Approval Date: November 23, 2015

Product: BioThrax

Proper Name: Anthrax Vaccine Adsorbed

Manufacturer: Emergent BioDefense Operations Lansing LLC

Indication: For the active immunization for the prevention of disease caused by Bacillus anthracis in persons between 18 and 65 years of age at high risk of exposure.

Description of Product: It is a sterile, milky-white suspension for intramuscular or subcutaneous injections made from cell-free filtrates of microaerophilic cultures of an avirulent, non-encapsulated strain of Bacillus anthracis.

BLA: BL 103821

Regulatory Milestone:

BioThrax, the only anthrax vaccine currently approved for use in the U.S., was originally approved in the 1970s. The original approval was for a six-dose regimen (Week 0, 2, and 4; and Month 6, 12, and 18) administered subcutaneously to prevent disease caused by Bacillus anthracis in persons 18 through 65 years of age at high risk of exposure. On December 11, 2008 the FDA approved a change to an intramuscularly (IM) administered five-dose primary series (Week 0 and 4; and Month 6, 12, and 18) followed by an annual booster thereafter.

A further change in dosing schedule for BioThrax was approved on May 17, 2012. This approval changed the schedule to a three-dose primary series (Month 0, 1, and 6), followed by booster injections at 12 and 18 months, and an annual booster thereafter.

With the approval of this supplement BioThrax will be the first vaccine to be approved for an indication based on the Animal Rule. The indication and schedules will be revised to read:

BioThrax is a vaccine indicated for the active immunization for the prevention of disease caused by Bacillus anthracis in persons 18 through 65 years of age. BioThrax is approved for:

1. Pre-exposure prophylaxis of disease in persons at high risk of exposure.

Schedule	**Route of Administration**	**Dosing Schedule**
Primary Series	Intramuscular	0,1, and 6 months
Booster Series	Intramuscular	6 and 12 months after completion of the primary series and at 12-month intervals thereafter

2. Post-exposure prophylaxis of disease following suspected or confirmed Bacillus anthracis exposure, when administered in conjunction with recommended antibacterial drugs.

Schedule	**Route of Administration**	**Dosing Schedule**
Primary Series	Subcutaneous	0, 2, and 4 weeks post-exposure combined with antimicrobial therapy

On April 11, 2014 Emergent received orphan drug-designation for the indication of "postexposure prophylaxis of anthrax disease resulting from suspected or confirmed exposure to Bacillus anthracis."

PDUFA Goal Date: November 29, 2015

Package Insert: BioThrax

Summary Basis for Regulatory Approval: November 11, 2015 Summary Basis for Regulatory Action - BIOTHRAX

European Public Assessment Report: Not available

Advisory Committee:

Using the Animal Rule, the FDA may license a biological product, for which safety has been established in humans, based on adequate and well-controlled animal studies when the results of those animal studies establish that the biological product is "reasonably likely to produce clinical benefit in humans." The Animal Rule stipulates that the FDA can rely on data from animal studies to provide evidence of effectiveness of a product if four criteria are fulfilled. The four criteria are: There is a reasonably well-understood pathophysiological mechanism of the toxicity of the substance and its prevention or substantial reduction by the product.

The effect is demonstrated in more than one animal species expected to react with a response predictive for humans, unless the effect is demonstrated in a single animal species that represents a sufficiently well-characterized animal model for predicting the response in humans. The animal study endpoint is clearly related to the desired benefit in humans, which is generally the enhancement of survival or prevention of major morbidity. The data or information on the kinetics and pharmacodynamics of the product or other relevant data or information, in animals and humans, allows selection of an effective dose in humans.

Previously, CBER partnered with other U.S. Government agencies, including the NIH/NIAID and the Department of Defense, in sponsoring workshops to discuss implementation

of the Animal Rule for anthrax vaccines. The first workshop, titled Anthrax Vaccines: Efficacy Testing and Surrogate Markers of Immunity, was held in April 2002. A second workshop, titled Anthrax: Bridging Correlates of Protection in Animals to Immunogenicity in Humans, was held in November 2007. At these workshops, scientific consensus was reached in certain important areas. First, pathogenic mechanisms of Bacillus anthracis were reviewed and were thought to be reasonably well understood. Second, NHPs and rabbits were determined to be appropriate animal models to use to generate the pivotal animal data that would serve as a basis for assessing efficacy of PA-based anthrax vaccines. Third, animal protection study designs were discussed for PA-based vaccines in which survival of animals following an anthrax challenge could be tested. Scientific consensus was achieved that the first three criteria of the Animal Rule had been met in regard to PA-based anthrax vaccines.

The fourth criterion of the Rule focuses on establishing a scientifically sound bridge between animal protection data and the human immune response in order to determine an effective human dose. CBER's stated position is that the anthrax vaccine dose used in humans should elicit an immune response in humans comparable to that of animals protected by the vaccine. The question of which immune response and what study design should be used to determine protective antibody levels in the animals that could be extrapolated to humans for a postexposure prophylaxis indication was discussed at the VRBPAC held on November 16, 2010. At that meeting, a scientific strategy for bridging animal protection data to humans for PA-based vaccines, including BioThrax, was agreed upon. In particular, three study designs were discussed: a GUP design, a PEP design, and a passive immunization study design. The three study designs were presented and evaluated along with the pros and cons of each model for predicting the immune response that would be protective in humans for a post-exposure prophylaxis indication.

The GUP study design was judged by the VRBPAC to be the most appropriate design to estimate protective TNA antibody levels in animals and to extrapolate these to vaccine induced TNA levels in humans via an antibody bridge to support a post-exposure prophylaxis indication. The VRBPAC acknowledged that animal studies using a PEP study design and passive immunization studies in animal models could serve as further proof-of-concept that the vaccine can protect in a post-exposure setting and that use of antibodies to bridge animal protection data to humans is appropriate. However, the VRBPAC agreed that data from such studies would not be pivotal and would not be used to estimate protective antibody levels since complexities encountered with PEP and passive immunization studies confound estimates of protective antibody levels and preclude accurate estimations of such levels.

Emergent conducted two pivotal GUP studies as well as additional supportive PEP and passive immunization studies.

Safety:

The safety data from three clinical studies, combined with extensive post-marketing experience with BioThrax in the military population, do not suggest any new safety concerns that the proposed indications might raise. The safety profile of BioThrax is well-characterized since the vaccine was licensed in the U.S. in the 1970s. In the studies submitted to support this proposed indication, no deaths were reported. Of the two serious adverse events (SAEs) reported, neither were considered to be related to vaccination. There were no pregnancies reported or subject withdrawals due to adverse events. Review of the safety data for 504 subjects who participated in studies EBS.AVA.005, EBS.AVA.006, and EBS.AVA.009 did not reveal any new safety signals or adverse events that are not already described in the package insert for BioThrax.

NCT Numbers:

- NCT01491607
- NCT01753115
- NCT03877926
- NCT03518125
- NCT01770743
- NCT01263691
- NCT00114621
- NCT00170469
- NCT00057525
- NCT01979406
- NCT02239172
- NCT00063843
- NCT01867957
- NCT02655549
- NCT00170456
- NCT04067011
- NCT00103467

EudraCT Numbers: No data available

Publications:

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