

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

Date: January 26, 2015

From: Alpita Popat, Pharm.D., MBA
Consumer Safety Officer
CBER/OCBQ/DCM/APLB

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To: L. Ross Pierce, Medical Officer, CBER/OBRR/DHCR/CRB
Ilana Valencia, RPM, CBER/OBRR/DBA

Subject: Labeling Review
Anthrasil™ [Anthrax Immune Globulin Intravenous (Human)]
BLA 125562/0
Sponsor: Cangene Corporation

Background: The sponsor submitted:

New Approval
 Changes Being Effectuated (CBE) supplement
 Prior Approval Supplement (PAS) Amendment
 Major Amendment

Submission contains:

Prescribing Information (PI)
 Patient Package Insert (PPI)
 Carton and/or container labels
 Other

Submission Date: July 25, 2014

PDUFA Action Date: March 25, 2015

APLB Comments/Recommendations

On July 25, 2014, Cangene Corporation (Cangene) submitted a Biologics License Application (BLA) for Anthrasil™ [Anthrax Immune Globulin Intravenous (Human)]. Anthrasil is a sterile gamma globulin (IgG) fraction of human plasma containing antibodies to *Bacillus anthracis*. The product is indicated for the treatment of adult and pediatric patients with toxemia associated with inhalational anthrax.

APLB has reviewed the revised PI submitted by the sponsor on November 21, 2014 and January 12, 2015. The following comments and recommendations are provided. The comments below address the January 22, 2015 revised version of the January 12, 2015 PI (attached).

GENERAL

- Proofread the PI to ensure that there are no editorial errors. Ensure that changes in sectioning and subsectioning are carried through within the document, including cross-references.
- Use command language whenever possible.

The **FULL PRESCRIBING INFORMATION** should contain only headings and subheadings. In addition, some sections have subsection numbering and titles that are dictated by regulations (see 21 CFR 201.57). We recommended revising the **5 WARNINGS AND PRECAUTIONS** and **13 NONCLINICAL TOXICOLOGY** sections to remove the sub-sub headings under the subheadings.

- Ensure that the **TABLE OF CONTENTS** reflects the sections in the **FULL PRESCRIBING INFORMATION (FPI)**.
- Delete the trademark information and “rights reserved” paragraph from the end of the content of labeling. All that is necessary at the end of the prescribing information is the manufacturer’s information.

HIGHLIGHTS

- Please ensure that the **HIGHLIGHTS** section, excluding the Boxed Warning section, is limited in length to one-half page. Consider revising the **DOSAGE AND ADMINISTRATION** and the **WARNINGS AND PRECAUTIONS** sections to accomplish this. In addition, the **DRUG INTERACTIONS** section is not necessary for the **HIGHLIGHTS** when there is no identified risk from a drug interaction.
- For clarity and comprehension, please provide two tables in the **DOSAGE AND ADMINISTRATION** section: Adult and Pediatric Dosing and Pediatric Dosing Based on Body Weight. The following statements then become superfluous and may be deleted

- Pediatric dosing was derived from allometric scaling
 - See Table 2 for pediatric dosing
 - The adult dose is seven vials and the dose in pediatric patients ≤ 16 years is determined by body weight.
- List the **WARNINGS AND PRECAUTIONS** in descending order of severity and public health significance. Revise these items to short sentences or summaries.
 - Delete the comment regarding pediatric dosing (i.e., allometric scaling) from the **USE IN SPECIFIC POPULATIONS**. This information is in the **DOSAGE AND ADMINISTRATION**.
 - Please remove the revision date at the end of the **HIGHLIGHTS**. This revised date is added to the **HIGHLIGHTS** when a supplement is approved.

FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

- We recommend removing the statement, “There have been no studies of ANTHRASIL in the pediatric, geriatric, or obsess populations” because statements about the absence of information are not required unless there is clinical relevance.

2 DOSAGE AND ADMINISTRATION

- The first bullet is relevant to preparation, not to the overall dose and administration. For clarity, consider reordering this section. For example, **2.1 Dose** and **2.2 Preparation and Administration**.
- We recommend revising this section into improve readability. For example, use command language and present the steps in a logical sequence.
- In the second bullet, comments about monotherapy use and the statement, “Data suggests that administration of higher doses may result in improved survival” is considered promotional in tone. We recommend deleting this bullet.
- Information in the third bullet belongs in 6.1 Clinical Trials Experience and/or 10 OVERDOSAGE.
- The information in the fourth and fifth bullets is provided in Table 1. We recommended associating this information with Table 1 and deleting these bullets.

- The statement “The pediatric dosing is derived from allometric scaling based on observed adult exposure” is listed multiple times in this section. We recommend limiting this statement to one time in the section.
- A clean separation between dosing and administration would allow appropriate emphasis and clarity to statements such as, “Use of an in-line filter is optional.”

5 WARNINGS AND PRECAUTIONS

- Please use command language in the section wherever possible.
- This section should be in ordered by severity and public health significance (see above comment).
- The first paragraph in subsection **5.1 Hypersensitivity Reactions** minimizes the risk of such reactions with ANTHRASIL. We recommend revising this statement to “Hypersensitivity reactions, including anaphylaxis and shock, may occur with ANTRHASIL.” Combine this sentence with the existing second paragraph.
- Overall, subsection **5.1 Hypersensitivity Reactions** is cumbersome and redundant. For readability, we suggest deleting the last sentence in the third paragraph.
- Subsection **5.3 Thrombotic Events** minimizes the risk of thrombotic events for ANTHRASIL. We recommend directing the first sentence to ANTRHASIL rather than the entire class effect.
- Delete **5.6 Infusion Rate Precautions**. This information is redundant to information in other subsections that discuss situations in which monitoring and infusion rate changes are necessary.
- Please revise the **5.11 Transmission of Infectious Agents from Human Plasma** subsection to the following regulatory language:

5.11 Transmissible Infectious Agents

Because ANTHRASIL is made from human plasma, it may carry a risk of transmitting infectious agents, e.g. viruses, and, theoretically, the Creutzfeldt-Jakob disease (CJD) agent. No cases of transmission of viral diseases or CJD have been associated with the use of ANTHRASIL. All infections suspected by a physician possibly to have been transmitted by this product should be reported by the physician or other healthcare provider to Cangene Corporation at 1-800-768-2304.

6 ADVERSE REACTIONS

- A simple statement of the common adverse reactions across the clinical trials, with a cutoff frequency, should be stated beneath this section header. This statement is the same statement that is used in the corresponding section in the **HIGHLIGHTS**.
- Only those events that meet the regulatory definition of adverse reaction belong in **6 ADVERSE REACTIONS** (see 21 CFR 201.57 and *Guidance for Industry – Adverse Reactions Section of Labeling for Human Prescription Drug and Biological Products – Content and Format*).
- The statement “No serious adverse reactions were reported during the clinical study” minimizes the fact that there may be serious adverse reactions with ANTHRASIL. The limited clinical experience with this product was not a safety study, and it was not performed in patients with anthrax exposure. We recommend deleting this statement.
- The experience in anthrax patients (expanded access) should be included as an unnumbered subsection of 6.1 Clinical Trials Experience. This may be introduced by an italicized header.
- Please include the adverse reactions that occurred in the eleven anthrax patients.

8 USE IN SPECIFIC POPULATIONS

- The dosing regimen for pediatric patients was not based on safety or effectiveness in the pediatric population. We recommend deleting this information from **8.4 Pediatric Use**.
- There were no studies in geriatric patients. We recommend deleting the second sentence in subsection **8.5 Geriatric Use**.
- In subsection **8.6 Renal Insufficiency**, we recommend including information on how to administer ANTHRASIL “with caution.”
- Since there is no data, we recommend deleting **8.7 Use in Obese Population**.

13 NONCLINICAL TOXICOLOGY

- The regulatory title for this section is **13 NONCLINICAL TOXICOLOGY**. Please revise this header.
- The first paragraph under the section header is not relevant to this section. We recommend deleting it.

- Please revise the sub-subsection headers to italicized or underlined headers. Bolding is reserved for headers and subsection headers with regulatory assignments (see 21 CFR 201.57).

14 CLINICAL STUDIES

It is unnecessary to subsection this section. When used to assist in the readability of a large amount of information, subsectioning is reserved for clinical studies addressing different indications or populations.

16 HOW SUPPLIED/STORAGE AND HANDLING

Please revise the latex statement to the following regulatory language: “ANTHRASIL does not contain natural rubber latex.”

17 PATIENT COUNSELING INFORMATION

- The reference to the FDA-approved patient labeling belongs directly beneath the section heading.
- Rather than cross-referencing the warnings and precautions, the bulleted directives should be able to stand along.
- Do not introduce new abbreviations in this section.

PATIENT INFORMATION

No objections to this section.

CARTON AND CONTAINER LABEL

The proper name of the product on the carton and container label shall be placed above any trademark or trade name identifying the product.

Firm name: CSL Behring

File name: LR_Anthrasil_2014 12 15_125562 0.doc

History

Prepared: Alpita Popat 01/22/15
Concur w/rev: Lisa Stockbridge 01/24/15
Final: Alpita Popat 01/26/15

Bcc: HFM-602 Lisa Stockbridge
HFM-602 Chron File
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