

DE Pharmacovigilance Plan Review Memo

From:	<i>David Menschik, Medical Epidemiologist</i>
To:	<i>Pei Zhang, Chair</i>
Through:	<i>Chris Jankosky, Acting Branch Chief David Martin, DE Director</i>
Subject:	<i>Pharmacovigilance Plan Review</i>
Applicant:	<i>Cangene Corporation</i>
Product:	<i>Varicella Zoster Immune Globulin (Human)</i>
Proposed Trade Name	<i>VariZIG®</i>
Proposed Indication:	<i>For post-exposure prophylaxis of varicella in high risk individuals</i>
Current Indication:	<i>N/A</i>
Submission type (original BLA, supplement, labeling supplement, etc.)	<i>Original BLA submission</i>
Serial Tracking Number	<i>125430/0</i>
Submission Date:	<i>June 29, 2012</i>
PVP Submission Date (if applicable):	<i>July 30, 2012</i>
Action Due Date:	<i>December 28, 2012 (accelerated approval)</i>

1. Introduction

A. Epidemiological Background and Public Health Context:

Varicella zoster virus (VZV) infection generally causes a relatively benign highly contagious disease in immune competent children. However, VZV disease can be severe with significant morbidity and mortality in newborns infants and pregnant women, as well as other immunocompromised, immunodeficient or immunosuppressed patients, and sometimes in otherwise healthy adults. Since the live virus vaccine is contraindicated in newborns infants and pregnant women, and is not approved for use under 12 months of age¹, VZV Immune Globulin (VZIG) offers an alternative means to prevent varicella or mitigate the risks of severe varicella complications including pneumonia, encephalitis and death. The Centers for Disease Control and Prevention recommends VZIG administration in persons at high risk for severe varicella who are not eligible to receive varicella vaccine.² Recommended indications include:

- newborns whose mothers have varicella from 5 days before to 2 days after delivery
- premature babies exposed to varicella in their first month of life, specifically:
 - premature infants born at ≥ 28 weeks of gestation who are exposed during the neonatal period and whose mothers do not have evidence of immunity
 - Premature infants born at < 28 weeks of gestation or who weigh $\leq 1,000$ grams at birth and were exposed during the neonatal period regardless of maternal immunity
- children with leukemia or lymphoma who have not been vaccinated
- people with cellular immune-deficiencies or other immune system problems
- people on medications (e.g., high-dose systemic steroids) that suppress the immune system
- pregnant women without evidence of immunity to varicella

The Advisory Committee on Immunization Practices (ACIP) has recommended that individuals without evidence of immunity³ who are eligible to receive varicella vaccine and are exposed to varicella or herpes zoster receive varicella vaccine ideally within 3-5 days after exposure. Recently, the recommended post-exposure interval for administration in the US has been expanded to ten days (though earlier is better).^{4,5} Additional recommendations for use of varicella vaccine in post-exposure settings can be found on the CDC website.⁶

B. Product description:

¹ Merck and Company. VARIVAX package insert, August 2011

² Centers for Disease Control and Prevention. Managing Persons at risk for Severe Varicella; Prevention for Susceptible Persons Who Cannot Receive Varicella Vaccine. Accessed July 26, 2012 at: <http://www.cdc.gov/chickenpox/hcp/persons-risk.html>

³ Centers for Disease Control and Prevention. Assessing Immunity to Varicella. Accessed August 27, 2012 at: <http://www.cdc.gov/chickenpox/hcp/immunity.html>

⁴ Food and Drug Administration. Varicella zoster immune globulin (VZIG) anticipated short supply and alternate product availability under an investigational new drug application expanded access protocol. Rockville, MD: US Department of Health and Human Services, Food and Drug Administration; 2006. Accessed July 26, 2012 at: <http://www.fda.gov/biologicsbloodvaccines/safetyavailability/ucm176029.htm>

⁵ Centers for Disease Control and Prevention. FDA Approval of an Extended Period for Administering VariZIG for Postexposure Prophylaxis of Varicella. *Morb Mortal Wkly Rep*. 2012 Mar 61(12):212.

⁶ Centers for Disease Control and Prevention. Post-exposure Varicella Vaccination. Accessed August 27, 2012 at: <http://www.cdc.gov/vaccines/vpd-vac/varicella/hcp-post-exposure.htm>

VariZIG (Note: proposed trade name used, though trade name approval pending to date), Varicella Zoster Immune Globulin (Human), is a sterile freeze-dried gamma globulin (IgG) fraction of human plasma containing antibodies to varicella zoster virus. VariZIG is provided as a lyophilized powder vial contained in a kit with sterile diluent for administration as intramuscular injection. Reconstituted VariZIG contains no preservatives and is intended for single use. VariZIG does not contain —b(4)----- VariZIG is purified from donor plasma pools containing high titers of antibodies (anti-VZV) to varicella zoster virus collected at plasma collection centers in the United States and Canada from donors who have been immunized or have naturally high titers of varicella zoster antibodies. In Canada, VariZIG is approved for intravenous (IV) or intramuscular (IM) administration; the proposed route of administration in the US is IM only.

C. Proposed indication: (verbatim from BLA submission)

Post-exposure prophylaxis in high risk individuals. High risk individuals include:

- Immunocompromised children and adults,
- Newborns of mothers with varicella shortly before or after delivery,
- Premature infants,
- Infants less than one year of age,
- Adults without evidence of immunity and Pregnant women.

VariZIG administration is intended to prevent or reduce the severity of varicella.

Note: These subpopulations intended for approval are consistent with those in the prior US licensed product⁷ to which pharmacokinetic non-inferiority and/or bioequivalence is being sought in this BLA application.

D. Proposed dosage: (verbatim from BLA submission)

For post-exposure prophylaxis in high risk individuals the minimum dose is 62.5 International Units (IU) for small infants under two kilograms (kg) body weight; the maximum dose is 625 IU for all patients greater than 40 kg in weight. A single dose of VariZIG should be administered intramuscularly (IM) as recommended:

Weight of Patient		VariZIG Dose
Kilograms	Pounds	IU
≤ 2.0	≤ 4.4	62.5
2.1 - 10.0	4.5 - 22.0	125
10.1 - 20.0	22.1 - 44.0	250
20.1 - 30.0	44.1 - 66.0	375
30.1 - 40.0	66.1 - 88.0	500
≥ 40.1	≥ 88.1	625

A second full dose of VariZIG should be considered for high risk patients who have additional exposure to varicella greater than three weeks after initial VariZIG administration.

E. Regulatory background

VariZIG has not previously been licensed in the US and this represents its initial BLA submission. The sponsor is seeking an ‘orphan’ designation for this product. A different VZIG product was discontinued by its manufacturer (Massachusetts Public Health Biological

⁷ Massachusetts Public Health Biologic Laboratories. VARICELLA-ZOSTER IMMUNE GLOBULIN (HUMAN) package inset. April, 2000.

Laboratories) in 2004 and is currently not available on the US Market. The sponsor requested that this BLA for VariZIG receive priority review particularly since this product fulfills an important unmet public health need (e.g., protecting vulnerable populations, in which varicella virus vaccine is contraindicated, from varicella zoster virus infection and sequelae) with no similar product licensed and available in the US. VariZIG has been available in the US via an expanded access protocol (VZ-009) as an investigational product (i.e., under IND 7201) described elsewhere.⁸ VariZIG is also available to US patients not meeting VZ-009 selection criteria via FDA emergency use/compassionate use authorization (21 CFR 312 Subpart 1).

F. Foreign Experience:

VariZIG was first registered on January 18, 2001 in Canada, and is not currently licensed in any other country. VariZIG is licensed in Canada for the prevention or reduction in severity of maternal infections within four days of exposure to VZV. Since initial market launch in March 2006, VariZIG has not been withdrawn from any market for safety reasons. During the most recent PSUR (included in this BLA submission) reporting period (1/18/2011 – 1/17/2012), an estimated –b(4)- vials were distributed to Canada (-b(4)- vials), US (b(4) vials) and the United Arab Emirates (b(4) vials). Of the vials distributed, an estimated b(4) doses of VariZIG (assuming the maximum 625 IU per dose) were administered to patients during this period. The sponsor reports that there have been no spontaneous adverse event reports after an estimated –b(4)--- marketed doses administered since product launch in March 2006. The sponsor states that a review of safety information through product launch in March 2006 reveals no adverse events that constitute a safety concern and that there have been no case reports of adverse events associated with off-label use since product launch in March 2006. The sponsor reports that there are no regulatory actions recommended for VariZIG and that the sponsor will continue to perform routine pharmacovigilance activities.

2. Materials reviewed

Materials reviewed in support of this assessment include:

- A. Pharmacovigilance plan
- B. Periodic surveillance update reports (reporting periods covering from 1/18/06-1/17/12)
- C. Original BLA cover letter
- D. Summary of clinical safety (selected portions)
- E. Proposed package insert
- F. VariZIG product monograph 2008 (Canadian label)
- G. Medical Literature (including references in footnotes)
- H. Sponsor's IR response letter dated 8/15/12
- I. Input from BLA review team members (e.g., verbal or written communications with other discipline reviewers)

3. Pharmacovigilance Plan Review

A. Sources of Exposure Data:

i. Clinical Trials:

There were a total of 457 individuals administered VariZIG among five clinical trials, with doses ranging from 10-50 IU/kg (maximum 625 IU) and with a majority receiving doses IM (as opposed to IV). Drug exposure by age group and gender are summarized in the following table:

⁸ Centers for Disease Control and Prevention. A New Product (VariZIG) for Postexposure Prophylaxis of Varicella Available Under an Investigational New Drug Application Expanded Access Protocol. *Morb Mortal Wkly Rep*. 2006 Mar 3;55(8):209-10.

AGE GROUP AND GENDER				
TOTAL				
Age group	Persons		Person time	
	Male	Female	Male	Female
Pediatric Population (overall)	139	134	Single dose IM or IV	
< 1 year	69	52	Single dose IM	Single dose IM
1 – 2 years	9	16	Single dose IM	Single dose IM or IV
3 – 11 years	47	42	Single dose IM	Single dose IM
12 – 18 years	14	24	Single dose IM or IV	Single dose IM
Adult Population (overall)	34	132	Single dose IM or IV	
19 – 39 years	29	121	Single dose IM	Single dose IM or IV
40 – 64 years	5	11	Single dose IM	Single dose IM
Geriatric Population (overall)	7	11	Single dose IM or IV	
> 65 years	7	11	Single dose IM or IV	Single dose IM or IV

Drug exposures by special populations are summarized as follows:

SPECIAL POPULATIONS		
INDICATION: Post-exposure prophylaxis of varicella		
	Persons	Person time
Pregnant women	121	Single dose IM or IV
Lactating women	0	N/A
Hepatic impairment	0	N/A
Renal impairment	0	N/A
Cardiac impairment	0	N/A
Sub populations with genetic polymorphism	0	N/A
Immunocompromised adults	22	Single dose IM
Immunocompromised pediatric patients	152	Single dose IM or IV
Infants (< 1 year old)	113	Single dose IM

The sponsor reports that it has received five case reports of serious adverse events from clinical trials and one from the special access program for compassionate use since product launch in March 2006. The five former cases were reported in VZ-009 and include the following adverse events: convulsion, drug ineffective, medication error, nausea and vomiting, hypersensitivity and serum sickness, varicella infection and varicella virus test negative. In the latter single case report, the patient developed renal failure and glomerulonephritis. The sponsor states (in the PVP and in an information request response referenced in note below) that all of the reported serious ADRs were isolated cases.

Reviewer note: The sponsor subsequently clarified in a written response that cases included in the PVP such as those above were assessed as possibly related to VariZIG and that cases assessed as unrelated to VariZIG were not included as they are not ADRs per ICHE6.⁹

- ii. Epidemiological Study Exposure: none
- iii. Postmarketing (non study) Exposure: VariZIG is only indicated abroad (in Canada) in pregnant women (although the Canadian National Advisory Committee on Immunization recommends broader use). As above, an estimated –b(4)-- doses of

⁹ Cangene Corporation. Response to FDA Information Request Dated August 15, 2012. (Application number 125430\0\4 received by CBER on August 22, 2012.

marketed VariZIG doses have been administered since product launch in March 2006. As of the PVP submission date (7/30/2012), the sponsor has not received any spontaneous post-marketing AE/ADR reports involving VariZIG exposure.

- iv. Populations underrepresented or not represented (per sponsor) in clinical trials include:
- 1) Healthy non-immune adults
 - 2) Patients with hepatic, renal and/or cardiac impairments
 - 3) Patients with other co-morbidities (e.g., cardiac disorders)
 - 4) Geriatric population
- Reviewer note: It is unclear to date if other study populations, particularly neonates and neonatal subpopulations (e.g., varying extents of prematurity, low or very low birth weight) are adequately represented in clinical trials.

B. Safety concerns

1. Important identified safety issues: The sponsor states (Section 1.4.1) that there are no identified safety concerns related to VariZIG exposure that require further evaluation.

2. Important potential safety issues:

The sponsor states (Section 1.4.2) that there are no potential safety concerns related to VariZIG postmarketing surveillance that require further evaluation of the product. The sponsor acknowledges that general *class-specific* events have been reported for IVIG and hyperimmune products administered intravenously. Accordingly, VariZIG could potentially result in hypersensitivity reactions in individuals with IgA deficiency, thrombotic events, and coagulation disorders due to procoagulant activity (e.g., due to elevated factor XIa).

A. Hypersensitivity (1.4.2.1)

1. Nature of risk: Depending on factors such as hypersensitivity type and severity, hypersensitivity reactions after immune globulin products can range from minor discomfort to death secondary to anaphylaxis if untreated.
2. Potential mechanisms: Type I, Type II, Type III, Type IV reactions
3. Background incidence: estimated at 20-21 cases per 100,000 exposed to immune globulin products (no postmarketing reports identified in association with VariZIG).
4. Risk factors/groups include: Individuals with IgA deficiency may develop IgA antibodies to the trace IgA quantities in VariZIG resulting in hypersensitivity reactions including urticaria, chest tightness, wheezing, hypotension and/or anaphylaxis. Additionally, individuals with hypersensitivity to blood products may develop allergic or anaphylactoid reactions following VariZIG.

B. Thrombotic Events (TEs)/ Coagulation Disorders (1.4.2.2)

1. Nature of risk: Exposure to immune globulin products has been associated with life-threatening thrombosis in pulmonary, coronary, cerebral and peripheral vessels. Such events are likely to occur during or within 24 hours of administration.
2. Potential mechanisms: unknown; high dosage and/or rapid infusion rate may increase blood viscosity or procoagulant activity (e.g., due to factor XIa).
3. Background incidence: Estimated venous TE incidence is 150-180 per 100,000. In the general population, 13 to 14 per 1,000 hospitalized patients develop postoperative pulmonary embolism. Deep vein thrombosis (DVT) has an annual incidence of 117 cases per 100,000. One fourth of the patients who develop DVT are complicated by pulmonary embolism.

4. Risk factors/groups include: Individuals with a history of atherosclerosis, multiple cardiovascular risk factors, advanced age, impaired cardiac output, coagulation disorders, prolonged periods of immobilization, and/or known/suspected hyperviscosity.

The sponsor summarizes the above potential risks (both pharmacological class effects) in the following table:

Risk	Frequency in clinical trials of Medicinal product	Frequency seen with other products in same pharmacological class (source of data/journal reference)	Comment
Hypersensitivity	One case of hypersensitivity (reporting allergic reaction and serum sickness), has been reported during clinical trials involving VariZIG.	Rare cases of true allergic reactions including anaphylaxis have been reported in the medical literature with similar products (VZIG, GamaSTAN® S/D as per labelling.	Hypersensitivity has been associated with the use of immunoglobulins. To date, no spontaneous post-marketing cases reporting hypersensitivity reactions associated with VariZIG have been received.
Thrombotic Events (Pulmonary embolism, deep vein thrombosis) /Coagulation Disorders	No cases of embolism have been reported during clinical trials attributed to with the use of VariZIG in clinical trials.	Products like Gamunex®, GamaSTAN® S/D, Gammagard® and Gamimune® the labelling includes information regarding thromboembolic events	Although reports of thromboembolism have been reported with the use of other immunoglobulins, there have been no reports of thromboembolism with the use of VariZIG.

C. Other potential concerns:

- i. **Drug interactions:** The passive transfer of antibodies with immune globulin administration may impair the efficacy of live attenuated virus vaccines such as measles, rubella, mumps and varicella. The proposed label advises to “(d)efer vaccination with live virus vaccines until approximately three months after VariZIG administration. Inform the immunizing physician of recent therapy with VariZIG so that appropriate measures can be taken.”
- ii. **Transmission of adventitious agents:** Despite a number of measures taken during the manufacturing process to decrease the risk of transmitting adventitious agents, a potential inherent risk remains. Since product launch in March 2006, the sponsor has not received any post-marketing reports of blood borne infections involving VariZIG

D. Potential for off-label use:

If any proposed indications/ages are not approved, there would be potential for off label use, particularly if supported by CDC recommendations. Assuming all proposed indications are approved, there would still be the potential for use to treat varicella or related conditions (e.g., post-herpetic neuralgia) rather than to prevent or reduce the severity of varicella in a post-exposure setting.

E. Sponsor’s proposed action plans for potential risks (no *identified* risks):

Safety Concern	Planned Action(s)
Hypersensitivity	Routine Pharmacovigilance Activities Signal Detection Labelling: Proposed US labeling will include language in CONTRAINDICATIONS excluding use of the product in individuals who are deficient in IgA, or have a history of anaphylactic or other systemic reactions to immune globulins. Note that all cases reporting hypersensitivity will be monitored regardless of their severity.
Thromboembolic Events/Coagulation disorders	Routine Pharmacovigilance Activities Signal Detection Labelling: Proposed US labelling will include language in the WARNINGS AND PRECAUTIONS indicating that there is a potential risk of thrombotic events/coagulation disorders following administration of immune globulin products. Patients at risk of TEs include those with a history of atherosclerosis, multiple cardiovascular risk factors, advanced age, impaired cardiac output, coagulation disorders, prolonged periods of immobilization, and /or suspected hyper viscosity. Baseline assessments of blood viscosity (including those for cryoglobulins, fasting chylomicronemia/markedly high triacylglycerols (triglycerides), or monoclonal gammopathies) should be considered in patients at risk of hyperviscosity. For coagulation disorders, IM administration of VariZIG is advised. In addition, for patients with severe thrombocytopenia or any coagulation disorder that would contraindicate IM injections, the expected benefits of VariZIG should outweigh the risks. Note that all cases reporting TEs/Coagulation disorders will be monitored regardless of their severity.

- No additional surveillance activities or postmarketing studies planned

4. Review of other information from the Managed Review process

At the BLA mid-cycle review meeting held on 10/1/2012, no discipline reviewer identified any known serious risk or signal of a serious risk for VariZIG and there were no recommendations for any PMR or additional pharmacovigilance measures.

5. Postlicensure Safety Review

- A. Worldwide: Please see section 1F above for international postmarketing findings reported in most recent periodic surveillance update report. No AERS reports identified for this product.
 - i. An exploratory query of AERS since 1/1/2000 for any reported adverse event after any VZIG product revealed a total of 9 cases (6 serious including one death; 5 foreign) classified as follows: Hepatitis C transmission (n= 4; all foreign reports), 'lack of efficacy' (i.e., symptoms attributed to varicella despite VZIG receipt; n=3; 1 foreign report of fatal hemorrhagic varicella) and allergic reactions (n=2; both non-serious).
- B. U.S: not applicable (original BLA submission)

6. Integrated Risk Assessment

The above pharmacovigilance plan proposed by the sponsor appears adequate. To date, no discipline reviewer on this BLA committee has identified any known serious risk or signal of a serious risk for VariZIG that would warrant additional pharmacovigilance measures (e.g., PMR or REMS).

7. Conclusions/Recommendations

- A. The sponsor's plan to conduct routine pharmacovigilance practices appears adequate.
- B. Postmarketing adverse experiences should be reported to CBER in accordance with 21 CFR 600.80.
- C. Distribution reports should be provided to CBER in accordance with 21 CFR 600.81
- D. No REMS is warranted at this time
- E. No postmarketing safety studies are required at this time