

PRODUCT MONOGRAPH

VariZIG™

Varicella Zoster Immune Globulin (Human)

Powder for Injection 125 IU/vial

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

Passive Immunizing Agent

Cangene Corporation
155 Innovation Drive
Winnipeg, MB
R3T 5Y3
Canada

www.cangene.com

Control No #: 117221

Date of Approval: January 9, 2008

Table of Contents

PART I: HEALTH PROFESSIONAL INFORMATION.....	3
SUMMARY PRODUCT INFORMATION	3
DESCRIPTION.....	3
INDICATIONS AND CLINICAL USE.....	4
CONTRAINDICATIONS	4
WARNINGS AND PRECAUTIONS.....	5
ADVERSE REACTIONS.....	8
DRUG INTERACTIONS	10
DOSAGE AND ADMINISTRATION.....	11
OVERDOSAGE	13
ACTION AND CLINICAL PHARMACOLOGY	13
STORAGE AND STABILITY.....	14
SPECIAL HANDLING INSTRUCTIONS	14
DOSAGE FORMS, COMPOSITION AND PACKAGING	15
PART II: SCIENTIFIC INFORMATION	16
PHARMACEUTICAL INFORMATION.....	16
CLINICAL TRIALS.....	17
DETAILED PHARMACOLOGY	19
TOXICOLOGY	20
REFERENCES	20
PART III: CONSUMER INFORMATION.....	24

VarizIG™

Varicella Zoster Immune Globulin (Human)

PART I: HEALTH PROFESSIONAL INFORMATION

SUMMARY PRODUCT INFORMATION

Route of Administration	Dosage Form / Strength	Clinically Relevant Nonmedicinal Ingredients
Intravenous or Intramuscular	Powder for Injection / 125 IU	<i>For a complete listing see Dosage Forms, Composition and Packaging section.</i>

DESCRIPTION

VarizIG™ (Varicella Zoster Immune Globulin (Human) Injection) is a sterile freeze-dried gamma 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^{1,2}.

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 Planova 20 nm virus filter that effectively removes lipid-enveloped and non-enveloped viruses based on size and a solvent/detergent treatment step (using tri-n-butyl phosphate and Triton X-100®) that effectively inactivates lipid-enveloped viruses³⁻⁵. 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 (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 formulation includes addition of sodium chloride to yield 0.04 M, glycine to yield 0.1 M and polysorbate 80 to yield 0.01%. The accompanying sterile diluent contains 0.8% sodium chloride and 10 mM sodium phosphate. The reconstituted product 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^{6,7}. 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 populations⁷⁻⁹, 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 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 administration of VariZIG™ (IV or IM), 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 Planova 20 nm virus filter that effectively removes lipid-enveloped and non-enveloped viruses based on size and a solvent/detergent treatment step (using tri-n-butyl phosphate and Triton X-100®) that effectively inactivates lipid-enveloped viruses by irreversibly destroying the lipid coat³⁻⁵. 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 provider to Cangene Corporation at 1-800-768-2304 (phone) or 1-800-768-2281 (fax).

Cardiovascular

Rare thrombotic events have been reported in association with immune globulin intravenous (Human) (IGIV)¹⁰⁻¹². 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™ intramuscularly as thrombotic adverse events have only been reported following intravenous administration of immune globulins.

Renal

IGIV products have been reported to be associated with renal dysfunction, acute renal failure, osmotic nephrosis, proximal tubular nephropathy, and death^{13,14}. 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 number¹⁵.

VariZIG™ does not contain sucrose as a stabilizer, and the recommended dose of VariZIG™ contains significantly lower amounts of protein than IGIV products (i.e. <0.75 g per dose vs. >20 g per dose). 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 IGIV¹⁶. 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™ intramuscularly as severe respiratory adverse events have only been reported following intravenous 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™ (Varicella Zoster Immune Globulin (Human)) 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 individuals¹⁷.

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 women¹⁸. Clinical use of other immune globulins, such as Rh₀(D) immune globulin^{19;20}, 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^{21;22}. 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™ (Varicella Zoster Immune Globulin (Human)) are rare and mild in intensity. In the intended patient population, 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 intravenous 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^{7;23-26}.

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 or IM; N=41)			VZIG (IM; N=19)		
System Organ Class	Preferred Tern	# of events	# of subj	% of subj	# of events	# of subj	% of subj
All body systems	All preferred Terns	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
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

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

		VariZIG™ (IV or IM; N=41)			VZIG (IM; N=19)		
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, VariZIG™ safety data was also collected from two other clinical studies conducted in either normal healthy subjects (VZ-001)²⁷ or geriatric patients with post-herpetic neuralgia (VZ-003)²⁸. Similar incidences and types of adverse events were reported in these patient populations following administration of VariZIG™.

Post-Market Adverse Drug Reactions

There is no post-marketing experience.

DRUG INTERACTIONS

<p>Serious Drug Interactions</p> <ul style="list-style-type: none"> • 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).

Overview

Immune globulin administration may impair the efficacy of live attenuated vaccines such as measles, rubella, mumps and varicella^{7;21;22}. 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 dose is 125 IU/10 kg body weight up to a maximum of 625 IU. VariZIG™ should be given by intravenous or intramuscular 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^{7,8}.

Reconstitution:

Route of Administration	Vial Size	Volume of Diluent to be added to vial	Approximate Available Volume	Nominal Concentration per mL
Intravenous	6 mL	2.5 mL	2.4 mL	50 IU/mL
Intramuscular	6 mL	1.25 mL	1.2 mL	100 IU/mL

VariZIG™ should be reconstituted only with the accompanying vial of Sterile Diluent. Use aseptic technique throughout. Reconstitute shortly before use.

To reconstitute:

1. Remove caps from the diluent and product vials.
2. Wipe exposed central portion of each rubber stopper with suitable disinfectant.
3. Withdraw 2.5 mL of diluent for IV administration or 1.25 mL diluent for IM administration using a suitable syringe and needle.
4. Inject diluent slowly at an angle so that the liquid is directed onto the inside glass wall of the vial containing the freeze-dried pellet.
5. Wet pellet by gently tilting and inverting the vial. Avoid frothing. Gently swirl upright vial until dissolved (less than ten minutes). **Do not shake.**

Parenteral products such as VariZIG™ (Varicella Zoster Immune Globulin (Human)) should be inspected for particulate matter and discoloration prior to administration. Reconstituted product can be stored for up to 12 hours at 2-8°C prior to use.

Administration:

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

If VariZIG™ is administered by an intramuscular 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.

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)^{7;27;28}. 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%²⁹ 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^{7;29}.

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™ (Varicella Zoster Immune Globulin (Human)) 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 intramuscular administration³⁰⁻³⁴. 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 drug³⁵. The half-life of hyperimmune products is approximately 18-24 or 24-30 days following IV or IM administration, respectively³⁴⁻³⁸. Upon absorption into the circulation, varicella zoster antibodies are expected to persist for at least 6 weeks. Thus, an intravenous administration is expected to

lead to a higher peak passive antibody level that is achieved earlier than with an intramuscular 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 days³⁹. 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^{35;40}, IM administration is expected to be nearly 100% bioavailable.

Metabolism: Immune globulins and immune complexes are metabolized in the reticuloendothelial system³⁹.

Excretion: Based on the studies with other immune globulin products³⁴⁻³⁸, an elimination half-life of 18-24 or 24-30 days for VariZIGTM is expected following IV or IM administration, respectively. The half-life is expected to vary from patient to patient³⁹.

STORAGE AND STABILITY

VariZIGTM is stable at 2-8°C until the expiry date indicated on the label.
Store VariZIGTM 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. Following reconstitution, 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™ (Varicella Zoster Immune Globulin (Human)) is available as a kit containing the following:

Contents One 6 mL type 1 glass tubing vial containing approximately 125 IU of freeze-dried VariZIG™ (Varicella Zoster Immune Globulin (Human)), fitted with a 20 mm lyophilization stopper of rubber formulation and a 20 mm flip-off seal, and one vial of 8.5 mL, Sterile Diluent (0.8% Sodium Chloride, 10mM Sodium Phosphate) for reconstitution of VariZIG™.

Product Code FP004

Composition: VariZIG™ is a sterile freeze-dried gamma globulin (IgG) fraction of human plasma containing antibodies to varicella zoster virus. Non-medicinal ingredients include 0.04 M sodium chloride, 0.1 M glycine, and 0.01% polysorbate 80. Each 125 IU vial contains 60-200 mg human immunoglobulin G. It contains no preservative.

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™ (Varicella Zoster Immune Globulin (Human)) is a sterile freeze-dried gamma globulin (IgG) fraction of human plasma containing antibodies to varicella zoster virus, prepared by an anion-exchange column chromatography method.

Viral Inactivation

The manufacturing steps are designed to reduce the risk of transmission of viral disease. The solvent/detergent treatment step, using tri-n-butyl phosphate and Triton® X-100^a 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 Planova™ 20 nm Virus Filter^b, is effective in reducing some known enveloped and nonenveloped model viruses. The inactivation and reduction of known enveloped and non-enveloped model viruses were validated in laboratory studies as summarized in table 3 below:

Table 3- Viral validation of model viruses in laboratory studies

Test Virus	Mean Log ₁₀ Virus Reduction			Model for	Virus Type
	Anion Exchange Chromatography	20N Filtration	Solvent and Detergent		
HIV-1	Not evaluated	≥ 4.7	> 4.7	HIV-2, relevant for HIV-1	lipid enveloped RNA
BVDV	Not evaluated	≥ 3.5	≥ 7.1	HCV, WNV	lipid enveloped RNA
PRV	Not evaluated	≥ 5.6 ^a	≥ 5.4	Large enveloped DNA viruses, including herpes	lipid enveloped DNA
HAV	2.3	Not evaluated	Not evaluated	Small non-enveloped viruses, relevant for HAV	Non-lipid enveloped RNA
EMC	Not evaluated	4.4	Not evaluated	Small non-enveloped viruses, HAV	Non-lipid enveloped RNA
MMV	3.4	Not evaluated	Not evaluated	Small non-enveloped viruses, human B19 parvovirus	Non-lipid enveloped DNA
PPV	Not evaluated	3.5 ^b	Not evaluated	Small non-enveloped viruses, human B19 parvovirus	Non-lipid enveloped DNA

Abbreviations:

HIV: human immunodeficiency virus

BVDV: bovine viral diarrhea virus

HCV: human hepatitis C virus

WNV: West Nile virus

PRV: pseudorabies virus

HAV: human hepatitis A virus

EMC: encephalomyocarditis virus

MMV: murine minute virus

PPV: porcine parvovirus

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

^b One of the five PPV runs for the 20N filter yielded a 1.25 log clearance over the 0.1 µm pre-filter. Since production employs a 0.1 µm pre-filter before the 20N filter, the 1.25 logs were added to the 2.2 log clearance obtained over the 20N filter, and the value of 3.5 was used for determination of the mean log reduction factor.

^aTriton® is a trademark of Rohm and Haas Company.

^bPlanova™ is a trademark of Asahi Kasei Kogyo Kabushiki Kaisha Corporation.

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-006¹⁸ 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 4- Summary of patient demographics for VariZIG™ clinical trials

Study #	Trial design	Dosage, route of administration and duration	Study subjects (n=number)	Mean age (± 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.	10 subjects (5 in each arm)	27 ± 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.	Placebo N=8 VariZIG™ (10 IU/kg) N=6 VariZIG™ (50 IU/kg) N=10	66 ± 11 years 76 ± 10 years 71 ± 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.	VZIG IM N= 19 VariZIG™ (IM) N=17 VariZIG™ (IV) N=21	29± 4 years 29 ± 6 years 31 ± 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 VZIG¹⁸. 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 4). In addition, the patients that received VariZIG™ or VZIG had comparable varicella contacts with respect to duration of exposure, time since exposure and type of varicella exposure.

Study results

Table 5- 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 is a subjective measure that assesses pruritus, anorexia, pyrexia and lethargy⁴¹.

The efficacy of VariZIG™ and licensed VZIG was evaluated through a comparison of the numbers of patients contracting varicella, the constitutional illness score (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^{29,42}. 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 group⁴¹.

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°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°C.

These results demonstrate that VariZIG™, given either IM or IV, is similar in effectiveness to commercial IM VZIG^{7,8}.

DETAILED PHARMACOLOGY

Animal studies

Nonclinical pharmacology studies have not been performed with VariZIG™ as there is broad experience in humans with intravenous or intramuscular 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 intravenous acute toxicity study was conducted in mice with Rh_o(D) Immune Globulin (Human), WinRho®. An LD₅₀ was not determined, as the maximal dose used did not kill any experimental animals. A lower limit of 18,750 IU (3,750 µg) WinRho®/kg body weight, or 233 mg human IgG/kg, was established as the LD₅₀ for this drug. Neither observation nor necropsy of the experimental animals revealed any acute toxicity related to the study drug. Based on the maximum human IgG content of 200 mg per 125 Units dose of VariZIG™, 146 Units of VariZIG™ contains 233 mg of human IgG.

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 Planova™ 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 women¹⁸. 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.

REFERENCES

1. Bowman JM, Friesen AD, Pollock JM, Taylor WE. WinRho: Rh immune globulin prepared by ion exchange for intravenous use. Can Med Assoc J 1980; 123(11):1121-1127.
2. Friesen A, Bowman J, Price H. Column Ion-Exchange Preparation And Characterization Of An Rh Immune Globulin (WinRho) For Intravenous Use. Journal Of Applied Biochemistry 1981; 3(2):164-175.
3. Horowitz B. Investigations into the application of tri(n-butyl)phosphate/detergent mixtures to blood derivatives. Curr Stud Hematol Blood Transfus 1989;(56):83-96.

4. Unpublished viral validation on file. 2005.
5. Burnouf T. Value of virus filtration as a method for improving the safety of plasma products. *Vox Sang* 1996; 70(4):235-236.
6. Paryani SG, Arvin AM. Intrauterine infection with varicella-zoster virus after maternal varicella. *N Engl J Med* 1986; 314(24):1542-1546.
7. Zaia JA, Levin MJ, Preblud SR, Leszczynski J, Wright GG, Ellis RJ et al. Evaluation of varicella-zoster immune globulin: protection of immunosuppressed children after household exposure to varicella. *J Infect Dis* 1983; 147(4):737-743.
8. Varicella-zoster immune globulin for the prevention of chickenpox. Recommendations of the Immunization Practices Advisory Committee, Centers for Disease Control. *Ann Intern Med* 1984; 100(6):859-865.
9. Orenstein WA, Heymann DL, Ellis RJ, Rosenberg RL, Nakano J, Halsey NA et al. Prophylaxis of varicella in high-risk children: dose-response effect of zoster immune globulin. *J Pediatr* 1981; 98(3):368-373.
10. Wolberg AS, Kon RH, Monroe DM, Hoffman M. Coagulation factor XI is a contaminant in intravenous immunoglobulin preparations. *Am J Hematol* 2000; 65(1):30-34.
11. Dalakas MC. High-dose intravenous immunoglobulin and serum viscosity: risk of precipitating thromboembolic events. *Neurology* 1994; 44(2):223-226.
12. Woodruff RK, Grigg AP, Firkin FC, Smith IL. Fatal thrombotic events during treatment of autoimmune thrombocytopenia with intravenous immunoglobulin in elderly patients. *Lancet* 1986; 2(8500):217-218.
13. Perazella MA, Cayco AV. Acute renal failure and intravenous immune globulin: sucrose nephropathy in disguise? *Am J Ther* 1998; 5(6):399-403.
14. Cayco AV, Perazella MA, Hayslett JP. Renal insufficiency after intravenous immune globulin therapy: a report of two cases and an analysis of the literature. *J Am Soc Nephrol* 1997; 8(11):1788-1794.
15. Centers for Biologics Evaluation and Research FDA. Important Drug Warning ("Dear Doctor") letter. 1998.

16. Rizk A, Gorson KC, Kenney L, Weinstein R. Transfusion-related acute lung injury after the infusion of IVIG. *Transfusion* 2001; 41(2):264-268.
17. Burks AW, Sampson HA, Buckley RH. Anaphylactic reactions after gamma globulin administration in patients with hypogammaglobulinemia. Detection of IgE antibodies to IgA. *N Engl J Med* 1986; 314(9):560-564.
18. Koren G, Money D, Boucher M, Aoki F, Petric M, Innocencion G et al. Serum concentrations, efficacy, and safety of a new, intravenously administered varicella zoster immune globulin in pregnant women. *J Clin Pharmacol* 2002; 42(3):267-274.
19. Bowman JM, Chown B, Lewis M, Pollock JM. Rh isoimmunization during pregnancy: antenatal prophylaxis. *Can Med Assoc J* 1978; 118(6):623-627.
20. Bowman JM. The prevention of Rh immunization. *Transfus Med Rev* 1988; 2(3):129-150.
21. Miura M, Katada Y, Ishihara J. Time interval of measles vaccination in patients with Kawasaki disease treated with additional intravenous immune globulin. *Eur J Pediatr* 2004; 163(1):25-29.
22. Ruderman JW, Barka N, Peter JB, Stiehm ER. Antibody response to MMR vaccination in children who received IVIG as neonates. *Am J Dis Child* 1991; 145(4):425-426.
23. Roche B, Samuel D. Liver transplantation for hepatitis B virus-related liver disease: indications, prevention of recurrence and results. *J Hepatol* 2003; 39 Suppl 1:S181-S189.
24. Hong F, Ruiz R, Price H, Griffiths A, Malinoski F, Woloski M. Safety profile of WinRho anti-D. *Semin Hematol* 1998; 35(1 Suppl 1):9-13.
25. Bussel JB, Eldor A, Kelton JG, Varon D, Brenner B, Gillis S et al. IGIV-C, a novel intravenous immunoglobulin: evaluation of safety, efficacy, mechanisms of action, and impact on quality of life. *Thromb Haemost* 2004; 91(4):771-778.
26. Scaradavou A, Woo B, Woloski BM, Cunningham-Rundles S, Ettinger LJ, Aledort LM et al. Intravenous anti-D treatment of immune thrombocytopenic purpura: experience in 272 patients. *Blood* 1997; 89(8):2689-2700.
27. Unpublished data on file, VZ-001 study report. 2005.
28. Unpublished data on file, VZ-003 study report. 2005.

29. Enders G. Management of varicella-zoster contact and infection in pregnancy using a standardized varicella-zoster ELISA test. *Postgraduate Med. J* 1985; 61(Suppl. 4), 23-30.
30. Unpublished data on file, WS-031 study report. 2005.
31. Unpublished data on file, WS-029 study report. 2005.
32. Unpublished data on file, HB-002 study report. 2005.
33. Unpublished data on file, WS-038 study report. 2005.
34. Unpublished data on file, HB-008 study report. 2005.
35. Unpublished data on file, WS-031 study report. 2001.
36. Unpublished data on file, HB-002 study report. 2001.
37. Unpublished data on file, WS-038 study report. 2004.
38. Unpublished data on file, WS-029 study report. 2004.
39. Committee for medicinal products for human use. Core SPC for human varicella immunoglobulin for intramuscular use. European Medicines Agency . 2005.
40. Finlayson JS, Tankersley DL. Availability of intramuscular immunoglobulin. *Lancet* 1984; 2(8397):296-297.
41. Wallace MR, Bowler WA, Murray NB, Brodine SK, Oldfield EC, III. Treatment of adult varicella with oral acyclovir. A randomized, placebo-controlled trial. *Ann Intern Med* 1992; 117(5):358-363.
42. Enders G, Miller E, Cradock-Watson J, Bolley I, Ridehalgh M. Consequences of varicella and herpes zoster in pregnancy: prospective study of 1739 cases. *Lancet* 1994; 343(8912):1548-1551.

PART III: CONSUMER INFORMATION

VariZIG™

Varicella Zoster Immune Globulin (Human)

This leaflet is part III of a three-part "Product Monograph" published when VariZIG™ was approved for sale in Canada and is designed specifically for Consumers. This leaflet is a summary and will not tell you everything about VariZIG™. Contact your doctor or pharmacist if you have any questions about the drug.

ABOUT THIS MEDICATION

What the medication is 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).

What it does:

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.

When it should not be used:

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

What the medicinal ingredient is:

Varicella Zoster Immune Globulin (Human)

What the important nonmedicinal ingredients are:

Human plasma protein

Sodium Chloride

Glycine

Polysorbate 80

VariZIG™ may contain trace amounts of tri-n-butyl phosphite and Triton X-100®.

What dosage forms it comes in:

VariZIG™ is provided in single use 6 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. VariZIG™ will be administered either intravenously or intramuscularly.

WARNINGS AND PRECAUTIONS

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.**

BEFORE you receive VariZIG™ talk to your doctor or pharmacist if:

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

INTERACTIONS WITH THIS MEDICATION

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.

PROPER USE OF THIS MEDICATION

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:

The consequences of an overdose are not known. In case of an overdose, consult your doctor.

SIDE EFFECTS AND WHAT TO DO ABOUT THEM

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.

This is not a complete list of side effects. For any unexpected effects while taking VariZIG™, contact your doctor or pharmacist.

SERIOUS SIDE EFFECTS, HOW OFTEN THEY HAPPEN AND WHAT TO DO ABOUT THEM

Symptom / effect		Talk with your doctor or pharmacist		Stop taking drug and call your doctor or pharmacist
		Only if severe	In all cases	
Common	Not applicable*			
Uncommon	Allergic reaction		✓	✓

*Serious side effects are not common.

HOW TO STORE IT

Store VariZIG™ under refrigeration. Do not freeze. Do not use after expiration date.

Keep out of reach of children.

REPORTING SUSPECTED SIDE EFFECTS

To monitor drug safety, Health Canada collects information on serious and unexpected effects of drugs. If you suspect you have had a serious or unexpected reaction to this drug you may notify Health Canada by:

toll-free telephone: 866-234-2345
 toll-free fax: 866-678-6789
 By email: cadmp@hc-sc.gc.ca

By regular mail:
 National AR Centre
 Marketed Health Products Safety and Effectiveness
 Information Division
 Marketed Health Products Directorate
 Tunney's Pasture, AL 0701C
 Ottawa ON K1A 0K9

NOTE: Before contacting Health Canada, you should contact your physician or pharmacist.

MORE INFORMATION

This document plus the full product monograph, prepared for health professionals can be found at:
http://www.cangene.com/pdf/vz_mono_e.pdf
 or by contacting Cangene Corporation's Pharmacovigilance Department at 1-800-768-2304 (phone) or 1-800-768-2281 (fax).

This leaflet was prepared by Cangene Corporation.

Last revised: January 3, 2008.