



Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Biologics Evaluation and Research

BLA: 125430/0

From: Evi Struble, Ph.D., Pharmacologist, CBER, DH, LPD

Through: Dorothy Scott, M.D., Laboratory Chief, CBER, DH, LPD

CC: Pei Zhang, PhD
Nannette Cagungun, RPM

Applicant: Cangene Corporation

Product: Varicella Zoster Immune Globulin (Human), Intramuscular

Indication: For post-exposure prophylaxis of varicella in high risk individuals

Subject: Preclinical Pharm-Tox Review

Executive Summary

There were no pharmacology and toxicology studies performed with the preparation. Given the preclinical and clinical experience with immune globulin products produced from the –b(4)-----, this is considered acceptable. A risk analysis of the excipients and impurities was performed that raised no toxicological concerns for the preparation. As such, there are no preclinical pharmacology and toxicology issues that would prevent the preparation from being approved.

1. Recommendations

There are no preclinical pharm/tox issues that would prevent this application from being approved.

2. Introduction

VariZIG is prepared by an anion-exchange column chromatography method, has a pH range of –b(4)----- and is formulated with 0.1 M glycine, 0.01% PS80 and 0.04 M NaCl. The final product is supplied in two vials: one containing lyophilized VariZig (–b(4)–, potency b(4)125 IU for each vial) and one containing Sterile Diluent for reconstitution (–b(4)– containing 0.8% –b(4)----- NaCl, 10 mM phosphate –b(4)-----). The potency is expressed in International Units (IU) comparing it to the WHO international anti-varicella zoster immune globulin standard.

Indication: VariZIG is indicated for post-exposure prophylaxis of high risk individuals that 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, pregnant women and is intended to prevent or reduce the severity of varicella.

Dose: Single use by IM administration at a dose 125 IU (1 vial) per 10 kg body weight, up to a maximum of 625 IU (5 vials of VariZIG for a body weight greater than 40 kg).

3. Pharmacology and Toxicology

There were no pharmacology and toxicology studies performed with the preparation. A risk analysis of the excipients and impurities was performed that concluded there are no concerns with the preparation. This reviewer agrees with this conclusion.

In addition, the –b(4)----- immune globulin products (a comparison is shown in the table below). Although, these compounds in reconstituted VariZig are present at a higher concentration than in the IGIV products shown, please note that:

1. The maximum volume of injection for VariZig is 6 mL whereas for a 500 mg/kg dose of IGIV the volume of infusion would be 5 and 10 mL/kg (for 10 and 5% formulation, respectively), and
2. The release specifications for impurities (PS80, TnBP and Triton X) are similar to other IGIV products specifications (likely reflecting the analytical method limits). The higher values are due to a concentration effect following lyophilization and reconstitution of VariZig drug product.

Glycine	VariZig (Cangene) – ----b(4)----- Gamunex C 10% (Talecris) – -b(4)- 0.24 M (18 mg/ml) Gammagard Liquid 10% (Baxter) – NMT –b(4)---
Polysorbate 80	VariZig (Cangene) – NMT –b(4)----- -----b(4)-----
Residual TnBP	VariZig (Cangene) NMT –b(4)----- -----b(4)----- Octagam 5% (Octapharma) NMT 1 µg/mL
Triton X	VariZig (Cangene) NMT –b(4)----- Octagam 5% (Octapharma) NMT 5 µg/mL