

From: Cagungun, Nannette
Sent: Thursday, October 04, 2012 12:15 PM
To: 'Terry Kraynyk'
Cc: Virata, Maria Luisa; Zhang, Pei
Subject: Information Request- Varizig

Importance: High

Our Reference: STN 125430/0

Cangene Corporation
Attention: Mr. Terry Kraynyk
October 4, 2012

Dear Mr. Kraynyk:

We are reviewing your biologics license application for Varicella Zoster Immune Globulin (Human) submitted on June 29, 2012 for post-exposure prophylaxis of varicella in high-risk individuals. We have the following request for information:

BIMO

The following questions 1-7 pertain to Study VZ-009:

1. Please provide documentation showing the specific dates that each clinical investigator at each study site was contacted by FFF Enterprises for follow-up after the investigator requested his / her use of Varizig.
2. Please provide documentation showing the specific dates each clinical investigator signed and returned the Form FDA 1572, *Statement of Investigator*, to the sponsor.
3. Please furnish a copy of the complete sponsor instructions (standard operating procedure and/or training manual) telling VZ-009 clinical investigators how to enroll subjects, complete the case report forms, utilize any computer system after subject enrollment, and report the data. Please furnish documentation showing how and when the sponsor furnished these instructions to each clinical investigator
4. Please furnish a complete description of how the sponsor assigned individual subject numbers, including a list of any subject numbers assigned, re-used subject numbers, or reassigned subject numbers from other study sites. Please describe how the sponsor determined whether or not a specific subject number was or was not used.

5. Please provide a copy of all written instructions given to each study site for shipment receipt, storage and handling of Varizig. Please furnish representative copies of Varizig labels used for shipments sent to each study site.
6. Please describe your monitoring activities for all VZ-009 study sites and include a complete list of all site monitoring visits throughout the study.
7. Please provide a complete description of how test article accountability was reviewed during monitoring visits. Please furnish a copy of documentation showing the study monitor accounted for all vials of Varizig used during the study.

CMC

8. Please provide the robustness studies conducted for the anion-exchange chromatography step to determine viral clearance capacity during extremes of the process parameters including ----b(4)-----

9. Please confirm that --b(4)----- will be performing the viral NAT testing of the plasma minipools, and that the --b(4)----- will be performing the viral NAT testing of the plasma manufacturing pools.
10. Please provide the pool sizes, NAT sensitivities, and cut-off levels for minipool testing and original single plasma donation for each of the viruses tested.
11. Please provide the pool sizes, NAT sensitivities, and cut-off levels for manufacturing pool testing for each of the viruses tested.
12. Please provide a detailed summary about how the quarantine and proper disposal of NAT-positive donations for HIV/HBV/HCV/HAV/parvovirus B19 are done.
13. You did not list a drug product specification for appearance in Section 3.2.P.5.1. Please set two specifications for appearance (one for the lyophilized product, one for the reconstituted product) in order to ensure the product quality of Varizig. In addition, please provide your method SOP for visual inspection of a lyophilized product and a reconstituted product.

DBSQC

14. Please provide the Lot Release Testing Protocol template for Varizig.

DMPQ

15. Please clarify the following equipment cleaning procedures:

- a. Define the Manual and Cleaning-in-Place cleaning solutions, concentrations, and washing conditions (temperature, duration, conductivity)
- b. Define how the -----b(4)-----
will be cleaned, stored and tested before potential re-use and expiration

CLINICAL

16. Antibodies against human protein S of the coagulation system have been observed in patients who experienced post-infectious purpura fulminans after varicella infection (e.g., see *Journal of Thrombosis and Haemostasis* **3**: 1243–1249 (2005).

----b(4)-----

17. Adverse event monitoring and causality categorization appears to be inconsistent between studies VZ-006 and VZ-009. Following are examples of these inconsistencies:

- a. On June 22, 2006, there was a varicella exposure incident in the NICU at Wesley Medical Center in Wichita, KS. Thirteen (13) premature infants were treated with VariZIG i.m. There were 21 non-serious adverse events in 6 subjects, and 10 serious adverse events (including 2 deaths) in 3 subjects, as shown in the following table:

SUBJID	Non-Serious AE	Serious AE	Day after last dose
--b(6)----- -----			
--b(6)----- -----	Dermatitis Diaper		4
	Haematochezia		5
--b(6)----- -----			
--b(6)----- -----			
--b(6)----- -----			
--b(6)----- -----			
--b(6)----- -----	Metabolic Acidosis		2
	Hypoalbuminaemia		6
--b(6)----- -----	Hypothermia		5
	Sepsis		5

--b(6)----- -----	Haematochezia		3
		Death [Bronchopulmonary Dysplasia]	6
--b(6)----- -----		Intraventricular Haemorrhage	1
		Disseminated Intravascular Coagulation	2
		Convulsion	2
		Pulmonary Haemorrhage	2
		Death	3
--b(6)----- -----	Sepsis		4
	Metabolic Acidosis		15
	Skin Disorder “Skin Breakdown”		21
--b(6)----- -----		Staphylococcal Sepsis	3
		Coagulopathy	6
		Thrombocytopenia	6
	Convulsion		6
	Hypotension		8
	Pneumonia		9
	Metabolic Acidosis		9
	Adrenal Insufficiency		13
	Dermatitis Diaper		14
	Hydronephrosis		22
	Bronchopulmonary Dysplasia		25
	Staphylococcal Sepsis		25
	Pneumonia		28
	Necrotising Enterocolitis Neonatal		36
--b(6)----- -----			

In contrast to this, the VZ-009 study report (page 47 of 306) states “9 pre-term infants (VM-00510 to VM-00518) exposed in the neonatal intensive care unit at Winthrop University Hospital in Mineola, NY; and five immunocompromised pediatric patients exposed at Children’s Hospital at Montefiore Bronx, NY were amongst 10 patients exposed to an immunocompromised host with zoster lesions.”

The ADMIN database shows that these premature infants were treated with Varizig on March 18, 2008; however, the AE database contains no adverse events for these subjects.

- b. The following table shows the causality profile across all reported adverse events in studies VZ-006 (maternal exposure) and VZ-009 (expanded access for high risk):

	Definitely Related	Probably Related	Possibly Related	Unlikely Related	Conditional
VZ-006 (N = 133 AEs)	26 (20%)	0 (0%)	13 (10%)	93 (70%)	1 (1%)
VZ-009 (N = 341 AEs)	4 (1%)	4 (1%)	17 (5%)	287 (84%)	27 (8%)

It can be seen that adverse events in study VZ-009 were only rarely categorized as “probably” or “definitely” related to NP001 administrations, whereas adverse events judged “definitely” related accounted for 20% of the adverse events, perhaps including adverse events that other might categorize as “probably” related.

For example in study VZ-006 (N = 60), the adverse events “Injection Site Pain”, “Injection Site Haematoma”, “Injection Site Induration”, or “Injection Site Pruritus” occur in 20 subjects receiving intramuscular administration, and for 19 of these 20 cases the event is judged “definitely” related to the product. However, in study VZ-009 (N = 372), the adverse events “Injection Site Paraesthesia” and “Injection Site Haematoma” occur in just 2 subjects, judged “definitely” and “probably” related, respectively. Study VZ-009 predominantly used the intramuscular route of administration, rendering these differences difficult to interpret.

Attribution of causality is a judgment arrived at by the investigator, followed by a re-assessment by the sponsor. It is clear that different assessment procedures were followed in these two studies, thereby confounding the analysis of the safety profile of this product.

Therefore, please revise the adverse events databases for 1) completeness, 2) appropriate seriousness categorization, and 3) causality assessment, and submit the revised adverse events databases to this BLA.

18. Please submit the 95% confidence intervals for the infection rates observed in study VZ-006 for stratum 1 (1-4 days since exposure) and for stratum 2 (5-14 days since exposure).

PVP

19. You list 'signal detection' as a planned action (e.g., in the context of potential risks such as hypersensitivity reactions) in your pharmacovigilance plan. Can you please clarify/elaborate on your specific signal detection methods?

Please submit your response to this information request as an amendment to this file by October 18, 2012 referencing the date of this request. If you anticipate you will not be able to respond by this date, please contact the Agency immediately so a new response date can be identified.

If you have any questions, please contact me at (301) 827-6174.

Sincerely,

Nannette Cagungun, MS, PD, RAC
Regulatory Project Manager
OBRR/CBER/FDA, HFM-380
1401 Rockville Pike Rockville, MD 20852-1448
Tel: (301) 827 6174
Fax: (301) 827 2857
Email: nannette.cagungun@fda.hhs.gov

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