PRODUCT MONOGRAPH

INCLUDING PATIENT MEDICATION INFORMATION

BioThrax®

Anthrax Vaccine Adsorbed

Suspension for Injection, Anthrax Antigen Filtrate 50 micrograms per 0.5 mL dose, Intramuscular or Subcutaneous injection

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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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

EUND

BioThrax is indicated for the active immunization for the prevention of disease caused by *Bacillus anthracis*, in individuals 18 through 65 years of age.

BioThrax is approved for:

1. Pre-exposure prophylaxis of disease in persons whose occupation or other activities place them at high risk of exposure.
2. Post-exposure prophylaxis of disease following suspected or confirmed *Bacillus anthracis* exposure, when administered in conjunction with recommended antibacterial drugs.

1.1 Pediatrics

Pediatrics (<18 years of age): No data is available.

1.2 Geriatrics

Geriatrics (>65 years of age): No data is available.

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 of ingredients, see the **DOSAGE FORMS, STRENGTHS, COMPOSITION, AND PACKAGING** section of the product monograph.

3 DOSAGE AND ADMINISTRATION

3.1 Dosing Considerations

EUND

For pre-exposure prophylaxis, BioThrax should be administered intramuscularly in the deltoid region.

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

For post-exposure prophylaxis, BioThrax should be administered subcutaneously.

3.2 Recommended Dose and Dosage Adjustment

BioThrax (Anthrax Vaccine Adsorbed) is administered as a three-dose primary series (0.5 mL dose).

For pre-exposure prophylaxis, BioThrax is administered at 0, 1, and 6 months. Subsequent booster injections of 0.5 mL of BioThrax at three-year intervals are recommended.

For post-exposure prophylaxis, BioThrax is administered at 0, 2, and 4 weeks post-exposure combined with antimicrobial therapy.

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 administration, use a 23- or 25-gauge (1-inch (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 25- or 27-gauge (5/8-inch (16 mm)) needle. Use a different site for each sequential injection of this vaccine. Do not mix BioThrax with any other vaccine or product in the same syringe or vial.

- Shake the vial thoroughly to ensure that the suspension is homogeneous during withdrawal and visually inspect the product for particulate matter and discolouration prior to administration. If the product appears discoloured or has visible particulate matter, DISCARD THE VIAL.
- Wipe the rubber stopper with an alcohol swab and allow to dry before inserting the needle.
- Clean the area to be injected with an alcohol swab or other suitable antiseptic.
- For pre-exposure prophylaxis, the vaccine should be injected in the deltoid muscle region. Avoid the triceps area to avoid damage to the ulnar nerve.
- For intramuscular administration, hold the needle at a 90° angle to the skin (like a dart) and inject the vaccine into the muscle.
- If pre-exposure prophylaxis requires subcutaneous administration, administer over the deltoid muscle. Administer post-exposure prophylaxis vaccinations subcutaneously over the deltoid muscle.
- For subcutaneous administration, 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 the subcutaneous tissue.
- 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 who 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) immunization 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 (AEs) 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	Nonmedicinal Ingredients
Intramuscular or Subcutaneous	Suspension for Injection / Anthrax Antigen Filtrate 50 micrograms per 0.5 mL dose adsorbed on aluminum hydroxide (0.6 mg per 0.5 mL 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, non-encapsulated 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 83 kDa 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 aluminum hydroxide (0.6 mg aluminum per dose)

7 WARNINGS AND PRECAUTIONS

Immune Response

Persons with impaired immune responsiveness due to congenital or acquired immunodeficiency, or immunosuppressive therapy may not be adequately immunized following administration of BioThrax. Vaccination during chemotherapy, high-dose corticosteroid therapy of greater than 2 weeks' 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 Allergy

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.

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.

Results of a large observational study (**Ryan et al., 2008**) that examined the rate of birth defects among 37,140 infants born to US military service women who received anthrax vaccine in pregnancy between 1998 and 2004 showed that birth defects were slightly more common in first trimester-exposed infants (odds ratio = 1.18; 95% confidence interval: 0.997, 1.41) when compared with infants of women vaccinated outside of the first trimester.

Pregnant women should not be vaccinated against anthrax unless the potential benefits of vaccination have been determined to outweigh the potential risk to the fetus.

7.1.2 Breastfeeding

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

7.1.3 Pediatrics

Pediatrics (<18 years of age): No data is available.

7.1.4 Geriatrics

Geriatrics (>65 years of age): No data is available.

EUND

8 ADVERSE REACTIONS

8.1 Adverse Drug Reaction Overview

The safety profile presented is based on analysis in one controlled clinical study, three open-label safety studies, and post-marketing experience with the product since its original licensure in the US in the 1970's. Cumulatively, over 15 million doses have been administered to over 4 million individuals (up to the end of December 2018). The most frequently reported adverse events were headache, arthralgia, erythema, injection-site erythema, pyrexia, myalgia, injection-site pain, and injection-site swelling.

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.

Pre-Exposure Prophylaxis Dose Regimen

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 paraesthesia, 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	Paraesthesia, 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 immunization.		

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, aqueductal stenosis with generalised seizure, arthralgia of the metacarpophalangeal joints, ductal carcinoma of the breast, and supraspinatus tendon tear.

Post-Exposure Prophylaxis Dose Regimen

A phase 3, open-label, single-group, multi-centre study evaluated the three-dose subcutaneous post-exposure prophylaxis BioThrax schedule (Week 0, 2, and 4) in 200 healthy adult subjects. The most common solicited adverse reactions on the diary cards reported 7 days after each vaccination were administration site reactions including symptoms of tenderness, pain, and lump. The most common solicited systemic reactions comprised myalgia, fatigue, and headache. The majority of the reported administration site and systemic solicited reactions were mild in nature, requiring minimal or no treatment and did not interfere with subjects' daily activity. The most common (>2.0%) unsolicited related adverse reactions reported following at least one dose up to 100 days after the third dose were headache (4.0%), fatigue (3.5%), skin hyperpigmentation (3.0%), decreased joint range of motion (2.5%), myalgia (2.5%). No deaths were reported and neither of the two serious adverse events (SAEs) reported were considered to be related to vaccination. There were no pregnancies reported or subject withdrawals from the study due to adverse events.

No adverse safety interactions were reported in a study involving concurrent treatment with antibiotics.

8.3 Post-Marketing Adverse Events

Post-marketing adverse event reports concerning US-licensed vaccines are retrieved from the Vaccine Adverse Event Reporting System (VAERS) or obtained from spontaneous sources including consumers, healthcare professionals and non-sponsored clinical trials. A post-marketed adverse event can also be identified from a literature article. The reporting of an adverse event does not imply causal association with receipt of a vaccine – the event may have occurred by coincidence after vaccination. Over 15 million doses of BioThrax have been administered to over 4 million individuals. BioThrax is often administered concurrently with other non-live and live vaccines, making causality determinations difficult.

The most frequently reported were headache, arthralgia, erythema, injection-site erythema, pyrexia, myalgia, injection-site pain, and injection-site swelling.

Anaphylaxis and/or other generalised hypersensitivity reactions, including urticaria, angioedema, erythema multiforme, and Stevens Johnson syndrome have been reported following administration of BioThrax. None of these hypersensitivity reactions have been fatal. Serious injection-site reactions including cellulitis have been reported following BioThrax administration. Syncope, paraesthesia, and neuropathy have also been reported. 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 separately at a different injection site.

Use with antibiotics:

BioThrax may be administered simultaneously with ciprofloxacin.

Use with other medicinal products:

The immunological response may be diminished if the patient is undergoing immunosuppressant (e.g., chemotherapy, corticosteroid) treatment.

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

Animal Pharmacology:

Since it is not feasible or ethical to conduct controlled clinical trials with anthrax, the efficacy of BioThrax in a post-exposure setting is based on studies in animals. Pre-exposure prophylaxis animal models were used to derive protective antibody thresholds to bridge animal efficacy and human immunogenicity data and predict efficacy in humans.

Pivotal efficacy animal studies were conducted in rabbits and nonhuman primates (NHPs). Animals received two IM vaccinations four weeks apart with serial dilutions of BioThrax and were subjected to lethal challenge on study day 70 with a lethal dose of aerosolized *B. anthracis* spores. Serum samples were collected at various time points prior to challenge for immune response analysis via anthrax lethal toxin-neutralizing antibody (TNA) assay. The relationship between pre-challenge serum TNA levels and survival was evaluated. Logistic regression analysis demonstrated that a 70% probability of survival was associated with a TNA NF_{50} (50% neutralization factor; defined as the ratio of the 50% effective dilution [ED_{50}] of test serum sample to the ED_{50} of the reference serum standard) level of 0.56 in rabbits and 0.29 in NHPs.

The ability of BioThrax to increase survival after the cessation of the post-exposure antimicrobial treatment, as compared with antimicrobial treatment alone, was investigated in two post-exposure animal model studies in rabbits. In these studies, rabbits were challenged via inhalation with a lethal dose of aerosolized *B. anthracis* spores and subsequently treated with levofloxacin administered via oral gavage once daily for 7 days starting at 6-12 hours post-exposure, with or without two intramuscular injections of BioThrax one week apart. Survival among animals that received both antimicrobial treatment and vaccination was between 70 – 100% and increased in a vaccine dose-dependent manner. In contrast, only 44% and 23% survival was observed among animals that received antimicrobial treatment only in the first and the second study.

Clinical efficacy and safety:

Pre-Exposure Prophylaxis

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 northeastern United States that processed imported animal hides. During the trial, 26 cases of anthrax were reported across the four mills−five inhalational and 21 cutaneous. Of the five inhalational 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 inhalational 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 immunized versus non-immunized persons is not known. These data provide confirmation that the risk of disease still existed for those persons who were not vaccinated.

In a randomized, double-blinded, placebo-controlled study, 782 participants were assigned to receive BioThrax by the intramuscular route of administration using an initial schedule of 0, 1, and 6 months. The anti-PA IgG Concentration (GMC) one month after the month 1 vaccination was 46 mcg/mL and one month after the month 6 immunization was 206 mcg/mL. A subgroup (268 participants) received a booster vaccination at month 42 (3 years) following the first immunization. One month following this 3-year booster, the anti-PA GMC was 433 mcg/mL in this subgroup. This compares with an anti-PA GMC of 320 mcg/mL when vaccinations were administered using a schedule of 0, 2, 4 weeks followed by additional intramuscular vaccinations at 6, 12, 18, 30, and 42 months.

Post-Exposure Prophylaxis

An open-label, single-group, multi-centre immunogenicity and safety study evaluated a three-dose vaccination schedule of 0.5 mL BioThrax administered by the SC route at 0, 2, and 4 weeks in 200 healthy adult subjects. Overall, 71.2% of the 184 subjects in the per protocol population achieved a NF_{50} value of ≥ 0.56 on Day 63.

11 STORAGE, STABILITY, AND DISPOSAL

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

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

After first opening, the vial is to be used within 28 days.

Shelf life: Four (4) years (unopened vial). Do not use more than 28 days after first opening.

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 and follow 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, non-encapsulated strain of *Bacillus anthracis*. The final product, prepared from the sterile filtrate culture fluid, contains proteins, including the 83 kDa protective antigen (PA) protein.

14 CLINICAL TRIALS

14.1 Trial Design and Study Demographics

Table 2 Summary of Subject Demographics for BioThrax Clinical Trials

Study Title (Protocol #)	Trial Design	Dosage, Route of Administration, and Regimen	Study Subjects (N)	Mean Age (Range)	Gender
CDC Dose Reduction / Route Change Study – (BB-IND 10031)	Multi-centre, Randomized, Double-Blind, Placebo-Controlled, Parallel, Assign	Dosage: BioThrax 0.5 mL Route: IM or SC Regimen: See **Table 3** Study Duration: 42 months	N = 1564[a]	< 30 = 439 30 to <40 = 361 40 to <50 = 460 ≥50 = 303 (Range 18 – 61)	Male = 763 Female = 800
Dose Reduction, Route Change Comparison (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

Study Title (Protocol #)	Trial Design	Dosage, Route of Administration, and Regimen	Study Subjects (N)	Mean Age (Range)	Gender
Immunogenicity Study of a Three-Dose Subcutaneous BioThrax® Regimen for Post-Exposure Prophylaxis in Healthy Adults (EBS.AVA.005)	Multi-centre, Open-Label, Single-group	Dosage: BioThrax 0.5 mL 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
Phase 1/2, Proof-of-Concept, Double-Blind, Randomized, Controlled Trial Assessing the Immunogenicity and Safety of Anthrax Vaccine Adsorbed (BioThrax®) Combined with CPG 7909 in Normal Volunteers (V011)	Multi-centre, Double-Blind, Randomized, Parallel Group, Controlled	Dosage: BioThrax 0.5 mL or VaxImmune™ 1 mg Route: IM Regimen: Injections at Weeks 0, 2, and 4	N = 69 [22 (AVA); 23 (CPG); 24 (AVA+CPG)]	Mean: 27.5 ± 5.9 (Range 19 – 44)	Male = 34 Female = 35
Immunogenicity and Safety Study of a Three-Dose BioThrax® Regimen for Post-Exposure Prophylaxis in Healthy Adults (EBS.AVA.006)	Multi-centre, Open-Label, Single-group	Dosage: BioThrax 0.5 mL Route: SC Regimen: Injections at Weeks 0, 2, and 4	N = 200	Mean: 33.2 ± 10.7 (Range: 18 – 60)	Male = 98 Female = 102
A Study of the Effects of Co-Administering Ciprofloxacin and BioThrax on the Pharmacokinetics of Ciprofloxacin in Healthy Adults (EBS.AVA.009)	Multi-centre, Open-Label, Randomized	Dosage: BioThrax 0.5 mL and Ciprofloxacin (doses recommended in the product label for bacterial infections of 500 mg p.o. q 12 hr) Route: SC (BioThrax) and Oral (Ciprofloxacin) Regimen: Injections at Weeks 0, 2, and 4	N = 144[b]	Mean: 30.5 ± 7.9 (Range: 18 – 45)	Male = 73 Female = 71

a. One patient withdrew consent prior to the first injection, therefore actual study N = 1563

b. N=144 refers to the Safety Population, whereas N=154 is the ITT Population; data provided for the Mean Age and Gender in the table is in reference to the Safety Population

14.2 Study Results

Pre-Exposure Prophylaxis

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 prophylaxis indication.

In addition, **EBS.AVA.005** (0, 2, 4 weeks schedule, subcutaneous (SC) 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-centre 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. The route and schedule used in the Brachman efficacy trial, and originally licensed for BioThrax in the US, is the 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 intramuscular (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 antibody (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)

	Anti-PA IgG GMC (µg/mL) (95% CI)	Anti-PA IgG GMT (95% CI)	4-fold rise in antibody (95% CI)
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)
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.

Post-Exposure Prophylaxis

Two clinical studies have been conducted to evaluate the immunogenicity and safety of a subcutaneous administration schedule of BioThrax in healthy adults following 3 doses at 0, 2, and 4 weeks. The initial study was conducted to determine the timing and peak of the immune response following BioThrax administration [**EBS.AVA.005**]. One hundred and fifty healthy subjects were enrolled. The overall group mean antibody response reached peak at Day 42 (two weeks after the third dose). The TNA NF_{50} GMTs were 1.672 on Day 42, and 0.97 on Day 63 (five weeks after the third dose).

The immunogenicity data from this pilot clinical study were used to inform the design and analysis for the Phase 3 study, which was the pivotal clinical study intended to support

licensure of the post-exposure prophylaxis indication. Two hundred healthy subject were enrolled. The primary objective was to assess immunogenicity following the completion of three subcutaneous doses of BioThrax. The primary immunogenicity endpoint was the proportion of subjects achieving a TNA NF_{50} value ≥ 0.56 at Day 63, five weeks after the third vaccination. Success was concluded if the lower bound of the 2-sided 95% CI of the proportion of human subjects exceeding the TNA NF_{50} threshold was ≥ 40%. Overall, 71.2% of the 184 subjects in the per protocol population achieved a NF_{50} value ≥ 0.56 on Day 63. The lower bound of the 95% CI was 64.1%.

An open-label, Phase 2 study was also performed to investigate the potential interactions of ciprofloxacin and BioThrax in 154 healthy adult subjects 18 to 45 years of age, inclusive [**EBS.AVA.009**]. Co-administration of three doses (two weeks apart) of BioThrax (0.5 mL) SC with oral ciprofloxacin in healthy adults did not alter the pharmacokinetics of ciprofloxacin or the immunogenicity of BioThrax as measured by the anthrax lethal toxin neutralization assay.

15 DETAILED PHARMACOLOGY

The evaluation of new treatment options for anthrax in placebo-controlled human trials is unethical and infeasible. Therefore, the effectiveness of BioThrax for the active immunization for the prevention of disease caused by *Bacillus anthracis* is based on well-controlled efficacy studies conducted in rabbits and NHPs.

15.1 Animal Studies

The endpoint of the primary pharmacodynamic studies performed with AVA was defined as the protection against lethal challenge with virulent strains of *B. anthracis.* Additionally, most studies also quantified the immunological response to AVA vaccination, measured by anti-PA antibody titers. The expected immunogenicity was evaluated in terms of levels of antibody production, class and subclass of antibodies produced, and duration of immune response. The neutralizing effect of antibodies against PA is determined in a TNA assay in most 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 intradermal (ID). Most studies were conducted by administering vaccine IM. For the post-exposure non-clinical studies with a levofloxacin regimen, the antibiotic was given orally.

Challenge with *B. anthracis* spores

A well-established methodology for assessing anthrax vaccines is by means of 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 the 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 were challenged with ID injection of *B. anthracis* spores after SC inoculation with vaccine. On the other hand, rabbit and macaque 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.

Dosing scheme

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).

In two post-exposure prophylaxis rabbit studies, AVA was administered IM several hours following *B. anthracis* exposure at a dose of 0.5 mL or dilutions thereof. In rabbits, AVA or sham vaccinations was administered twice at Day 0 and 7, either alone or in combination with levofloxacin. The antibiotic was administered orally once a day for 7 days at a dose of 50 mg/kg of body weight.

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 multidose reproductive toxicity study in which AVA was administered to female rabbits prior to mating and during gestation, and a more recently completed repeated-dose toxicity study in rabbits.

Single-dose (Acute) Toxicity

One single-dose toxicology study 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 (Chronic) Toxicity

Conclusions from the repeated-dose toxicity study 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 studies

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 mating, fertility, pregnancy, embryo / fetal development, parturition, or post-natal / pre-weaning development.

It was observed that anti-PA IgG antibody passed from the does to their foetuses and that the foetuses had somewhat higher amounts of anti-PA IgG than the does. In the natural delivery cohort, the surviving kits still maintained detectable antibody levels, but the quantity was lower than that found in the maternal sera.

17 REFERENCES

1. Brachman PS, Gold H, Plotkin SA, Fekety FR, Werrin M, Ingraham NR. Field evaluation of a human anthrax vaccine. Am J Pub Health. 1962;52(4):632–645.
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3. Payne DC, Aranas A, McNeil MM, Duderstadt S, Rose CE. Concurrent Vaccinations and U.S. Military Hospitalizations. Ann Epidemiol. 2007;17(9):697-703.

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 18 and 65 years of age who are at risk for exposure to anthrax through contact with animal products such as hides, hair, or bones that come from anthrax endemic areas, or that may be contaminated with *Bacillus anthracis* spores. BioThrax is also indicated for individuals who are at risk of exposure to *Bacillus anthracis* spores, such as exposure resulting from acts of bio-warfare or bioterrorism, regardless of route of exposure. BioThrax is also indicated for individuals following suspected or confirmed *Bacillus anthracis* exposure, when administered in conjunction with recommended antibacterial drugs.

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 the bacteria.

Anthrax infection can occur in the following ways:

I) *Cutaneous* (skin): The first sign of a *skin infection* with anthrax can be a small red mark similar to an insect bite appearing on the skin. Then, after a short period of time, a small pus-filled blister is formed. The skin around the blister will start to turn red, then a black, hard ulcer will form with swelling around the area. Occasionally, the lymph nodes will be painfully swollen. Without antibiotics, approximately 20% of cutaneous anthrax can be fatal due to the spread of the organism throughout the blood system (sepsis).

II) *Inhalational* anthrax is caused by breathing in airborne spores of anthrax. The first symptoms are non-specific and similar to cold or flu symptoms. Later, a severe disease will develop with high fever, chills, shortness of breath, and shock. Even after treatment with antibiotics, a large number of patients die within 3 to 5 days.

III) *Gastrointestinal* (gut): In rare instances, anthrax may be *ingested with contaminated foods* and is known as gastrointestinal anthrax. Infected patients experience abdominal pain and flatulence. Within a short period of time, bloody diarrhoea and peritonitis will develop. High mortality is associated with the disease from this route of exposure.

IV) *Injectional*: In 2000, a novel form of cutaneous anthrax, termed injectional anthrax, was proposed after anthrax was diagnosed in individuals following injection of illicit drugs. Injectional anthrax symptoms are more severe than those of cutaneous anthrax and are typified by severe soft tissue infection at the injection site, which can progress to septic shock, meningitis, and death.

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 injection

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 each.

Do not use BioThrax if:

- If you have a history of severe *allergic reactions* (anaphylactic or anaphylactic-like) 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:

- 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 *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, 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 multidose vial. The dose will be administered either through an *intramuscular* or *subcutaneous* injection in your upper arm.

What are possible side effects from using BioThrax?

The most common side effects of BioThrax are:

- Soreness, pain, redness, bruising, itching, swelling, or warmth at the injection site
- Motion limitation of 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 injection, notify your doctor or healthcare provider immediately as this could be a sign of a severe reaction.

These are not all the side effects you may feel when taking BioThrax. Please also see **WARNINGS AND PRECAUTIONS**. If you experience any side effects, contact your doctor or healthcare provider. 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;
- Calling toll-free at 1-866-234-2345

NOTE: Contact your healthcare 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 to 8 ºC). **Do not freeze**.

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

After first opening, the vial is to be used within 28 days.

Shelf life: Four (4) years (unopened vial). Do not use more than 28 days after first opening.

Keep out of the reach and sight of children.

If you want more information about BioThrax:

- Talk to your healthcare professional
- Obtain the full Product Monograph that is prepared for healthcare professionals and includes this Patient Medication Information by visiting the Health Canada website or the manufacturer's website http://www.emergentbiosolutions.com, calling 1-877-246-8472, or sending an email to medicalinformation@ebsi.com.

This leaflet was prepared by Emergent BioSolutions Inc.

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