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July 2015

# IMPORTANT DRUG WARNING

**Subject: Risk of Thrombotic Adverse Reactions with Anthrasil™, Anthrax Immune Globulin Intravenous (Human) [AIGIV]**

Dear Health Care Provider:

The purpose of this letter is to inform you of important safety information for Anthrasil, Anthrax Immune Globulin Intravenous (Human) [AIGIV].

The FDA has received post-marketing reports of serious thrombotic adverse reactions associated with administration of other marketed intravenous and subcutaneous immune globulin products (IGIV, IGSC) in a wide range of patient populations. These thrombotic events have been linked to measurable procoagulant activity in the immune globulin products (1, 2, 3, 4). Results of an in-house analysis revealed measurable levels of procoagulant activity (Factor XIa) in lots of Anthrasil. Safe levels of procoagulant activity have not been established. Thus, Anthrasil may present a potential risk for arterial and venous thrombosis. Patients with pre-existing thrombogenic risk factors are at greater risk. Patients at risk include those with cardiovascular risk factors, advanced age, impaired cardiac output, hypercoagulable disorders, prolonged periods of immobilization, history of arterial or venous thrombosis, estrogen use, indwelling central vascular catheters, and/or known or suspected hyperviscosity. For patients at risk of thrombosis, administer Anthrasil at the minimum infusion rate practicable. Ensure adequate hydration in patients before administration. Monitor for signs and symptoms of thrombosis and assess blood viscosity in patients at risk of hyperviscosity.

To mitigate the potential for development of thromboembolic events, changes to the manufacturing process for Anthrasil have been made to minimize the occurrence of procoagulant activity. The following lots manufactured prior to this change contain measurable levels of procoagulant activity:

- 10602912, 10804605, 10804812, 10805116, 10905931, 10906047, 10906095, 10906222

## Dosing and Administration

Anthrasil is an immune globulin product indicated for the treatment of inhalational anthrax in adult and pediatric patients in combination with appropriate antibacterial drugs.

Per the FDA approved package insert (PI), the initial dose of Anthrasil for the treatment of inhalational anthrax in adults in combination with appropriate antimicrobial therapy is 420 units (seven vials). An initial dose of 840 units (14 vials) may be considered, depending on the clinical

status of the patient. Depending on the severity of symptoms and the response to treatment, consider an initial dose of 840 units (14 vials) and repeat dosing especially in patients experiencing substantial hemorrhage as reflected in large transfusion requirements, patients with significant compartmental fluid losses such as from large volume and/or repeated therapeutic thoracentesis and/or abdominal paracentesis, and in patients whose own immune response may be impaired/delayed. Increasing the dose from 420 units to 840 units as well as repeat dosing may increase the risk of thrombotic events in patients with thrombogenic risk factors. Repeat dosing and single doses greater than 840 units in humans have not been studied.

**Prescriber Action**

Physicians should be aware of the risk of thrombotic events with the use of Anthrasil and refer to the Warnings and Precautions section of the Prescribing Information. The benefit of Anthrasil must be carefully balanced against the risk of thrombosis based on the clinical situation.

Physicians should inform patients and monitor for any symptoms of a thrombotic reaction, including shortness of breath, pain and swelling of a limb, focal neurological deficits, chest pain, and other manifestations of thrombotic and embolic events.

**Reporting Adverse Events**

Health care providers and patients are encouraged to report adverse events in patients taking Anthrasil to Cangene Pharmacovigilance at 1-800-768-2304. You also may report negative side effects to the U.S. Food and Drug Administration at 1-800-FDA-1088 or online at www.fda.gov/medwatch. Please provide the lot number(s) of products associated with reported adverse events whenever possible.

You may also contact our medical information department at medicalaffairs@ebsi.com if you have any questions about the information contained in this letter or the safe and effective use of Anthrasil.

This letter is not intended as a complete description of the benefits and risks related to the use of Anthrasil. Please refer to the enclosed Prescribing Information.

Sincerely,

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**References**


1. CSL Behring. Health Canada Endorsed Important Safety Information on Vivaglobin®: Risk of Thrombotic Events with Subcutaneous or Inappropriate Intravenous Use of Vivaglobin® [Immune Globulin Subcutaneous (Human)]. 2011 Apr 11. Available at: http://healthycanadians.gc.ca/recall-alert-rappel-avis/hc-sc/2011/14109a-eng.php.
2. Daniel GW, Menis M, Sridhar G, Scott D, Wallace AE, Ovanesov MV, et al. Immune globulins and thrombotic adverse events as recorded in a large administrative database in 2008 through 2010. Transfusion 2012 Mar 12 [Epub ahead of print].
3. Roemisch JR, Kaar W, Zoechling A, Kannicht C, Putz M, Kohla G, et al. Identification of Activated FXI as the Major Biochemical Root Cause in IVIG Batches Associated with Thromboembolic Events. Analytical and Experimental Approaches Resulting in Corrective and Preventive Measures Implemented into the Octagam Manufacturing Process. WebmedCentral IMMUNOTHERAPY 2011;2(6):WMC002002.
4. Etscheid M, Breitner-Ruddock S, Gross S, Hunfeld A, Seitz R, Dodt J. Identification of kallikrein and FXIa as impurities in therapeutic immunoglobulins: implications for the safety and control of intravenous blood products. Vox Sang 2012 102:40-6. [Article first published online: 5 MAY 2011]