

ANTHRAX VACCINE ADSORBED (BIOTHRAX™)

DESCRIPTION

Anthrax Vaccine Adsorbed, (BioThrax™) 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 production cultures are grown in a chemically defined protein-free medium consisting of a mixture of amino acids, vitamins, inorganic salts and sugars. The final product, prepared from the sterile filtrate culture fluid contains proteins, including the 83kDa protective antigen protein, released during the growth period. The final product contains no dead or live bacteria. The final product is formulated to contain 1.2 mg/mL aluminum, added as aluminum hydroxide in 0.85% sodium chloride. The product is formulated to contain 25 µg/mL benzethonium chloride and 100 µg/mL formaldehyde, added as preservatives.

CLINICAL PHARMACOLOGY

Epidemiology

Anthrax occurs globally and is most common in agricultural regions with inadequate control programs for anthrax in livestock. Anthrax is a zoonotic disease caused by the Gram-positive, spore-forming bacterium *Bacillus anthracis*. The spore form of *Bacillus anthracis* is the predominant phase of the bacterium in the environment and it is largely through the uptake of spores that anthrax disease is contracted. Spore forms are markedly resistant to heat, cold, pH, desiccation, chemicals and irradiation. Following germination at the site of infection, the bacilli can also enter the blood and lead to septicemia. Antibiotics are effective against the germinated form of *Bacillus anthracis*, but are not effective against the spore form of the organism.

The disease occurs most commonly in wild and domestic animals, primarily cattle, sheep, goats and other herbivores. In humans, anthrax disease can result from contact with animal hides, leather or hair products from contaminated animals, or from other exposures to *Bacillus anthracis* spores. It occurs in three forms depending upon the route of infection: cutaneous anthrax, gastrointestinal anthrax and inhalation anthrax.

Cutaneous anthrax is the most commonly reported form in humans (> 95% of all anthrax cases). It can occur when the bacterium enters a cut or abrasion on the skin, such as when handling contaminated meat, wool, hides, leather or hair products from infected animals or other contaminated materials. The symptoms of cutaneous anthrax begin with an itchy reddish-brown papule on exposed skin surfaces and may appear approximately 1-12 days after contact. The lesion soon develops a small vesicle. Secondary vesicles are sometimes seen. Later the vesicle ruptures and leaves a painless ulcer that typically develops a blackened eschar with surrounding swollen tissue. There are often associated systemic symptoms such as swollen glands, fever, myalgia, malaise, vomiting and headache. The case fatality rate for cutaneous anthrax is estimated to be 20% without antibiotic treatment.

Gastrointestinal anthrax usually begins 1-7 days after ingestion of meat contaminated with anthrax spores. There is acute inflammation of the intestinal tract with nausea, loss of appetite, vomiting and fever followed by abdominal pain, vomiting of blood and bloody diarrhea. There can also be involvement of the pharynx with sore throat, dysphagia, fever, lesions at the base of the tongue or tonsils and regional lymphadenopathy. The case fatality rate is unknown but estimated to be 25% to 60%.

Inhalation (pulmonary) anthrax has been reported to occur from 1-43 days after exposure to aerosolized spores.¹ Studies in rhesus monkeys indicate that a small number of inhaled spores may remain viable for at least 100 days following exposure.² However, information on how long spores remain viable in the lungs of humans is unavailable and the incubation period for inhalation anthrax is unknown. Initial symptoms are non-specific and may include sore throat, mild fever, myalgia, coughing and chest discomfort lasting up to a few days. The second stage develops abruptly with

findings such as sudden onset of fever, acute respiratory distress with pulmonary edema and pleural effusion followed by cyanosis, shock and coma. Meningitis is common. The fatality rate for inhalation anthrax in the U.S. is estimated to be approximately 45% to 90%. From 1900 to October 2001, there were 18 identified cases of inhalation anthrax in the U.S., the latest of which was reported in 1976, with an 89% (16/18) mortality rate. Most of these exposures occurred in industrial settings, i.e., textile mills.³ From October 4, 2001, to December 5, 2001, a total of 11 cases of inhalation anthrax linked to intentional dissemination of *Bacillus anthracis* spores were identified in the U.S. Five of these cases were fatal.⁴

Mechanism of Action

Virulence components of *Bacillus anthracis* include an antiphagocytic polypeptide capsule and three proteins known as protective antigen (PA), lethal factor (LF) and edema factor (EF). Individually these proteins are not cytotoxic but the combination of PA with LF or EF results in the formation of the cytotoxic lethal toxin and edema toxin, respectively. Although an immune correlate of protection is unknown, antibodies raised against PA may contribute to protection by neutralizing the activities of these toxins.⁵ The contribution of *Bacillus anthracis* proteins other than PA, that may be present in BioThrax, to the protection against anthrax has not been determined.

CLINICAL STUDIES

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. 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.⁶ During the trial, 26 cases of anthrax were reported across the four mills - five inhalation and 21 cutaneous. Prior to vaccination, the yearly average number of human anthrax cases was 1.2 cases per 100 employees in these mills. Of the five inhalation cases (four of which were fatal), two received placebo and three were in the observational group. Of the 21 cutaneous cases, 15 received placebo, three were in the observational group, and three received anthrax vaccine. Of those three 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. In a comparison of anthrax cases between the placebo and vaccine groups, including only those who were completely vaccinated, the calculated vaccine efficacy level against all reported cases of anthrax combined was 92.5% (lower 95% CI = 65%).

From 1962 to 1974, based on information reported to Centers for Disease Control and Prevention (CDC), 27 cases of anthrax occurred in mill workers or those living near mills in the United States. 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 the recommended six doses of anthrax vaccine. These individuals received either an earlier version of a protective antigen-based anthrax vaccine or BioThrax.

In an open-label safety study conducted by the CDC, BioThrax was administered in 0.5 mL doses according to a 0, 2, 4 week initial dose schedule followed by additional doses at 6, 12 and 18 months to complete the 6 dose vaccination series. Annual boosters were administered thereafter. In this study, 15,907 doses of BioThrax were administered to approximately 7,000 textile employees, laboratory workers and other at risk individuals and the incidence rates of local and systemic adverse reactions were recorded. (See ADVERSE REACTIONS)

A randomized clinical study was conducted by the U.S. Army Medical Research Institute of Infectious Diseases (USAMRIID) from 1996-1999 in 173 volunteers to evaluate changes to the vaccination

schedule and route of vaccine administration. Of those, 28 were enrolled into the study arm to receive the licensed schedule (initial injections at 0, 2 and 4 weeks followed by additional doses at 6, 12 and 18 months) and were subsequently monitored for the occurrence of local and systemic adverse events. (See ADVERSE REACTIONS)

INDICATIONS AND USAGE

BioThrax is indicated for the active immunization against *Bacillus anthracis* of individuals between 18 and 65 years of age who come in contact with animal products such as hides, hair or bones that come from anthrax endemic areas, and that may be contaminated with *Bacillus anthracis* spores. BioThrax is also indicated for individuals at high risk of exposure to *Bacillus anthracis* spores such as veterinarians, laboratory workers and others whose occupation may involve handling potentially infected animals or other contaminated materials.

Since the risk of anthrax infection in the general population is low, routine immunization is not recommended.

The safety and efficacy of BioThrax in a post-exposure setting has not been established.

CONTRAINDICATIONS

The use of BioThrax is contraindicated in subjects with a history of anaphylactic or anaphylactic-like reaction following a previous dose of BioThrax, or any of the vaccine components.

WARNINGS

Preliminary results of a recent unpublished retrospective study of infants born to women in the U.S. military service worldwide in 1998 and 1999 suggest that the vaccine may be linked with an increase in the number of birth defects when given during pregnancy (unpublished data, Department of Defense). Although these data are unconfirmed, 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.

Animal reproduction studies have not been conducted with BioThrax.

PRECAUTIONS

Before administration, the patient's medical immunization history should be reviewed for possible vaccine sensitivities and/or previous vaccination-related adverse events, in order to determine the existence of any contraindications to immunization.

Pregnant women should not be vaccinated against anthrax unless the potential benefits of vaccination clearly outweigh the potential risks to the fetus.

BioThrax should not be administered to individuals with a history of Guillain-Barré Syndrome (GBS) unless there is a clear benefit that outweighs the potential risk of a recurrence.

History of anthrax disease may increase the potential for severe local adverse reactions.

Patients 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-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.⁷

The administration of BioThrax to persons with concurrent moderate or severe illness should be postponed until recovery.⁷ Vaccination is not contraindicated in subjects with mild illnesses with or without low-grade fever.⁷

This product should be administered with caution to patients with a possible history of latex sensitivity since the vial stopper contains dry natural rubber.

Epinephrine solution, 1:1000, should always be available for immediate use in case an anaphylactic reaction should occur.

Pregnancy

PREGNANCY CATEGORY D.

See Warnings.

Nursing Mothers

It is not known whether exposure of the mother to BioThrax poses a risk of harm to the breast-feeding child. However, administration of non-live vaccines (e.g., anthrax vaccine) during breast-feeding is not medically contraindicated.⁷

Pediatric Use

Safety and effectiveness in pediatric patients have not been established.

Geriatric Use

No data regarding the safety of BioThrax are available for persons aged > 65 years.

ADVERSE REACTIONS

Pre Licensure

Local Reactions- In an open-label safety study, 15,907 doses of BioThrax were administered to approximately 7,000 textile employees, laboratory workers and other at risk individuals (*See Clinical Studies*). Over the course of the 5-year study, there were 24 reports (0.15% of doses administered) of severe local reactions (defined as edema or induration measuring greater than 120 mm in diameter or accompanied by marked limitation of arm motion or marked axillary node tenderness). There were 150 reports (0.94% of doses administered) of moderate local reactions (edema or induration greater than 30 mm but less than 120 mm in diameter) and 1373 reports (8.63% of doses administered) of mild local reactions (erythema only or induration measuring less than 30 mm in diameter).

Systemic Reactions- In the same open label study, four cases of systemic reactions were reported during a five-year reporting period (<0.06% of doses administered). These reactions, which were reported to have been transient, included fever, chills, nausea and general body aches.

Post Licensure

Recently (1996-1999), an assessment of safety was conducted as part of a randomized clinical study conducted by the U.S. Army Medical Research Institute of Infectious Diseases (USAMRIID) (*See Clinical Studies*). A total of 28 volunteers were enrolled to receive subcutaneous doses of BioThrax according to the licensed schedule. Each volunteer was observed for approximately 30 minutes after administration of AVA and scheduled for follow-up evaluations at 1-3 days, 1 week and 1 month after vaccination. Four volunteers reported seven acute adverse events within 30 minutes after the subcutaneous administration of BioThrax. These included erythema (3), headache (2), fever (1) and elevated temperature (1). Of these events, a single patient reported the simultaneous occurrence of headache, fever and elevated temperature (100.7°F).

Local Reactions- The most common local reactions reported after the first dose (n=28) in this study were tenderness (71%), erythema (43%), subcutaneous nodule (36%), induration (21%), warmth (11%) and local pruritus (7%). The most frequently reported local reactions after the second dose (n=28) were tenderness (61%), subcutaneous nodule (39%), erythema (32%), induration (18%), local pruritus (14%), warmth (11%) and arm motion limitation (7%). After the third dose (n=26), the most frequently reported local reactions were tenderness (58%), warmth (19%), local pruritus (19%), erythema (12%), arm motion limitation (12%), induration (8%), edema (8%) and subcutaneous nodule (4%). Local reactions were found to occur more often in women. No abscess or necrosis was observed at the injection site.

Systemic Reactions- All systemic adverse events reported in this study were transient in nature. The systemic reactions most frequently reported after the first dose (n=28) were headache (7%), respiratory difficulty (4%) and fever (4%). After the second dose (n=28), the most frequently reported systemic reactions were malaise (11%), myalgia (7%), fever (7%), headache (4%), anorexia (4%) and nausea or vomiting (4%). After the third dose (n=26), the most frequently reported systemic reactions were headache (4%), malaise (4%), myalgia (4%) and fever (4%). There was one report of delayed hypersensitivity reaction beginning with lesions 3 days after the first dose. The subject was reported to have diffuse hives by day 17, 3 days after the second dose, and had swollen hands, face and feet by day 18 and discomfort swallowing. The subject did not receive any subsequent scheduled doses.

Post Licensure Adverse Event Surveillance

Data regarding potential adverse events following anthrax vaccination are available from the Vaccine Adverse Event Reporting System (VAERS).⁸ The report of an adverse event to VAERS is not proof that a vaccine caused the event. Because of the limitations of spontaneous reporting systems, determining causality for specific types of adverse events, with the exception of injection-site reactions, is often not possible using VAERS data alone. The following four paragraphs describe spontaneous reports of adverse events, without regard to causality.

From 1990 to October 2001, over 2 million doses of BioThrax have been administered in the United States. Through October 2001, VAERS received approximately 1850 spontaneous reports of adverse events. The most frequently reported adverse events were erythema, headache, arthralgia, fatigue, fever, peripheral swelling, pruritus, nausea, injection site edema, pain/tenderness and dizziness.

Approximately 6% of the reported events were listed as serious. Serious adverse events include those that result in death, hospitalization, permanent disability or are life-threatening. The serious adverse events most frequently reported were in the following body system categories: general disorders and administration site conditions, nervous system disorders, skin and subcutaneous tissue disorders, and musculoskeletal, connective tissue and bone disorders. Anaphylaxis and/or other generalized hypersensitivity reactions, as well as serious local reactions, were reported to occur occasionally following administration of BioThrax. None of these hypersensitivity reactions have been fatal.

Other infrequently reported serious adverse events that have occurred in persons who have received BioThrax have included: cellulitis, cysts, pemphigus vulgaris, endocarditis, sepsis, angioedema and

other hypersensitivity reactions, asthma, aplastic anemia, neutropenia, idiopathic thrombocytopenia purpura, lymphoma, leukemia, collagen vascular disease, systemic lupus erythematosus, multiple sclerosis, polyarteritis nodosa, inflammatory arthritis, transverse myelitis, Guillain-Barré Syndrome, immune deficiency, seizure, mental status changes, psychiatric disorders, tremors, cerebrovascular accident (CVA), facial palsy, hearing and visual disorders, aseptic meningitis, encephalitis, myocarditis, cardiomyopathy, atrial fibrillation, syncope, glomerulonephritis, renal failure, spontaneous abortion and liver abscess. Infrequent reports were also received of multisystem disorders defined as chronic symptoms involving at least two of the following three categories: fatigue, mood-cognition, musculoskeletal system.

Reports of fatalities included sudden cardiac arrest (2), myocardial infarction with polyarteritis nodosa (1), aplastic anemia (1), suicide (1) and central nervous system (CNS) lymphoma (1).

Post Licensure Survey Studies

In addition to the VAERS data, adverse events following anthrax vaccination have been assessed in survey studies conducted by the Department of Defense in the context of their anthrax vaccination program. These survey studies are subject to several methodological limitations, e.g., sample size, the limited ability to detect adverse events, observational bias, loss to follow-up, exemption of vaccine recipients with previous adverse events and the absence of unvaccinated control groups. Overall, the most reported events were localized, minor and self-limited and included muscle or joint aches, headache and fatigue. Across these studies, systemic reactions were reported in 5-35% of vaccine recipients and included reports of malaise, chills, rashes, headaches and low-grade fever. Women reported these symptoms more often than men.

Reporting Adverse Events

Adverse events following immunization with BioThrax should be reported to the Medical Affairs Division of BioPort Corporation (517) 327-1675 during regular working hours and (517) 327-7200 during off hours. Adverse events may also be reported to the U. S. Department of Health and Human Services (DHHS) Vaccine Adverse Event Reporting System. Report forms and reporting requirement information can be obtained from VAERS through a toll free number 1-800-822-7967.

DOSAGE AND ADMINISTRATION

Dosage

Immunization consists of three subcutaneous injections, 0.5 mL each, given 2 weeks apart followed by three additional subcutaneous injections, 0.5 mL each, given at 6, 12, and 18 months. Subsequent booster injections of 0.5 mL of BioThrax at one-year intervals are recommended.

Administration

Use a separate 5/8-inch, 25- to 27-gauge sterile needle and syringe for each patient to avoid transmission of viral hepatitis and other infectious agents. Use a different site for each sequential injection of this vaccine and do not mix with any other product in the syringe.

1. 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.
2. Wipe the rubber stopper with an alcohol swab and allow to dry before inserting the needle.
3. Clean the area to be injected with an alcohol swab or other suitable antiseptic.
4. Holding the needle at a 45° angle to the skin, inject the vaccine subcutaneously.
5. DO NOT inject the product intravenously. Follow the usual precautions to ensure that you have not entered a vein before injecting the vaccine.
6. After injecting, withdraw the needle and briefly and gently massage the injection site to promote dispersal of the vaccine.

HOW SUPPLIED/STORAGE

Anthrax Vaccine Adsorbed (BioThrax™) is supplied in 5 mL multidose vials.

THIS PRODUCT IS TO BE STORED AT 2°C TO 8°C (36 TO 46°F). Do not freeze. Do not use after the expiration date given on the package.

Nonclinical Toxicology

Carcinogenesis, Mutagenesis, Impairment of Fertility

Animal studies have not been performed to ascertain whether BioThrax has carcinogenic action, or any effect on fertility.

REFERENCES

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Revision: January 31, 2002

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