PRODUCT MONOGRAPH

INCLUDING PATIENT MEDICATION INFORMATION

BioThrax®

Anthrax Vaccine Adsorbed

Suspension for Injection, Anthrax Antigen Filtrate 50 micrograms per 0.5 mL dose

Pharmaco-therapeutic group: J07AC

"HEALTH CANADA HAS AUTHORIZED THE SALE OF THIS EXTRAORDINARY USE NEW DRUG FOR THE ACTIVE IMMUNIZATION FOR THE PREVENTION OF DISEASE CAUSED BY *BACILLUS ANTHRACIS* (ANTHRAX) IN INDIVIDUALS 18 THROUGH 65 WHOSE OCCUPATION OR OTHER ACTIVITIES PLACE THEM AT RISK OF EXPOSURE, REGARDLESS OF THE ROUTE OF EXPOSURE BASED ON LIMITED CLINICAL TESTING IN HUMANS"

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Table of Contents

BioThrax®

Anthrax Vaccine Adsorbed, Suspension for Injection

PART I: HEALTH PROFESSIONAL INFORMATION

"HEALTH CANADA HAS AUTHORIZED THE SALE OF THIS EXTRAORDINARY USE NEW DRUG FOR THE ACTIVE IMMUNIZATION FOR THE PREVENTION OF DISEASE CAUSED BY *BACILLUS ANTHRACIS* (ANTHRAX) IN INDIVIDUALS 18 THROUGH 65 WHOSE OCCUPATION OR OTHER ACTIVITIES PLACE THEM AT RISK OF EXPOSURE, REGARDLESS OF THE ROUTE OF EXPOSURE BASED ON LIMITED CLINICAL TESTING IN HUMANS"

1 INDICATIONS AND CLINICAL USE

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BioThrax (Anthrax Vaccine Adsorbed) is indicated for active immunization for the prevention of disease caused by *Bacillus anthracis*, in individuals 18 through 65 years of age, whose occupation or other activities place them at risk of exposure, regardless of the route of exposure.

1.1 Pediatrics

Pediatrics (<18 years of age): No data are available to Health Canada; therefore, Health Canada has not authorized an indication for pediatric use.

1.2 Geriatrics

Geriatrics (>65 years of age): No data are available to Health Canada; therefore, Health Canada has not authorized an indication for geriatric use.

2 CONTRAINDICATIONS

BioThrax should not be administered to patients with:

- History of anaphylactic or anaphylactic-like reaction following a previous dose of BioThrax or any component of the vaccine. For a complete listing, see the DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING section of the product monograph.

3 DOSAGE AND ADMINISTRATION

3.1 Dosing Considerations

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BioThrax should be administered intramuscularly in the deltoid region.

BioThrax may be administered the subcutaneous route when medically indicated (for example, in persons with coagulation disorders)

3.2 Recommended Dose and Dosage Adjustment

BioThrax (Anthrax Vaccine Adsorbed) is administered as a three-dose primary series (0.5mL dose) at 0, 1 and 6 months. Subsequent booster injections of 0.5 mL of BioThrax at three-year intervals are recommended.

Health Canada has not authorized an indication for pediatric and geriatric use. See **Sections 1.1** and **1.2**.

3.3 Administration

Use a separate sterile needle and syringe for each person to avoid transmission of viral hepatitis and other infectious agents. For intramuscular injections, use a 25- or 23- gauge (1inch (25 mm)- or 1½ inch (38 mm)) needle. After assessing the depth of the subcutaneous tissue at the intended injection site, select a needle length sufficient to reach the muscle. For subcutaneous injections, use a 27- or 25- gauge (5/8inch (16 mm)) needle. Use a different site for each sequential injection of this vaccine and do not mix with any other product in the syringe.

- Shake the bottle thoroughly to ensure that the suspension is homogeneous during withdrawal and visually inspect the product for particulate matter and discoloration. If the product appears discolored or has visible particulate matter, DISCARD THE VIAL.
- Wipe the rubber stopper with an alcohol swab and allow to dry before inserting the needle.
- **For intramuscular injections,** the vaccine should be injected in the deltoid muscle region. Holding the needle at a 90° angle to the skin (like a dart), inject the vaccine into the muscle.
- **For subcutaneous injections,** gently pinch the tissue in the deltoid area and insert the needle at approximately a 45° angle, ensuring the beveled tip of the needle is in subcutaneous tissue.
- Avoid the triceps area to avoid damage to the ulnar nerve. Clean the area to be injected with an alcohol swab or other suitable antiseptic.
- DO NOT inject the product intravascularly or intradermally.
- After injecting, withdraw the needle and dispose of properly.
- Any unused product or waste material should be disposed of in accordance with local requirements.

3.4 Missed Dose

Doses of BioThrax should be administered as close to the recommended intervals as possible. The optimal schedule for catch-up or missed or delayed booster doses is unknown.

Never administer a “double dose” of BioThrax to correct a previously missed dose.

4 OVERDOSAGE

No formal studies have been conducted to evaluate the impact of excessive doses of BioThrax. A group of medical personnel, however, compared the impact of inadvertently doubling the first dose of BioThrax to 1.0 mL in 25 subjects, with that of 12 subjects who received the standard 0.5 mL first dose. Surveys of the subjects that received the overdose revealed that 92 percent had a sore arm, 88 percent had a lump at the injection site, and 84 percent had swelling. The frequency of lumps and swelling were significantly higher than in those who received the standard dose. Following the next (standard dose) immunisation two weeks later, the subjects who first received the double dose tended to have more local reactogenicity to the vaccine. None of the adverse events required emergency room visits, or were determined to be serious.

Consequences of an overdose are not known.

For management of a suspected drug overdose, contact your regional poison control centre.

5 DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING

Route of Administration	**Dosage Form / Strength / Composition**	**Non-medicinal Ingredients**
Intramuscular injection Subcutaneous injection (only if medically indicated)	Suspension for Injection / Anthrax Antigen Filtrate 50 micrograms per 0.5 mL dose adsorbed on aluminum hydroxide (0.6 mg per 0.5mL dose)	Benzethonium chloride Formaldehyde Sodium Chloride Water for injection

Dosage Form and Packaging: BioThrax (Anthrax Vaccine Adsorbed) is supplied in 5 mL multidose vials, with one 5 mL multidose vial per carton. The multidose vial contains sufficient medicinal product to deliver 10 doses (where a single dose is 0.5 mL). The vial is made from Type I borosilicate glass sealed with a 13 mm chlorobutyl dry natural rubber blend stopper (may contain trace amounts of latex).

Composition: BioThrax (Anthrax Vaccine Adsorbed) is a sterile, milky-white suspension (when mixed) made from cell-free filtrates of microaerophilic cultures of an avirulent, nonencapsulated strain of *Bacillus anthracis*.

6 DESCRIPTION

BioThrax (Anthrax Vaccine Adsorbed) is a sterile, milky-white suspension (when mixed) made from cell-free filtrates of microaerophilic cultures of an avirulent, non-encapsulated

strain of *Bacillus anthracis*. The final product, prepared from the sterile filtrate culture fluid, contains proteins, including the 83kDa protective antigen protein. The final product contains no dead or live bacteria.

One dose (0.5 mL) is formulated to contain:

Anthrax antigen filtrate: 50 micrograms (50 µg)

Adsorbed on aluminium hydroxide (0.6 mg aluminium per dose)

Product potency, as determined by the guinea-pig challenge assay, is expressed in BioThrax Units (BU) and a multi-dose 5 mL vial (10 x 0.5 mL dose) contains ≥69 BU.

7 WARNINGS AND PRECAUTIONS

Immune Response

Persons with impaired immune responsiveness due to congenital or acquired immunodeficiency, or immunosuppressive therapy may not be adequately immunised following administration of BioThrax. Vaccination during chemotherapy, high dose corticosteroid therapy of greater than 2-week duration, or radiation therapy may result in a suboptimal response. Deferral of vaccination for 3 months after completion of such therapy may be considered.

As with other vaccines, a protective immune response may not be elicited in all vaccinees.

The administration of BioThrax to persons with concurrent moderate or severe illness should be postponed until recovery. Vaccination is not contraindicated in people with mild illnesses with or without low-grade fever.

Latex Allergies

This product should be administered with caution to people with a possible history of latex sensitivity, because the vial stopper contains a dry natural rubber blend which has the potential to contain trace amounts of latex proteins.

Hypersensitivity

Acute allergic reactions, including anaphylaxis, have occurred with BioThrax administration. Providers who administer vaccines should have an emergency protocol and supplies to treat anaphylaxis. Epinephrine solution, 1:1000, should always be available for immediate use in case an anaphylactic reaction should occur. Providers should observe subjects after BioThrax administration by following procedures used for other vaccines within their clinic.

For more information on Warnings and Precautions, refer to **Module 2.5, Section 2.5.6.1.**

7.1 Special Populations

7.1.1 Pregnant Women

No prospective controlled clinical studies have been performed to assess the impact of BioThrax on pregnancy.

Pregnant women should not be vaccinated against anthrax unless the potential benefits of vaccination clearly outweigh the potential risks to the fetus. For more information, refer to **Module 2.5, Section 2.5.5.3.4.**

One retrospective cohort study evaluated birth defects, in relation to maternal BioThrax vaccination, among all infants born to US military service women between 1998 and 2004. There were a total of 115,169 infants born to military women during this period; and 3,465 of them were born to women vaccinated in the first trimester of pregnancy. The rates of birth defects were 4.03% (3,145/78,029) for the never vaccinated group, 4.56% (652/14,306) for the pre-pregnancy vaccination group, 4.68% (162/3,465) for the first trimester vaccination group, 3.77% (25/663) for the second or third trimester vaccination group, and 3.85% (720/18,706) for the post-pregnancy vaccination group.

7.1.2 Breast-Feeding

It is not known whether exposure of the mother to BioThrax poses a risk of harm to the breast-feeding child.

7.1.3 Pediatrics

Pediatrics (<18 years of age): No data are available to Health Canada; therefore, Health Canada has not authorized an indication for pediatric use.

7.1.4 Geriatrics

Geriatrics (>65 years of age): No data are available to Health Canada; therefore, Health Canada has not authorized an indication for geriatric use.

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8 ADVERSE REACTIONS

8.1 Adverse Drug Reaction Overview

The safety profile presented is based on analysis in one controlled clinical study (**BB-IND-10031**), and post-market experience with the product since its original licensure in the US in the 1970's, cumulatively over 14 million doses in over 3 million individuals (up to December 2016). The most frequently reported adverse events were headache; arthralgia; erythema; injection-site erythema; pyrexia; myalgia; and injection-site pain.

8.2 Clinical Trial Adverse Drug Reactions

Because clinical trials are conducted under very specific conditions the adverse reaction rates observed in the clinical trials may not reflect the rates observed in practice and should not be compared to the rates in the clinical trials of another drug. Adverse drug reaction information from clinical trials is useful for identifying drug-related adverse events and for approximating rates.

Approximately 60% of the 1564 clinical trial subjects who received BioThrax by any route, intramuscular or subcutaneous, were reported to have injection-site adverse reactions, and approximately 20% of recipients reported systemic adverse events, the vast majority of

which were rated as "mild". The proportion of participants with severe injection site or systemic adverse reactions reported by adverse reaction category after each dose was very low (generally <1%).

Undesirable effects assessed in the 1044 adult participants who were assigned to receive BioThrax by the intramuscular route are shown below. Adverse event frequencies, which were classified as possible, probable, or very likely/certain, are listed according to the per-dose frequency:

Very common:	≥1/10
Common:	≥1/100, <1/10
Uncommon:	≥1/1,000, <1/100
Rare:	≥1/10,000, <1/1,000
Very rare:	<1/10,000, including isolated reports

Table 1 Clinical Trial Reported Adverse Events

System Organ Class	Frequency	Adverse Reaction (Preferred Term)
Cardiac Disorders	Uncommon	Tachycardia NOS
Eye Disorders	Uncommon	Conjunctivitis allergic
Gastrointestinal Disorders	Common	Dyspepsia, nausea
	Uncommon	Abdominal pain upper, vomiting NOS
General Disorders and Administration Site Conditions	Very Common	Fatigue*, injection site bruising*, injection site erythema*, injection site joint movement impairment*, injection site pain*, injection site pruritis*, injection site swelling/lump*, injection site tenderness*, injection site warmth*
	Common	Axillary pain*, pyrexia*, rigors
	Uncommon	Feeling hot, hangover, influenza-like illness, injection site anaesthesia, injection site paresthesia, injection site rash, malaise, pain NOS
	Rare	Feeling cold
Infections and Infestations	Common	Nasopharyngitis, sinusitis NOS
	Uncommon	Herpes zoster
Metabolism and Nutrition Disorders	Uncommon	Appetite decreased
Musculoskeletal and Connective Tissue Disorders	Very common	Myalgia*
	Common	Arthralgia, back pain, neck pain
	Uncommon	Joint stiffness, muscle spasms, musculoskeletal stiffness, pain in extremity
Nervous System Disorders	Very common	Headache*
	Common	Dizziness
	Uncommon	Paresthesia, syncope
	Rare	Burning sensation NOS
Psychiatric Disorders	Common	Insomnia

System Organ Class	Frequency	Adverse Reaction (Preferred Term)
Reproductive System and Breast Disorders	Uncommon	Dysmenorrhoea
Respiratory, Thoracic and Mediastinal Disorders	Common	Cough, pharyngolaryngeal pain
	Uncommon	Dyspnoea, postnasal drip, respiratory tract congestion, sneezing
Skin and Subcutaneous Tissue Disorders	Common	Pruritus, rash NOS
	Uncommon	Erythema, skin burning sensation, urticaria NOS
	Rare	Cold sweat
Vascular Disorders	Uncommon	Flushing
NOS - Not Otherwise Specified *Solicited (clinic and diary) events, all assumed to be related to immunisation.		

Serious adverse events occurring in this study which were determined to be possibly associated with the receipt of BioThrax by any route or schedule in 1564 study subjects included: generalised allergic reaction, pseudotumor cerebri with bilateral disc oedema, aquaductal stenosis with generalised seizure, arthralgia of the metacarpophalangeal joints, ductal carcinoma of the breast, and supraspinatus tendon tear.

No adverse safety interactions were reported in a study involving concurrent treatment with antibiotics. For further discussion of Clinical Adverse Events, refer to **Module 2.7, Section 2.7.4.**

8.3 Post-Market Adverse Reactions

The following adverse events have been reported spontaneously. Since these events are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure. The reports included below are listed due to one or more of the following factors: (1) seriousness of the event, (2) number of reports, or (3) strength of causal relationship to the drug.

- **Blood and lymphatic system disorders**
- Lymphadenopathy
- **Gastrointestinal Disorders**
- Nausea
- **Immune system disorders**
- Allergic reactions (including anaphylaxis, angioedema, rash, urticaria, pruritus, erythema multiforme, anaphylactoid reaction, and Stevens Johnson syndrome)
- **Nervous system disorders**
- Paresthesia syncope, dizziness, tremor, ulnar nerve neuropathy
- **Musculoskeletal, connective tissue, and bone disorders**
- Arthralgia, arthropathy, myalgia, rhabdomyolysis, alopecia
- **General disorders and administration site conditions**
- Malaise, pain, cellulitis, flu-like symptoms
- **Psychiatric disorders**

- Insomnia
- **Skin and Subcutaneous disorders**
- Pruritis, rash, urticaria
- **Vascular disorders**
- Flushing

Infrequent reports were also received of multisystem disorders defined as chronic symptoms involving at least two of the following three categories: fatigue, mood-cognition, and musculoskeletal system.

9 DRUG INTERACTIONS

9.1 Drug-Drug Interactions

Use with other vaccines:

BioThrax can be given concurrently with any of the following monovalent or combination vaccines; cholera, diphtheria, hepatitis A and B, influenza, Japanese encephalitis, measles, meningitis, mumps, pertussis, plague, polio, rabies, rubella, smallpox, tetanus, varicella and yellow fever.

There are no data on the effects of co-administration of BioThrax with other vaccines on the immune response.

When given concomitantly with other vaccines, BioThrax must be administered at separate injection.

Use with antibiotics:

BioThrax may be administered simultaneously with ciprofloxacin.

Other medicinal products:

The immunological response may be diminished if the patient is undergoing immunosuppressant (e.g. chemotherapy, corticosteroid) treatment. For more information on Drug-Drug Interactions, refer to **Module 2.7, Section 2.7.4**

9.2 Drug-Food Interactions

Interactions with food have not been established.

9.3 Drug-Herb Interactions

Interactions with herbal products have not been established.

9.4 Drug-Laboratory Interactions

Drug-Laboratory interactions with BioThrax have not been established.

9.5 Drug-Lifestyle Interactions

Drug-Lifestyle interactions with BioThrax have not been established.

10 ACTION AND CLINICAL PHARMACOLOGY

10.1 Mechanism of Action

Anthrax bacteria produce three proteins known as protective antigen (PA), lethal factor (LF), and edema factor (EF). If the PA protein interacts with LF or EF on the surface of human or animal cells, the resultant toxins could be lethal to anyone who became infected with the bacteria.

BioThrax stimulates the immune system to produce protective antibodies against PA. When PA is blocked, LF and EF are not able to interact with PA and the toxins are thereby neutralized.

10.2 Pharmacodynamics

Clinical efficacy and safety:

A controlled field study using an earlier version of a protective antigen–based anthrax vaccine, developed in the 1950's, that consisted of an aluminum potassium sulfate-precipitated cell-free filtrate from an aerobic culture, was conducted from 1955-1959. At the time of the study, the yearly average number of human anthrax cases (both cutaneous and inhalational) in textile mills was 1.2 cases per 100 employees. This study included 1,249 workers [379 received anthrax vaccine, 414 received placebo, 116 received incomplete inoculations (with either vaccine or placebo) and 340 were in the observational group (no treatment)] in four mills in the north-eastern United States that processed imported animal hides. During the trial, 26 cases of anthrax were reported across the four mills–five inhalation and 21 cutaneous. Of the five inhalation cases (four of which were fatal), two received placebo and three were in the observational group: none had received the anthrax vaccine. Of the 21 cutaneous cases, 15 received placebo, three were in the observational group, and three received anthrax vaccine. Of those three cutaneous cases in the vaccine group, one case occurred just prior to administration of the scheduled third dose, one case occurred 13 months after an individual received the third of the scheduled 6 doses (but no subsequent doses), and one case occurred prior to receiving the scheduled fourth dose of vaccine. The analysis included cases of both cutaneous and inhalation anthrax that occurred in individuals who received at least three doses of vaccine or placebo and received subsequent doses on schedule. The calculated efficacy of the vaccine to prevent all types of anthrax disease combined, regardless of the route of exposure or manifestation of disease, was 92.5% (95% lower CI = 65%) (**Brachman et al., 1962**).

Between 1962 and 1974, the Centers for Disease Control and Prevention (CDC) collected surveillance data on the occurrence of anthrax disease in mill workers or those living near mills in the United States. During that time period, individuals received either BioThrax or the earlier protective antigen-based anthrax vaccine used in the field trial described above. Twenty-seven cases of anthrax disease were identified. Of those, 24 cases occurred in

unvaccinated individuals, one case occurred after the person had been given one dose of anthrax vaccine and two cases occurred after individuals had been given two doses of anthrax vaccine. No documented cases of anthrax were reported for individuals who had received at least three of the recommended six doses of anthrax vaccine. The relative proportion of immunised versus non-immunised persons is not known. These data provide confirmation that the risk of disease still existed for those persons who were not vaccinated.

A separate study also evaluated the incidence of injection site reactions for both subcutaneous and intramuscular routes of administration. An analysis from In-clinic exam data which was focused entirely on solicited AEs shows the rates (percentage) of participants with prospectively defined in-clinic solicited injection site adverse reactions for the IM route (N=1044), vs SC route (N=258) vs placebo (N=258), respectively, were as follows: warmth (10% vs. 39% vs. 0.6%), tenderness (46% vs. 60% vs. 7%), itching (5%, vs. 19% vs. 0.2%), pain (17% vs. 17% vs. 3%), arm motion limitation (12% vs. 8% vs. 1%), erythema (29% vs. 63% vs. 13%), induration (12% vs. 34% vs. 3%), oedema (17% vs. 32% vs. 5%), nodule (5% vs. 31% vs. 1%), bruise (4% vs. 6% vs. 4%).

10.3 Pharmacokinetics

Evaluation of pharmacokinetic studies is not required for vaccines.

11 STORAGE, STABILITY AND DISPOSAL

Store in a refrigerator (2 ºC – 8 ºC). Do not freeze.

Store in the original package in order to protect from light.

For storage of the vial after first opening, vial is to be used within 28 days.

Shelf life: Four (4) years

Any unused product or waste material should be disposed of in accordance with local requirements.

12 SPECIAL HANDLING INSTRUCTIONS

Keep out of the reach and sight of children.

Precautions for use of multidose vials:

- Mark newly opened vials with date and time of opening
- Keep multidose vials away from the immediate patient environment
- Never transport vials in clothing or pockets
- Never pool or combine leftover contents for later use
- Never leave a needle, cannulae or spike device (even if it has a two-way valve) inserted into the vial stopper because of contamination risk
- Always use a sterile needle and syringe for each withdrawal

- Cleanse the vial stopper thoroughly before and after each use.
- Allow the stopper to dry before inserting the needle
- Place the multidose vial into storage away from the immediate patient environment following the storage conditions.

PART II: SCIENTIFIC INFORMATION

13 PHARMACEUTICAL INFORMATION

13.1 Drug Substance

Proper name:	Anthrax Vaccine Adsorbed (AVA)
Structural formula:	The Anthrax Vaccine Adsorbed (AVA) Bulk Drug Substance (BDS) consists of the Anthrax Vaccine Filtrate (AV Filtrate) that has been adsorbed to aluminum hydroxide (AlOH) and resuspended in a saline preservative solution. The AV Filtrate consists of the contents of the production fermentation vessel after clarification and sterilization filtration. The formal definition of "structure" pertaining to a well-defined or characterized biologic does not apply to the AVA Bulk Drug Substance. The AV Filtrate consists of a complex mixture of Anthrax Antigen proteins. Therefore, the "structure" would be defined in terms of the principle immunogen protective antigen (PA) and potentially a small amount of lethal factor (LF). Edema factor (EF) is not detectable in AVA.

13.2 Product Characteristics

BioThrax Anthrax Vaccine Adsorbed is a sterile, milky-white suspension (when mixed) made from cell-free filtrates of microaerophilic cultures of an avirulent, nonencapsulated strain of *Bacillus anthracis*. The final product, prepared from the sterile filtrate culture fluid, contains proteins, including the 83kDa protective antigen (PA) protein.

For more information, please see **Module 3.2.S.1.3.**

14 CLINICAL TRIALS

14.1 Trial Design and Study Demographics

For details of trial design and demographics see Table 3.

Table 2 Summary of BioThrax Trial Design and Study Demographics

Study #	Trial Design	Dosage, route of administration and duration	Study subjects (n)	Mean age (Range)	Gender
BB-IND 10031	Multicenter, Randomized, Double-Blind, Placebo-Controlled, Parallel, Assign	Dosage: BioThrax 0.5 mL Route: IM or SC Regimen: See **Table 4** Study Duration: 42 months	N = 1564[a]	< 30 = 439 30 to <40 = 361 40 to <50 = 460 ≥50 = 303 (Range 18 - 61 yrs)	Male = 763 Female = 800
BB-IND 6847	Prospective, Open-Label, Randomized	Dosage: BioThrax 0.5 mL Route and Regimen (7 Groups): Control Group: SC at Weeks 0, 2, 4. and at 6, 12 and 18 months. SC groups • Week 0 • Weeks 0 and 2 • Weeks 0 and 4. IM groups • Week 0 • Weeks 0 and 2 • Weeks 0 and 4	N = 173	Mean: 33.3 (Range 19 – 64)	Male = 109 Female = 64
EBS.AVA.005	Multicentre, Post- Exposure Prophylaxis	BioThrax Route: SC Regimen: Injections at Weeks 0, 2, and 4	N = 150	Mean: 32.5 ± 12.7 (Range 18.3 – 65.8)	Male = 75 Female = 75
Protocol V011	Multicentre, Double- Blind, Randomized, Parallel Group, Controlled	BioThrax or VaxImmune™ Route: IM Regimen: Injections at Weeks 0, 2, and 4	N = 69	Mean: 27.5 ± 5.9 (Range 19 – 44)	Male = 34 Female = 35
a – One patient withdrew consent prior to the first injection, therefore actual study n = 1563					

14.2 Study Results

The study conducted by the CDC serves as the primary assessment of immunogenicity of BioThrax. Other immunogenicity studies, including the Pilot Study under **BB-IND 6847**, and **Study V011**, are considered supportive for the pre-exposure indication.

In addition, EBS.AVA.005 (0, 2, 4 week schedule, SQ route, with no subsequent doses) was intended to evaluate a route and schedule for post-exposure use, but these data are also supportive for the initial doses of the pre-exposure indication.

The GCP compliant CDC study, Anthrax Vaccine Adsorbed: Human Reactogenicity and Immunogenicity Trial to Address Change in Route of Administration and Dose Reduction (**BB-IND-10031**), was a randomized, double-blinded, placebo-controlled, multi- center clinical study, in which 1564 subjects were enrolled. The objective of this CDC study was to evaluate the effect of changing the route of vaccine administration and reducing the number of doses on the safety and immunogenicity of BioThrax, which is discussed further in **Module 2.7, Section 2.7.3.** The route and schedule used in the Brachman efficacy trial, and originally licensed for BioThrax in the US, is the subcutaneous (SC) route with doses administered at 0-2-4 weeks, 6-12-18 months. This originally licensed route/schedule was compared with the same schedule utilizing the IM route and with alternative schedules using the IM route as shown in Table 3:

Table 3 Comparison of Dosage Schedules and Routes of Administration

Study Group	Route	Month 0	Week 2	Month 1	Month 6	Month 12	Month 18	Month 30	Month 42
8SC	SC	V	V	V	V	V	V	V	V
8IM	IM	V	V	V	V	V	V	V	V
7IM	IM	V	-	V	V	V	V	V	V
5IM	IM	V	-	V	V	-	V	-	V
4IM	IM	V	-	V	V	-	-	-	V
Placebo	IM	-	-	-	-	-	-	-	-
Placebo	SC	-	-	-	-	-	-	-	-
V = Vaccine - = Saline									

The CDC Study final analysis included the 1564 subjects enrolled in the study and included all follow-up visits up through the 43-month visit. The final analyses included 1563 subjects that received at least one dose of vaccine and compared six groups:

- 8SC - BioThrax administered by the SC route, using the traditional dosing regimen (same as Brachman efficacy trial) at weeks -0, -2, -4, and months-6, -12, -18, -30, and 42 (n=259);

- 8IM - BioThrax administered by the IM route, using the traditional dosing regimen (n=262) at weeks -0, -2, -4, and months -6, 12, -18, -30, and 42; biennial
- 7IM - BioThrax® administered by the IM route, using traditional dosing regimen but without the 2-week doses (n=256) at weeks -0, -4, and months -6, -12, -18, -30, and 42;
- 5IM - BioThrax administered by the IM route (n=258) using a dosing regimen at weeks -0, -4 and months -6, -18, and 42;
- 4IM - BioThrax administered by the IM route (n=268) using a dosing regimen at weeks -0, -4 and months -6 and 42.
- Placebo (saline) administered by either the SC or IM route, using the traditional schedule (n=260).
- For the 754IM (7IM, 5IM and 4IM arms combined), BioThrax administered by the IM route (N=782) using a dosing regimen at weeks -0, -4 and at month -6.

Using an Enzyme-Linked Immunosorbent Assay (ELISA), Immunoglobulin G (lgG) antibodies directed against anthrax protective antigen (PA) were measured at the Week 8 and Months 7, 13, 19, 31, and 43 time points. The three primary immunogenicity endpoints were: (1) Geometric Mean Concentration (GMC) (mcg/mL), (2) Geometric Mean Titer (GMT), and (3) percentage with 4-fold rise in anti-PA antibody titer from baseline.

The criteria for non-inferiority of comparisons based on ratios of GMCs and GMTs and differences in the rates of 4-fold rise in antibody titer were defined as follows:

- Mean antibody concentration ratio: non-inferiority was achieved when the upper bound of the 95% confidence limit was <1.5
- Mean antibody titer ratio: non-inferiority was achieved when the upper bound of the 95% confidence limit was <1.5
- 4-fold rise in antibody titer: non-inferiority was achieved when the upper bound of the 95% confidence limit was <0.10

Table 4 Results from BB-IND 10031 Study

	Anti-PA IgG GMC (µg/mL) (95% CI)	Anti-PA IgG GMT (95% CI)	4-fold rise in anti-body (95% CI)
Week 8			
TRT-8SC	94.29 (82.08, 108.31)	1048.50 (913.05, 1204.05)	94.89 (91.25, 97.33)
TRT-8IM	84.46 (73.67, 96.82)	934.75 (815.59, 1071.32)	91.88 (87.61, 95.04)
TRT-754IM	46.39 (42.18, 51.01)	514.57 (468.08, 565.68)	78.80 (75.57, 81.77)
Month 7			
TRT-8SC	201.14 (174.71, 231.56)	2211.94 (1921.78, 2545.90)	98.63 (96.05, 99.72)
TRT-8IM	232.59 (202.37, 267.33)	2545.58 (2215.34,2925.06)	98.60 (95.98, 99.71)
TRT-754IM	206.09 (187.14, 226.96)	2257.09 (2050.12, 2484.94)	97.80 (96.33, 98.79)
Month 13			
TRT-8SC	201.67 (174.77, 232.71)	2184.59 (1893.62, 2520.26)	99.51 (97.29, 99.99)
TRT-81M	276.24 (240.09, 317.84)	3007.07 (2614.07, 3459.15)	100.00 (98.23, 100.00)
TRT-7IM	229.86 (203.20, 260.02)	2546.81 (2251.11, 2881.35)	100.00 (98.20, 100.00)
TRT-54IM (placebo on Month 12)	28.64 (25.79, 31.81)	296.08 (266.67, 328.74)	60.40 (55.41, 65.23)
Month 19			
TRT-8SC	193.45 (167.29, 223.69)	2080.89 (1799.87, 2405.79)	98.95 (96.25, 99.87)
TRT-8IM	264.89 (229.43, 305.82)	2853.50 (2471.93, 3293.97)	100.00 (98.03, 100.00)
TRT-7IM	204.95 (180.82, 232.29)	2254.56 (1988.85, 2555.75)	98.96 (96.29, 99.87)
TRT-5IM	293.60 (258.30, 333.73)	3167.26 (2785.88, 3600.85)	99.43 (96.84, 99.99)
TRT-4IM (placebo on Month 18)	13.71 (12.11, 15.53)	135.30 (119.44, 153.26)	37.82 (30.96, 45.07)
Month 31			
TRT-8SC	250.07 (215.38, 290.34)	2677.97 (2306.82, 3108.83)	100.00 (97.82, 100.00)
TRT-8IM	336.20 (290.56, 389.01)	3588.81 (3102.00, 4152.01)	100.00 (97.89, 100.00)
TRT-7IM	263.13 (231.09, 299.61)	2867.88 (2518.14, 3266.19)	100.00 (97.84, 100.00)

	Anti-PA IgG GMC (µg/mL) (95% CI)	Anti-PA IgG GMT (95% CI)	4-fold rise in anti-body (95% CI)
TRT-5IM (placebo on Month 30)	33.68 (29.48, 38.48)	348.89 (305.33, 398.66)	63.40 (55.24, 71.03)
TRT-4IM (placebo on Month 30)	7.80 (6.87, 8.86)	79.63 (70.10, 90.44)	22.35 (16.47, 29.16)
Month 43			
TRT-8SC	216.83 (185.80, 253.05)	2228.36 (1955.79, 2663.45)	100.00 (97.47, 100.00)
TRT-8IM	320.45 (275.99, 372.07)	3425.40 (2950.37, 3976.93)	100.00 (97.66, 100.00)
TRT-7IM	254.80 (222.03, 292.40)	2760.35 (2404.66, 3168.64)	100.00 (97.38, 100.00)
TRT-5IM	310.02 (270.49, 355.33)	3286.41 (2866.50, 3767.83)	99.29 (96.11, 99.98)
TRT-4IM	433.20 (379.58, 494.40)	4683.79 (4102.99, 5346.80)	99.36 (96.50, 99.98)

From Month 7 onwards, the immune responses, in terms of anti-PA IgG GMC and GMT, elicited by different administration route (8IM) and reduced vaccination schedules (7IM, 5IM, and 4IM) were non-inferior to the originally licensed route and schedule (8SC) four weeks following vaccine administration.

However, at Week 8, the dose schedule of Week 0-2-4 was much better than the dose schedule Week 0-4, in terms of anti-PA IgG level. The non-inferiority criteria were not met.

15 DETAILED PHARMACOLOGY

In the evaluation of new treatment options for anthrax, , any trial that would expose human subjects to anthrax are unethical. Therefore, the effectiveness of BioThrax for the active immunization for the prevention of disease caused by *Bacillus anthracis* is based on studies conducted in animals.

In one non-human primate (NHP) study, rhesus macaques were vaccinated with AVA (0.5mL) on a 3-dose (0, 1, and 6 months) intramuscular schedule, using either the full dose (undiluted) or saline-diluted) AVA (1:5).

After vaccination rhesus macaques were exposed to a target dose of 200 or 400, 50% lethal dose (LD_{50}) equivalents of aerosolized *Bacillus anthracis* Ames spores at 30, or 52 months after first vaccination. The survival rates are presented in the table below:

Table 5 NHP Survival Rates Following Challenge with *Bacillus anthracis*

# of animals challenged	Vaccine dilution	Challenge time (month)	Average challenge dose (LD_{50})	No. of survivors / no. of challenged animals (%)
10	Undiluted	52	403	8/10 (80.0%)
9	1:5	52	506	9/9 (100%)
10	Undiluted	30	573	10/10 (100%)
8	1:5	30	504	8/8 (100%)
12	Not vaccinated	30	672	2/12 (16.7%)
10	Not vaccinated	52	672	2/10 (20.0%)

For further information on Detailed Pharmacology, refer to **Module 2.4, Section 2.4.2.1**.

15.1.1 Animal Studies

The endpoint of the primary pharmacodynamic studies performed with AVA was defined as the protection against a challenge with virulent strains of *B. anthracis.* Additionally, most studies also quantified the immunological response to AVA vaccination, measured by anti-PA antibody titres. The expected immunogenicity was evaluated in terms of levels of antibody production, class and subclass of antibodies produced, and duration of immune response. The neutralising

effect of antibodies against PA is determined in a toxin-neutralising antibody (TNA) assay in some studies.

Route of administration

The approved clinical route of administration is IM for pre-exposure prophylaxis. In the non-clinical pharmacology studies, AVA has been administered in several fashions, including IM, SC, and ID. Most studies were conducted by administering vaccine IM.

Challenge with *B. anthracis* spores

A well-established methodology for assessing anthrax vaccines is by means animal survival following spore challenge studies and evaluation of the associated immune response. In early studies, challenge with *B. anthracis* spores was expressed as number of spores. In all subsequent studies, the challenge was expressed as multiples of LD_{50}, which is defined as the lethal dose causing death in 50% of the animals tested. Expressing the challenge dose in multiples of LD_{50}, provides a more reliable quantification of the virulence of each individual challenge, thereby enabling comparison among studies. In all studies, unvaccinated control animals were exposed to the same challenge dose level as vaccinated animals. All of the unvaccinated control animals died.

The route of challenge studied has varied, depending on animal model. In several non-clinical studies guinea pigs were challenged by IM inoculation with *B. anthracis* spores, while in routine guinea pig potency testing guinea pigs are challenged with ID injection of *B. anthracis* spores after SC inoculation with vaccine. On the other hand, rabbits and macaques models have been challenged by aerosol exposure to spores, which is the most likely route of exposure in the event of a bioterror attack. Regardless of the route of challenge, AVA has been shown to be effective for prevention of anthrax disease as demonstrated in the clinical study performed by Brachman in the 1960's. This study included inhalational and cutaneous cases of anthrax disease that occurred in individuals who received at least three doses of vaccine or placebo and were on schedule for the remaining doses of the six-dose schedule regardless of the routes of exposure or manifestation of disease.

Vaccination scheme in pre-exposure prophylaxis studies

Several different vaccination schemes were applied in the pharmacology studies. In the pre-exposure prophylaxis studies, vaccination usually consisted of two injections of 0.5 mL AVA or a dilution thereof at 4 weeks intervals (Day 0, Day 28). Ivins et al., (1996) applied a two- week interval (Day 0, Day 14). The early studies in guinea pigs employed three injections of AVA at 2-week intervals, and also used a single immunization dose of 0.5 mL AVA in macaques. Although a direct comparison among different vaccination schemes was not performed, all rabbits and macaques vaccinated with at least one 0.5 mL dose of AVA survived subsequent *B. anthracis* spore challenge regardless of the vaccination regimen. It should also be noted that only 1 or 2 doses of vaccine provided long-term protection against inhalation spore challenges in animals.

16 NON-CLINICAL TOXICOLOGY

Three GLP-compliant toxicity studies have been performed with AVA: a single dose toxicity study in rats in which AVA was administered IM alone or in combination with an immune enhancing agent, a multi-dose reproductive toxicity study in which AVA was administered to female rabbits prior to mating and during gestation, and a repeated dose toxicity study in rabbits. These studies are further discussed in **Module 2.4, Section 2.4.4**.

Single dose toxicity

One single dose toxicology study (971-003-CPG7909) in rats showed that BioThrax alone at a dose level of 0.5 mL caused the injection-site inflammation and possibly the observed splenic lymphoid hyperplasia. Both of these findings are commonly associated with the intended immunostimulatory effects of vaccination.

Repeated dose toxicity

Conclusions from the repeated dose toxicity study No. 1778-08239 with AVA in rabbits were that there were no apparent organ toxicities, no adverse effects, and no evidence for a delayed onset of toxicity although there were dose-related effects at the injection sites. Therefore, the no-observed-adverse-effect level (NOAEL) for AVA when administered by repeated (Day 1, 15, 29, and 43) intramuscular injection is at least 0.5 mL.

Reproductive performance and developmental toxicity

An animal reproductive toxicology study (PDP002-SP1), which included post-natal observation until weaning, has been performed. Female rabbits were administered (IM) AVA twice during the pre-mating period (each dosage separated by 4 weeks) and one during the gestation period (either day 7 or day 17 gestation). No adverse effects on fertility, pregnancy, embryo / fetal development, parturition or post-natal / pre-weaning development.

17 REFERENCES

1. Fellows PF, Linscott MK, Ivins BE, Pitt MLM, Rossi CA, Gibbs PH et al. Efficacy of a human anthrax vaccine in guinea pigs, rabbits, and rhesus macaques against challenge by Bacillus anthracis isolates of diverse geographical origin. Vaccine 2001; 19:3241-3247.
2. Marano N, Plikaytis BD, Martin SW et. al. Interim Analysis of a human dose and schedule optimization study of the approved US anthrax vaccine adsorbed (AVA). Tenth Annual Conference on Vaccine Research. April 30-May 2, 2007, Baltimore, MD.
3. Marano N, Plikaytis BD, Martin SW, et. al. Effects of a reduced dose schedule and intramuscular administration of Anthrax Vaccine Adsorbed on immunogenicity and safety at 7 Months. JAMA. 2008; 300(13): 1532-1543.

4. Pittman PR, Kim-Ahn G, Pifat DY, Coonan K, Gibbs P, Little S et al. Anthrax vaccine: immunogenicity and safety of a dose-reduction, route-change comparison study in humans. Vaccine 2002;20:1412-1420.
5. Pittman PR. Aluminum-containing vaccine associated adverse events: role of route of administration and gender. Vaccine 2002d; 20:S48-S50.
6. Wright J, Plikaytis B, Rose C, et al., Safety and Efficacy of a Reduced Schedule of Anthrax Vaccine. Interscience Conference on Antimicrobial Agents and Chemotherapy. San Francisco, 2009.

READ THIS FOR SAFE AND EFFECTIVE USE OF YOUR MEDICINE

PART III: PATIENT MEDICATION INFORMATION

BioThrax® (Anthrax Vaccine Absorbed), Suspension for Injection

This leaflet is a summary and will not tell you everything about this drug. Talk to your healthcare professional about your medical condition and treatment and ask if there is any new information about BioThrax.

"HEALTH CANADA HAS AUTHORIZED THE SALE OF THIS EXTRAORDINARY USE NEW DRUG FOR THE ACTIVE IMMUNIZATION FOR THE PREVENTION OF DISEASE CAUSED BY *BACILLUS ANTHRACIS* (ANTHRAX) IN INDIVIDUALS 18 THROUGH 65 WHOSE OCCUPATION OR OTHER ACTIVITIES PLACE THEM AT RISK OF EXPOSURE, REGARDLESS OF THE ROUTE OF EXPOSURE BASED ON LIMITED CLINICAL TESTING IN HUMANS"

What is BioThrax used for?

BioThrax Anthrax Vaccine Adsorbed is a vaccine used to prevent infection due to *Bacillus anthracis.*

Vaccination with BioThrax is indicated for use by individuals between the 18 and 65 years of age, who are at risk for exposure to anthrax through contact with animal product such as hides, hair or bones that come from anthrax endemic areas, or that may be contaminated with *Bacillus anthracis* spores, or who are at risk of exposure to *Bacillus anthracis* spores, such as exposure resulting from acts of bio-warfare or bio-terrorism, regardless of route of exposure.

How does BioThrax work?

Anthrax disease is a bacterial infection caused by exposure to *Bacillus anthracis* and your body's response to this infection. Vaccination with BioThrax prepares your body to fight off the infection by blocking the toxin that is produced by infection.

Anthrax infection can occur mainly in three forms: cutaneous (skin), inhalation, and gastrointestinal. Recently, a novel form of cutaneous anthrax, termed injectional anthrax, was proposed after anthrax was diagnosed in individuals following injection of illicit drugs.

What are the ingredients in BioThrax?

One dose (0.5 mL) contains:

- Anthrax antigen filtrate: 50 micrograms
- Adsorbed on aluminum hydroxide (0.6 mg aluminum per dose)
- Benzethonium chloride, as a preservative
- Formaldehyde, as a preservative

- Sodium chloride, as part of a saline solution
- Water for injections

The product is sterile and does **not** contain any living or dead bacteria.

BioThrax comes in the following dosage forms:

BioThrax is a milky-white suspension (when mixed) contained in a clear glass vial. The vial is closed with a chlorobutyl dry natural rubber blend stopper and sealed with an aluminum cap. The product is supplied sterile and one vial contains enough vaccine for 10 injections of 0.5 mL.

Do not use BioThrax if:

- If you have a history of severe *allergic reactions* (analphylactic or anaphylactic-like) reactions following a previous dose of BioThrax or any of the vaccine components.

To help avoid side effects and ensure proper use, talk to your healthcare professional before you are administered BioThrax. Talk about any health conditions or problems you may have, including if you:

- If you are *pregnant*, think you may be pregnant or are trying to get pregnant, ask your doctor or healthcare provider to advise before receiving any vaccination or medication. As a precaution, pregnant women should not be routinely vaccinated with anthrax vaccine.
- have had *anthrax disease* in the past;
- have an *impaired immune responsiveness* due to congenital or acquired immunodeficiency or
- are receiving *immunosuppressive* therapy;
- have a *moderate or severe illness*. Vaccination is allowed in people with mild illnesses with or without low-grade fever;
- have had an *allergic reaction* following a previous dose of BioThrax or any of the vaccine components;
- have a *latex allergy* or hypersensitivity, because the vial stopper contains dry natural rubber blend which may contain trace amounts of latex proteins.

Tell your healthcare professional about all the medicines you take, including any drugs, vitamins, minerals, natural supplements or alternative medicines.

The following may interact with BioThrax:

- Please tell your doctor or healthcare provider if you are being treated with immunosuppresive therapy, or high-dose corticosteroid therapy, or cytotoxic medicine (e.g. chemotherapy).

How to take BioThrax:

This vaccine has been prescribed for you and will be administered by your doctor or healthcare provider. To administer, a small sterile needle and syringe will be used to withdraw a 0.5 mL dose of BioThrax from the multi-dose vial. The dose will be administered through an

intramuscular (IM) injection in your upper arm or if you have a coagulation disorder it may be given by subcutaneous (SC) injection, again in your upper arm.

What are possible side effects from using BioThrax?

These are not all the side effects you may feel when taking BioThrax. If you experience any side effects not listed here, contact your healthcare professional. Please also see Warnings and Precautions.

The most common side effects of BioThrax are:

- Soreness, pain, redness, bruising, itching, swelling, or warmth at injection site
- Motion limitation in the injected arm
- A lump where the shot was given
- A burning sensation may occur immediately after the shot is given and can last about a minute
- Muscle aches, fatigue or headaches

If you experience any unusual condition, such as difficulty breathing, weakness, hoarseness or wheezing, a fast heartbeat, hives, dizziness, paleness or swelling of the throat, lips or face within a few minutes after the shot or within a few minutes to an hour after the shot, notify your doctor or healthcare provider immediately as this could be a sign of a severe reaction.

If you get any side effects, talk to your doctor. If you have a troublesome symptom or side effect that is not listed here or becomes bad enough to interfere with your daily activities, talk to your healthcare professional.

Reporting Side Effects

You can report any suspected side effects associated with the use of health products to Health Canada by:

- Visiting the Web page on Adverse Reaction Reporting (http://www.hc-sc.gc.ca/dhp-mps/medeff/report-declaration/index-eng.php) for information on how to report online by mail or by fax; or
- Calling toll-free at 1-866-234-2345;

NOTE: Contact your health professional if you need information about how to manage your side effects. The Canada Vigilance Program does not provide medical advice.

Reporting Suspected Side Effects:

For Healthcare professionals: If a patient experiences a side effect following the immunization, please complete the Adverse Events Following Immunization (AEFI) Form appropriate for your province/territory (http://www.phac-aspc.gc.ca/im/aefi-essi-form-eng.php) and send it to your local Health Unit.

Storage:

Store in a refrigerator (2 ºC – 8 ºC). Do not freeze.

Store in the original package in order to protect from light.

For storage of the vial after first opening, vial is to be used within 28 days.

Shelf life: Four (4) years

Keep out of the reach and sight of children.

If you want more information about BioThrax:

- Talk to your healthcare professional
- Find the full product monograph that is prepared for healthcare professionals and includes this Patient Medication Information by visiting the Health Canada website; the manufacturer's website http://www.emergentbiosolutions.com. Or by calling 1-877-246 8472 or email productinquiries@ebsi.com.

This leaflet was prepared by Emergent BioSolutions Inc.

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