV groups (0.90) compared to commercial VZIG (1.42). The mean weighted CIS at the time of varicella is significantly lower than expected CIS of 2.8 in this group.

The intensity of pruritus, anorexia, and lethargy was evenly distributed, with approximately two-thirds of 19 patients with varicella experiencing no symptom or symptoms of mild intensity. The majority of patients with clinical varicella (15 of 19; 79%) had a temperature of $<37.8^{\circ}\text{C}$. Three patients [VariZIG IV (1); VariZIG IM, (2)] had temperatures between 37.8°C and 38.3°C , and one patient who received commercial IM VZIG had a temperature of $>39.4^{\circ}\text{C}$.

These results demonstrate that VariZIG, given either IM or IV, is similar in effectiveness to commercial IM VZIG.

DETAILED PHARMACOLOGY

Animal studies

Nonclinical pharmacology studies have not been performed with VariZIG as there is broad experience in humans with IV or IM administration of immune globulin products. Since the product is of human origin, immunogenicity is expected when administered to animals.

Human Studies

No clinical pharmacokinetic or pharmacodynamic studies have been conducted with VariZIG. It is expected that VariZIG will have comparable pharmacokinetics as other immune globulins following IV or IM administration (see Part I: **ACTION AND CLINICAL PHARMACOLOGY**).

TOXICOLOGY

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

Acute Toxicity: The toxicologic properties of immune globulins manufactured by anion exchange chromatography and having the same formulation as VariZIG have been examined. An IV acute toxicity study was conducted in mice with Rh_o (D) Immune Globulin (Human), WinRho[®]. An LD₅₀ was not determined, as the maximal dose (233 mg/kg of WinRho or 3750 mg/kg of anti-D) used in the study did not kill any experimental animals. Neither clinical observation nor necropsy of the experimental animals revealed any acute toxicity related to the study drug. Based on the established safety of WinRho (>233mg/kg) the total protein in a single maximum clinical dose of VariZIG (≤19.5 mg/kg) is expected to be safe.

Neoantigen Studies: Studies were conducted investigating the effect of solvent detergent treatment and virus filtration on the immune globulin preparation. These studies concluded that no new antigens were formed by solvent detergent treatment or by 35 nm virus filtration of Rh_o (D) Immune Globulin (Human).

Reproductive Toxicity: Reproduction and teratology studies have not been conducted with VariZIG. No new risk in pregnancy was identified in a randomized trial of VariZIG to prevent or modify the course of varicella zoster virus infection in 60 pregnant women. Varicella Zoster Immune Globulin (Human) has been commercially available to pregnant women in Canada since 1997. Previous experience with other immune globulin products in pregnant women, including Rh_o (D) Immune Globulin, has revealed no reports of reproductive side effects.

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READ THIS FOR SAFE AND EFFECTIVE USE OF YOUR MEDICINE

PART III: PATIENT MEDICATION INFORMATION

VariZIG[®]

Varicella Zoster Immune Globulin (Human) Sterile Solution for Injection

Read this carefully before you start taking VariZIG and each time you get a refill. This leaflet is a summary and will not tell you everything about this drug. Talk to your healthcare professional about your medical condition and treatment and ask if there is any new information about VariZIG.

Serious Warnings and Precautions

- **VariZIG is made from human plasma, which may contain the causative agents of viral disease. The risk of getting a disease from this product has been reduced by screening plasma donors, testing for the presence of certain viruses and by utilizing manufacturing steps that inactivate and remove certain viruses. However, there is still a possibility that plasma products could transmit disease.**
- **Allergic or anaphylactic reactions are rare. These reactions can occur in patients with a history of allergies to blood products or in patients lacking the IgA blood protein.**

What is VariZIG used for?

Prevention or reduction in severity of maternal varicella infections (chickenpox) in non-immune pregnant women that have been exposed to individuals with a varicella zoster virus infection (chickenpox).

How does VariZIG work?

Although the exact mechanism by which VariZIG works is not fully known, it is believed that antibodies in VariZIG interact with the virus to prevent or decrease the severity of chickenpox in at-risk individuals.

If you have not had chickenpox before and become exposed to someone with chickenpox, please see your physician immediately to determine whether you should receive VariZIG. Your physician will determine whether you require VariZIG based on lab tests for pre-existing immunity, the type of exposure and the time since you were exposed to someone with chickenpox.

What are the ingredients in VariZIG?

Medicinal ingredients:

Varicella Zoster Immune Globulin (Human)

Non-medicinal ingredients:

Human plasma protein

Maltose

Polysorbate 80

VariZIG may contain trace amounts of solvent/detergent.

VariZIG comes in the following dosage forms:

VariZIG is provided in single use 3 mL glass vials that contain approximately 125 IU of varicella zoster antibody activity. You may be administered up to 5 vials depending on your body weight.

Do not use VariZIG:

- In patients with a history of allergic reactions to blood products.
- In patients deficient in IgA, which is a specific type of blood protein.

To help avoid side effects and ensure proper use, talk to your healthcare professional before you take VariZIG. Talk about any health conditions or problems you may have, including if you:

- You have experienced allergic reactions to blood products in the past,
- You have a known IgA deficiency,
- You have recently received any vaccinations.

Tell your healthcare professional about all the medicines you take, including any drugs, vitamins, minerals, natural supplements or alternative medicines.

Drugs that may interact with VariZIG have not been established.

Immune globulins like VariZIG may impair the effectiveness of certain live virus vaccines such as measles, rubella (i.e. German measles), mumps and varicella (i.e. chickenpox). Talk to your doctor if you have been recently vaccinated.

How to take VariZIG:

VariZIG will be administered by a health care provider by an injection either intravenously (in the vein) or intramuscularly (in the muscle).

Usual dose:

The standard dose of VariZIG is 125 IU/10 kg of body weight up to a maximum of 625 IU/patient. Your individual dose of VariZIG will be determined by your weight.

Overdose:

If you think you have taken too much VariZIG, contact your healthcare professional, hospital emergency department or regional Poison Control Centre immediately, even if there are no symptoms.

What are possible side effects from using VariZIG?

These are not all the possible side effects you may feel when taking VariZIG. If you experience any side effects not listed here, contact your healthcare professional. Please also see Warnings and Precautions.

The most common side effects are injection site pain, chills, fever, headaches, vomiting, nausea, joint pain and rash. These side effects are usually mild, but if they require treatment ask your health care professional.

| Serious side effects and what to do about them | | | |
|---|--------------------------------------|--------------|---|
| Symptom / effect | Talk to your healthcare professional | | Stop taking drug and get immediate medical help |
| | Only if severe | In all cases | |
| RARE Allergic reaction | | X | X |

If you have a troublesome symptom or side effect that is not listed here or becomes bad enough to interfere with your daily activities, talk to your healthcare professional.

Reporting Side Effects

You can help improve the safe use of health products for Canadians by reporting serious and unexpected side effects to Health Canada. Your report may help to identify new side effects and change the product safety information.

3 ways to report:

- Online at [MedEffect](#);
- By calling 1-866-234-2345 (toll-free);
- By completing a Patient Side Effect Reporting Form and sending it by:
 - Fax to 1-866-678-6789 (toll-free), or
 - Mail to: Canada Vigilance Program
Health Canada, Postal Locator 0701E
Ottawa, ON
K1A 0K9

Postage paid labels and the Patient Side Effect Reporting Form are available at [MedEffect](#).

NOTE: Contact your health professional if you need information about how to manage your side effects. The Canada Vigilance Program does not provide medical advice.

Storage:

Store VariZIG under refrigeration. Do not freeze. Do not use after expiration date. Keep out of reach and sight of children.

If you want more information about VariZIG:

- Talk to your healthcare professional
- Find the full product monograph that is prepared for healthcare professionals and includes this Patient Medication Information by visiting the [Health Canada website](#); or by calling Saol Therapeutics Research Limited at 1-877-443-0224.

This leaflet was prepared by Saol Therapeutics Research Limited.

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