

From: Cagungun, Nannette
To: [RAC Allison Kennedy \(akennedy@cangene.com\)](mailto:AKennedy@cangene.com)
Cc: [Tilghman, Tracy](#)
Subject: Labeling comments AIGIV BLA
Date: Friday, December 19, 2014 9:39:00 PM

Our Reference: BL 125562/0

Dear Ms. Kennedy:

I am conveying the following labeling comments and recommendations for Cangene's Anthrax Immune Globulin Intravenous (AIGIV) BLA on behalf of LT. Thomas Maruna.

General

1. Ensure that the PI is proof-read for editorial errors.
2. Use command language whenever possible.
3. The FULL PRESCRIBING INFORMATION should contain only headings and subheadings. We recommended revising the 5 WARNINGS AND PRECAUTIONS and 13 NONCLINICAL TOXICOLOGY sections to remove the sub-subheadings under the subheadings. In any case, do not separately number subsections of subsections (e.g. use 5.11 but not 5.11.1, 5.11.2, etc.).
- 4.

Highlights

5. Please ensure that the HIGHLIGHTS, excluding the Boxed Warning section, are limited in length to one-half page.
6. Please add the following language to the boxed warning in both HIGHLIGHTS and the FPI sections:

WARNING: THROMBOSIS

- Thrombosis may occur with immune globulin products, including Anthrasil. Risk factors may include advanced age, prolonged immobilization, hypercoagulable conditions, history of venous or arterial thrombosis, use of estrogens, indwelling vascular catheters, hyperviscosity and cardiovascular risk factors. Thrombosis may occur in the absence of known risk factors.
- 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.

7. Replace the second bullet under WARNINGS AND PRECAUTIONS in the HIGHLIGHTS section with the bulleted statement “Thrombosis may occur following treatment with immune globulin products including Anthrasil. (5.3)” Change the fourth bullet to read “Acute intravascular hemolysis may occur. Monitor for clinical signs and symptoms of hemolysis and hemolytic anemia. (5.5)” Move the fifth bullet down to be the next-to-the-last bullet in this section. Move the eighth bullet down to be the last bullet in this section.

Highlights (and, for some items, also Full Prescriber Information)

8. Please change the first paragraph of the INDICATIONS AND USAGE sections in HIGHLIGHTS and the full prescribing information (FPI) to read:

ANTHRASIL is an Anthrax Immune Globulin Intravenous (Human) indicated for the treatment of toxemia associated with inhalational anthrax in adult and pediatric patients in combination with appropriate antibacterial drugs.

9. Following the second paragraph in the INDICATIONS AND USAGE sections in HIGHLIGHTS and the FPI please add the following statement:

Although survival in rabbits and monkeys with inhalational anthrax was greatest among animals that received AIGIV plus antibiotic therapy, a statistically significant independent contribution to efficacy (survival) of ANTHRASIL above and beyond that conferred by appropriate antibiotic therapy was not demonstrated in animal efficacy trials (13.2). Although the efficacy of ANTHRASIL monotherapy was demonstrated with animal treatment models of inhalational anthrax, ANTHRASIL should be administered in combination with appropriate antibiotic therapy.

10. Please delete the first sentence in the third paragraph under the INDICATIONS AND USAGE sections in HIGHLIGHTS. Please move the second sentence in the third paragraph in the INDICATIONS AND USAGE sections in HIGHLIGHTS to the DOSAGE AND ADMINISTRATION section and change it to read “Pediatric dosing was derived using from allometric scaling. Please add this modified sentence to the beginning of the fourth bullet in to the DOSAGE AND ADMINISTRATION section of the FPI. Please add the statement “There have been no studies of ANTHRASIL in the pediatric, geriatric, or obese populations to the INDICATIONS AND USAGE section in the FPI. Please add the following statement to the DOSAGE AND ADMINISTRATION section in HIGHLIGHTS: “See section 2.1 for considerations regarding repeat dosing.”
11. In the boxed warning in the HIGHLIGHTS and FPI sections, please spell out IGIV as Immune Globulin Intravenous (Human).
12. In the DOSAGE AND ADMINISTRATION sections of HIGHLIGHTS, please state the adult dosage range and indicate that the dose in pediatric patients under age 13 (corresponding to a body weight of approximately 60 kg or less) is determined by body

weight.

13. In the dosing table showing infusion rates in the DOSAGE AND ADMINISTRATION sections of HIGHLIGHTS and the FPI, please change the Dose column entries to 7-14 vials for adults and 1-14 vials for Pediatric <1 year to < 16 years, and correct the fourth column to reflect for pediatric subjects incremental infusion rates if tolerated of 0.02 mL/kg/min. Eliminate the separate row for pediatric subjects <1 year.
14. In the CONTRAINDICATIONS section in HIGHLIGHTS, please revise the first bullet to include the word “immune” before globulins.
15. In the USE IN SPECIFIC POPULATIONS section in HIGHLIGHTS, change the last bullet to read “Pediatric dosing is based on allometric scaling.”

Full Prescriber Information (FPI)

16. In the Full Prescriber Information please change the recommended dose for adults from 420 U to the following language:

The minimum dose of ANTHRASIL for the treatment of inhalational anthrax in adults in combination with appropriate antimicrobial therapy is 420 U (7 vials). Animal data suggest that administration of the human equivalent of approximately 840 U (14 vials) may result in improved survival. It may be necessary to take into account the condition of the patient and/or availability of the product in relation to the size of the inhalational anthrax outbreak in determining the appropriate initial dose from a public health perspective.

17. Change the fifth bullet under DOSAGE AND ADMINISTRATION to read as follows:

Consider repeat dosing depending on the severity of symptoms and the response to treatment, 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.

18. Consider adding the following statement to the DOSAGE AND ADMINISTRATION section:

The patient’s clinical status and, where available, results of testing for

serum/pleural/peritoneal levels of anti-protective antigen and of anthrax lethal factor following dosing with ANTHRASIL may be taken into account in evaluating the adequacy of dosing.

19. Please modify your dosing algorithm for pediatric patients as follows:

Table 2 Pediatric Dosing Guide for ANTHRASIL¹:

Body wt (kg)	Number of ANTHRASIL Vials ²
<5	1
5-<10	1 - 2
10-<18	2 - 4
18-<25	3 - 6
25-<35	4 - 8
35-<50	5 - 10
50-<60	6 - 12
≥60	7 - 14

¹ The pediatric dosing in Table 2 is derived from allometric scaling based on observed adult exposure to ANTHRASIL at 420 or 840 Units by TNA dose.

² The lower number in each range is based on a 420 U adult dose and the higher number is based on an 840 U adult dose.

Please correct the exposure to protein in pediatric patients in section 5.4 accordingly.

20. Under DRUG INTERACTIONS in HIGHLIGHTS, change the first bullet to read “Based on animal studies, ANTHRASIL did not interfere with therapy with the antibiotics levofloxacin or ciprofloxacin.”
21. Change the last bullet in HIGHLIGHTS under WARNINGS AND PRECAUTIONS to read “Interference with blood and urine glucose testing (5.11).”
22. Please change the statement in section 2.2 Preparation to read “Once punctured, the thawed vials should be used to prepare the infusion bag within 6 hours.”
23. Change the first sentence in section 5.1 Hypersensitivity Reactions to read “Acute systemic allergic reactions were not seen in the clinical trial with ANTHRASIL”

24. In section 5.2 Interference with Blood Glucose Testing, change the second sentence to read “Maltose in ANTHRASIL and in Immune Globulin Intravenous (Human) products has been shown...”
25. In section 5.4 Aseptic Meningitis Syndrome (AMS), move the 2nd and 3rd sentences in the third paragraph to the top of section 5.2 and change them to read “For ANTHRASIL at the recommended adult dosages of 420 Units (seven vials) and 840 U (14 vials), an adult patient may be exposed to up to 0.368 g or 0.736 g protein per kg body weight, respectively. Exposure to protein in pediatric patients due to ANTHRASIL administration may range from 0.378 g per kg to 2.0 g per kg, depending on the pediatric dose (for body weight-dependent pediatric dosing; see Table 2 in 2.1 Dosage and Administration).” Precede these sentences at the top of section 5.2 with the statement, “The incidence and/or severity of some adverse reactions to ANTHRASIL and other Immune Globulin Intravenous (Human) products may be related to the total protein/polyclonal antibody load administered.”
26. In section 5.5 Hemolysis, change the second sentence in the third paragraph to read “Consider appropriate laboratory testing in higher risk patients, including measurement of hemoglobin or hematocrit prior to infusion and within approximately 36 to 96 hours, and again approximately 7-10 days post infusion.”
27. In section 6 ADVERSE REACTIONS, change the second sentence to read “This includes those adverse events (AEs) with an incidence of 5% or greater which were dose-dependent, and/or considered related by the Clinical Investigator, and/or which demonstrated a temporal relationship (within 72 hours of ANTHRASIL administration).” ***Please provide the data listing and SAS code for identifying the most common adverse reactions as defined above and as included in Table 3 in section 6.1. What criteria were applied to determine if AEs were dose-dependent?***
28. In section 6.1 Clinical Trials experience:
- Change the first sentence in the fifth paragraph of section 6.1 to read “No serious adverse reactions were reported during the clinical study. Change the second sentence in this paragraph to read “Infusion of ANTHRASIL was stopped for four subjects due to adverse reactions (ARs). Change the next sentence to read “One subject was withdrawn due to an AR consisting of chest discomfort, flushing, tachycardia, throat tightness, and headache.”
 - Replace the adverse drug reaction (ADR) with adverse reaction (AR).

- c. Strike the sentence in the 7th paragraph which begins “This includes all dose dependent AEs...”
 - d. Change the first sentence in the 8th paragraph to read “Headache, pain (including back pain and pharyngolaryngeal pain), and cough were reported in a dose-dependent fashion. In addition, nasal congestion, rhinorrhea, and neck pain occurred more frequently with higher doses of ANTHRASIL.” ***Please clarify the criteria used to determine these two categories of [possibly] dose-related ARs.***
 - e. Please redesign Table 3 to provide the numbers of subjects and events which occurred in the placebo group for the corresponding rows. Limit the data for the active subjects to the randomized, double-blind portion of the study. Include a narrative or separate tabular listing of the cumulative incidence by subject and event type for common ARs using all 74 subjects exposed to AIGIV for only those additional ARs not included in Table 3. Change the title of Table 3 to read “Adverse Reactions Observed in >5% of Subjects Administered ANTHRASIL or Placebo in Healthy Volunteer Clinical Trial.” Please note that healthy volunteers were not “treated” with ANTHRASIL because they did not have anthrax.
 - f. Change the last sentence to read “In addition to the reported ARs, dose-related elevations in urine glucose were noted transiently following dosing [*see 5.11 Elevated Glucose in Urine*].”
29. Change the last sentence in subsection 7.1 Ciprofloxacin and Levofloxacin to read “Concomitant administration of ANTHRASIL with levofloxacin or ciprofloxacin in exposed rabbits and cynomolgus macaques, respectively, did not reduce the efficacy of antibacterial therapy.”
30. Change subsection 8.4 Pediatric Use to read as follows:
- Safety and effectiveness of ANTHRASIL in the pediatric population (<16 yrs of age) have not been studied. Allometric scaling was used to derive dosing regimens to provide pediatric patients with exposure comparable to the observed exposure in adults receiving 420 to 840 Units. The dose for pediatric patients is based on body weight.
31. Change subsection 8.5 Geriatric Use to read as follows:
- Safety and effectiveness of ANTHRASIL in the geriatric population (>65 yrs of age) have not been studied. No safety data are available in elderly patients from either the AX-001 healthy volunteer study or from the compassionate use of AIGIV in patients with systemic anthrax.
32. Change subsection 8.7 Use in Obese Population to read as follows:

Safety and effectiveness of ANTHRASIL in the obese population have not been studied. Although empirically-based guidance for dosing for Immune Globulin Intravenous (Human) in morbidly obese patients has been reported in the medical literature, pharmacokinetic data for ANTHRASIL or IGIV in obese patients are lacking.

33. Add the following statement to section 12.1 Mechanism of Action:

ANTHRASIL is administered in combination with appropriate antibiotic therapy as the product by itself is not known to have bactericidal activity against anthrax bacteria which otherwise may continue to grow and produce anthrax toxins.

34. In section 12.3 Pharmacokinetics:

- a. In Table 5, delete $AUC_{(0-7d)}$ and provide all PK parameters as arithmetic means with the exception of T_{max} .
- b. Insert a new paragraph under Table 5 which reads “It is expected that the clearance of anti-PA antibodies from ANTHRASIL administration will be greater and the AUC will be lower in patients with inhalational anthrax compared to healthy subjects.”
- c. Change the next paragraph to read as follows:

Mean PK results (TNA data) were evaluated by sex and revealed no sex-related differences over the dose range studies. Systemic exposure of ANTHRASIL increased in a dose-proportional manner over the dose range studied. ANTHRASIL has a serum elimination half-life of 24 to 28 days in humans.

- d. Change the next paragraph to read as follows:

In compassionate use/ expanded access programs [see 14.2 Compassionate Use/Expanded Access Program], inhalational anthrax patients concomitantly treated with antibiotics and a single ANTHRASIL dose of 420 Units TNA exhibited increases in serum and pleural anti-PA levels; these levels remained at >50% of the peak anti-PA levels over the next five days. The peak anti-PA levels in these patients following ANTHRASIL administration (132 to 160 mcg/mL, mean 145 mcg/mL) overlapped with those obtained with the 420 Units ANTHRASIL dose in healthy volunteers (135 to 250 mcg/mL, median 192 mcg/mL), although mean levels were approximately 25% lower in the inhalational anthrax patients. In the three inhalational anthrax patients, serum and pleural levels of lethal factor declined after initiation of antibiotics and further decreased over the period of five days following ANTHRASIL administration. Unlike the situation in the animal treatment model studies, plasma levels of lethal factor remained detectable 1 to 2 days following ANTHRASIL administration, despite their decline.

- e. Change the last paragraph to read as follows:

Because the effectiveness of ANTHRASIL cannot ethically be tested in placebo-

controlled trials in humans, a comparison of ANTHRASIL exposures achieved in healthy human subjects to those observed in animal models of inhalational anthrax in therapeutic efficacy studies is necessary to support the dosage regimen of 420 Units to 840 Units IV as a single (or initial) dose for the treatment of inhalational anthrax in humans.

35. Change the heading for section 13 to NONCLINICAL TOXICOLOGY AND PHARMACOLOGY. Change the second paragraph in this section to read as follows:

The evaluation of new treatment options for anthrax using placebo controlled human trials is unethical and infeasible. Therefore, the effectiveness of ANTHRASIL for treatment of inhalational anthrax is based on controlled efficacy studies conducted in rabbits and cynomolgus macaques.

36. Change the second sentence in sub-subsection 13.2.2 to read “No significant difference between the control (normal immune globulin [IGIV] plus levofloxacin) and treatment groups (ANTHRASIL plus levofloxacin) was seen when combination treatment was delayed up to 60 hours post-challenge.
37. Change the third sentence in the third paragraph of sub-subsection 13.2.2 to read “Of the animals that survived to be treated (19% of those challenged), antibacterial drug plus ANTHRASIL (15 Units per kg) resulted in (58%) [sponsor fill in (number of surviving animals/number of animals surviving to be treated)] survival compared to 39% [sponsor fill in (number of surviving animals/number of animals surviving to be treated)] survival in rabbits treated with antibacterial drug and IGIV placebo ($p = 0.21$).” Round off the p value in the next paragraph to 0.02.
38. Please add the p value in parentheses for the survival difference in the cynomolgus macaque combination treatment study in the paragraph under Table 7 in sub-subsection 13.2.2.
39. Please modify the paragraph presently under 13.2.3 ANTHRASIL in Post-exposure prophylaxis to include the results to those in animals who were determined to be anti-PA positive, and both anti-PA positive and bacteremia at the time of dosing. Exclude the presentation of data from challenge dosing at 20 hours.
40. In section 14, please change the first sentence to read “Because it is not ethical or feasible to conduct placebo-controlled clinical trials in humans with inhalational anthrax..” Change the last sentence in this paragraph to read “The safety has been tested in healthy adults and evaluated in a limited number of patients with anthrax who were treated with ANTHRASIL under compassionate use or CDC’s expanded use programs.”
41. Strike the last sentence in section 14.1 which begins “The data collected in this study demonstrated...” as it is promotional in tone.

42. Change the title of subsection 14.2 to read Patient Experience (Compassionate Use/Expanded Access Program). (Note that not all human cases of systemic anthrax treated with AIGIV received the product under the Expanded Access Program.)
43. Strike the sentence in the first paragraph of section 14.2 which reads “To provide additional support...”
44. Change the second paragraph of section 14.2 to read “For the ANTHRASIL indication of inhalational anthrax, two out of three patients treated with ANTHRASIL plus appropriate antimicrobial therapy survived and one died from progression of anthrax disease. In all three patients, therapy included aggressive supportive measures including mechanical ventilation and pulmonary fluid drainage.’
45. Change the third paragraph of section 14.2 to read “In the three inhalational patients, the ANTHRASIL dose of 420 Units by TNA resulted in increased anti-PA levels (correlating with increased TNA activity); these levels remained comparatively stable up to 7 to 20 days post-administration, probably reflecting rising antibody production by the patient at the same time that the exogenously-administered antibody was being cleared.”
46. Add a fourth paragraph to section 14.2 to read as follows:

Unlike the case in animals, serum lethal factor remained detectable in patients’ serum following administration of ANTHRASIL, although substantial declines following product administration were observed. In some injectional anthrax cases complicated by substantial hemorrhage and pleural and/or peritoneal fluid losses from thoracentesis and/or paracentesis, serum anti-PA antibody levels fell as much as approximately 90% from their post-ANTHRASIL peak levels by 24 hours following ANTHRASIL administration.

47. In section 17 PATIENT COUNSELING INFORMATION change the term “legal guardian” to “legally authorized representative” in the first sentence. In the last bullet in this section, change the last sentence to read “The safety of ANTHRASIL has been tested in healthy adults, but no safety data are available in the pediatric population, the elderly, or pregnant women [*see 8 USE IN SPECIFIC POPULATIONS*].

Please make the following changes to the draft carton and container labels:

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

Please submit your response to this information request as an amendment to this file by January 8, 2015 referencing the date of this request. Please include both a red-line strike out and clean copy of the revised package insert in WORD format. 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.

The action due date for this file is March 25, 2015.

If you have any questions, please contact LT. Thomas Maruna at (240) 402-8454 or LT. Tracy Tilghman at (240) 401-3924 or at tracy.tilghman@fda.hhs.gov

Sincerely,

Nannette Cagungun, MS, PD, RAC
Regulatory Project Manager
OBRR/CBER/FDA
10903 New Hampshire Ave
WO71-4258
Silver Spring, MD 20993-0002
Tel: (240) 402-8267
Fax: (301) 595-1128

Email: nannette.cagungun@fda.hhs.gov

THIS MESSAGE IS INTENDED ONLY FOR THE USE OF THE PARTY TO WHOM IT IS ADDRESSED AND MAY CONTAIN INFORMATION THAT IS PRIVILEGED, CONFIDENTIAL, AND PROTECTED FROM DISCLOSURE UNDER LAW. If you are not the addressee, or a person authorized to deliver the document to the addressee, you are hereby notified that any review, disclosure, dissemination, copying, or other action based on the content of this communication is not authorized. If you have received this document in error, please immediately notify the sender immediately by e-mail or phone.