prepare. prevent. protect.

SPECIALTY PRODUCTS THAT ADDRESS SERIOUS PUBLIC HEALTH THREATS

emergent
biosolutions®

GLOBAL HEALTH SECURITY AGENDA:

"In a globally connected world


...a health threat anywhere
is a health threat everywhere."
Emergent BioSolutions is a global specialty biopharmaceutical company. Through our work, we envision protecting and enhancing 50 million lives with our products by 2025.

The Threat is Real

NATURAL THREATS

ACCIDENTAL THREATS

INTENTIONAL THREATS

"Time bomb: ISIS has recruited an army of scientists and already smuggled chemical and biological weapons into Europe."

– European Parliament Report, December 2015

"The Ebola epidemic has shown, once again, that in today's interconnected world, health challenges anywhere create health challenges everywhere– and the best way to overcome those challenges is to dedicate ourselves to the great cause of reducing the global burden of infectious disease."

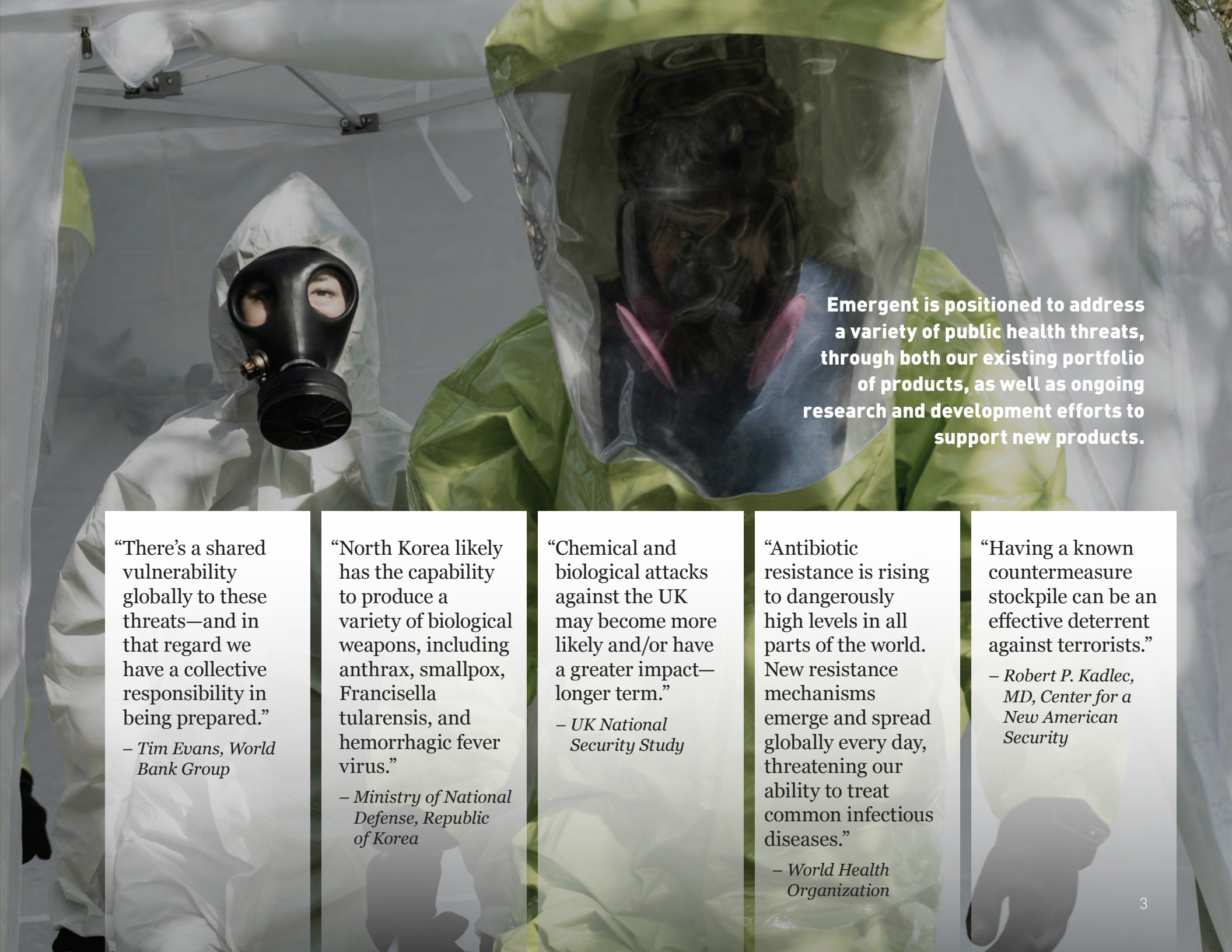
– Bill Gates

"Zika virus and its complications represent a new type of public health threat that requires a unique and integrated strategy."

– World Health Organization

"One area of public health emergency preparedness that has not been examined in depth is preparedness for incidents involving the release of chemical or radiological substances. Past experience—with chemical and nuclear plant accidents, train collisions, product tampering, and chemical terrorism—shows that such incidents can have serious public health consequences."

– RAND Corporation Think Tank



Emergent is positioned to address a variety of public health threats, through both our existing portfolio of products, as well as ongoing research and development efforts to support new products.

"There's a shared vulnerability globally to these threats—and in that regard we have a collective responsibility in being prepared."

– Tim Evans, World Bank Group

"North Korea likely has the capability to produce a variety of biological weapons, including anthrax, smallpox, Francisella tularensis, and hemorrhagic fever virus."

– Ministry of National Defense, Republic of Korea

"Chemical and biological attacks against the UK may become more likely and/or have a greater impact—longer term."

– UK National Security Study

"Antibiotic resistance is rising to dangerously high levels in all parts of the world. New resistance mechanisms emerge and spread globally every day, threatening our ability to treat common infectious diseases."

– World Health Organization

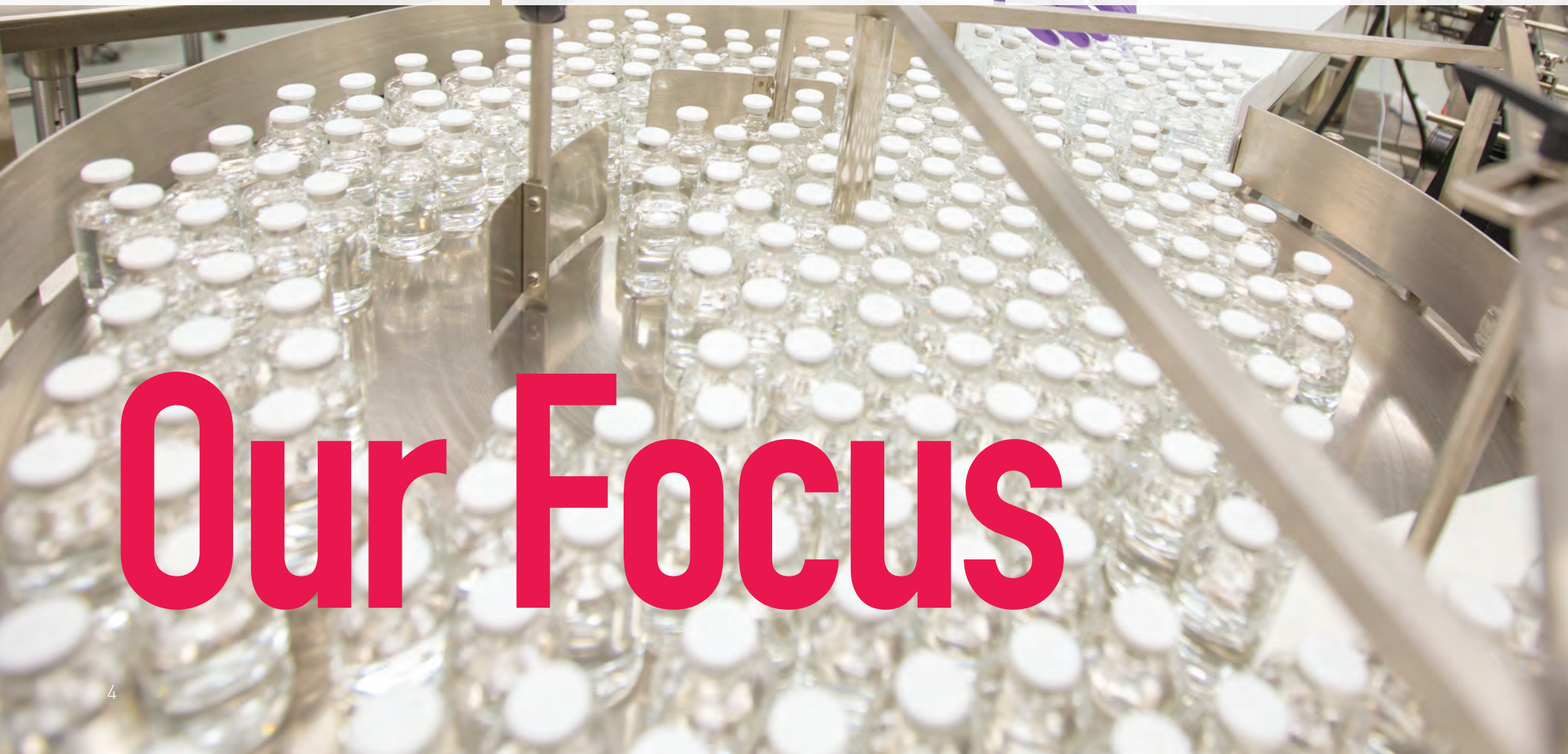
"Having a known countermeasure stockpile can be an effective deterrent against terrorists."

– Robert P. Kadlec, MD, Center for a New American Security

BIOLOGICAL THREATS

CHEMICAL THREATS

EMERGING INFECTIOUS DISEASES



Our Focus

MANUFACTURING INNOVATION

- **Five manufacturing facilities located in the United States and Canada**
  - Lansing, MI
  - Baltimore, MD – Camden Campus
  - Baltimore, MD – Bayview Campus
  - Winnipeg, Canada
  - Hattiesburg, MS
- **Manufacturing capabilities supporting all phases of drug development from project origin through fill-finish of final product**
- **Diverse experience: vaccines, devices, hyperimmunes, drug device combinations, blood plasma collection, viral**
- **Currently producing or supporting the manufacture of more than 20 commercial products**
- **Bayview Campus developed in a public-private partnership; one of only three Center for Innovation in Advanced Development and Manufacturing (CIADM) facilities in the U.S.**

Product Overview

PRODUCTS THAT TARGET
BIOLOGICAL THREATS

BioThrax®
Anthrax Vaccine Adsorbed

Please see Important Safety Information on p.8

Anthrasil™ *
Anthrax Immune Globulin Intravenous (human)

Please see Important Safety Information on p.9

BAT®
Botulism Antitoxin Heptavalent (A, B, C, D, E, F, G) – (Equine)

Please see Important Safety Information on p.10

VIGIV *
[Vaccinia Immune Globulin Intravenous (Human)]

Please see Important Safety Information on p.11

*Please see full Prescribing Information, including black box warning.

PRODUCTS THAT TARGET

CHEMICAL THREATS

RSDL™
Reactive Skin
Decontamination Lotion Kit

Please see Important Safety Information on p.12

AUTO-INJECTOR PLATFORM

The Auto-Injector is not approved by the U.S. FDA

PRODUCTS THAT TARGET
BIOLOGICAL THREATS

ANTHRAX

BioThrax®
Anthrax Vaccine Adsorbed

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

BioThrax is approved for:

1. Pre-exposure prophylaxis of disease in persons at high risk of exposure.
2. Post-exposure prophylaxis of disease following suspected or confirmed Bacillus anthracis exposure, when administered in conjunction with recommended antibacterial drugs. The effectiveness of BioThrax is based solely on efficacy studies conducted in animal models of inhalational anthrax.

Approvals: U.S. FDA, Germany PEI and Singapore HSA
Customers: More than 12.3 million BioThrax doses have been administered.

IMPORTANT SAFETY INFORMATION

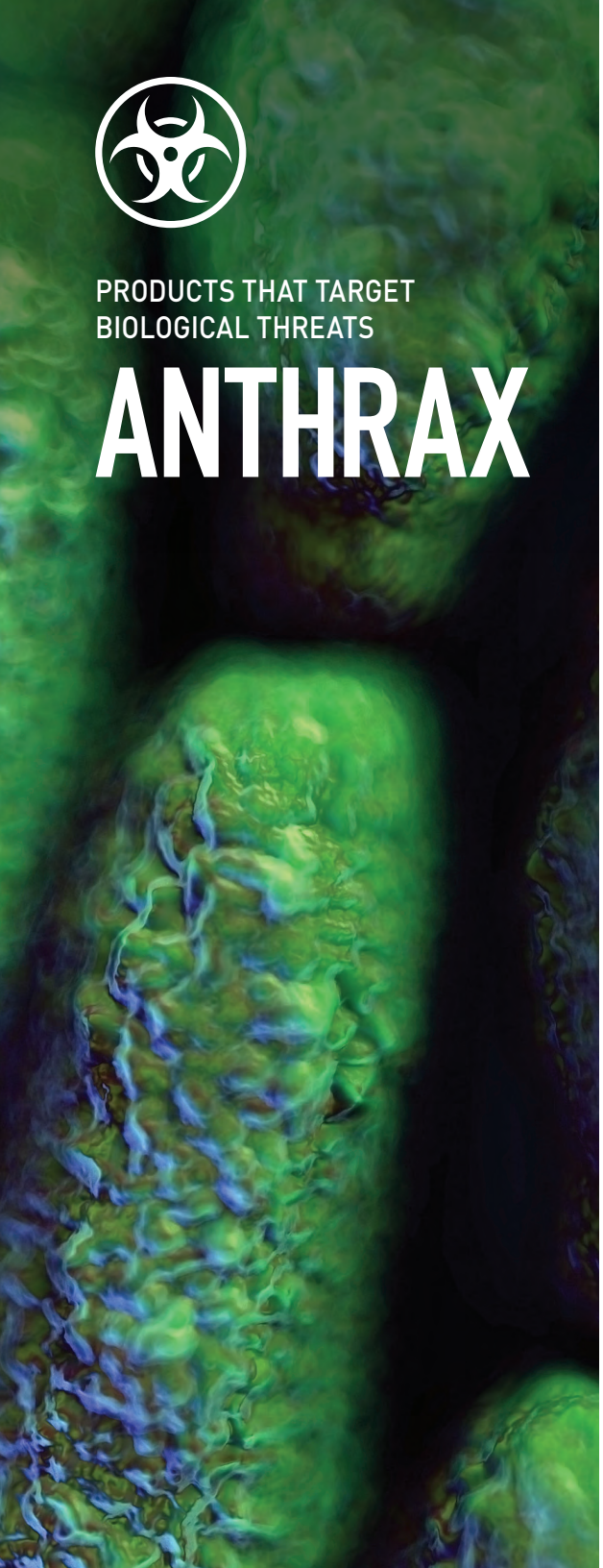
Contraindication
Severe allergic reaction (e.g. anaphylaxis) after a previous dose of BioThrax or a component of the vaccine.

Adverse Reactions
The most common (≥10%) local (injection-site) adverse reactions observed in clinical studies were tenderness, pain, erythema, edema, and arm motion limitation. The most common (≥5%) systemic adverse reactions were muscle aches, headache, and fatigue. Acute allergic reactions, including anaphylaxis, have occurred with BioThrax.

Warnings and Precautions
Vaccination with BioThrax should be avoided by individuals with a history of anaphylactic or anaphylactic-like reaction following a previous dose of BioThrax or any component of the vaccine. If BioThrax is used during pregnancy, or if the patient becomes pregnant during the immunization series, the patient should be apprised of the potential hazard to the fetus. Pregnant women should not be vaccinated unless the potential benefits of vaccination have been determined to outweigh the potential risk to the fetus. It is not known whether BioThrax is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when BioThrax is administered to a nursing woman.

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

Please see accompanying full U.S. Prescribing Information.



PRODUCTS THAT TARGET
BIOLOGICAL THREATS

ANTHRAX

Anthrasil™
Anthrax Immune Globulin
Intravenous (human)

Anthrasil is an Anthrax Immune Globulin Intravenous (Human) indicated for the treatment of inhalational anthrax in adult and pediatric patients in combination with appropriate antibacterial drugs. The effectiveness of ANTHRASIL is based solely on efficacy studies conducted in animal models of inhalational anthrax.

Approvals: U.S. FDA
Customers: More than 10,000 doses sold to the U.S. and other countries.

IMPORTANT SAFETY INFORMATION

WARNING: INTERACTIONS WITH GLUCOSE MONITORING SYSTEMS AND THROMBOSIS

- Maltose in immune globulin products, including ANTHRASIL, may give falsely high blood glucose levels with some point-of-care blood glucose testing systems (for example those based on the GDH-PQQ or glucose-dye-oxidoreductase methods) resulting in inappropriate administration of insulin and life-threatening hypoglycemia. To avoid interference by maltose contained in ANTHRASIL, perform blood glucose measurement in patients receiving ANTHRASIL with a glucose-specific method (monitor and test strips).
- Thrombosis may occur with immune globulin products, including ANTHRASIL. Risk factors may include advanced age, prolonged immobilization, hypercoagulable conditions, history of venous or arterial thrombosis, use of estrogens, indwelling vascular catheters, hyperviscosity and cardiovascular risk factors. Thrombosis may occur in the absence of known risk factors.
- For patients at risk of thrombosis, administer ANTHRASIL at the minimum infusion rate practicable. Ensure adequate hydration in patients before administration. Monitor for signs and symptoms of thrombosis and assess blood viscosity in patients at risk of hyperviscosity.

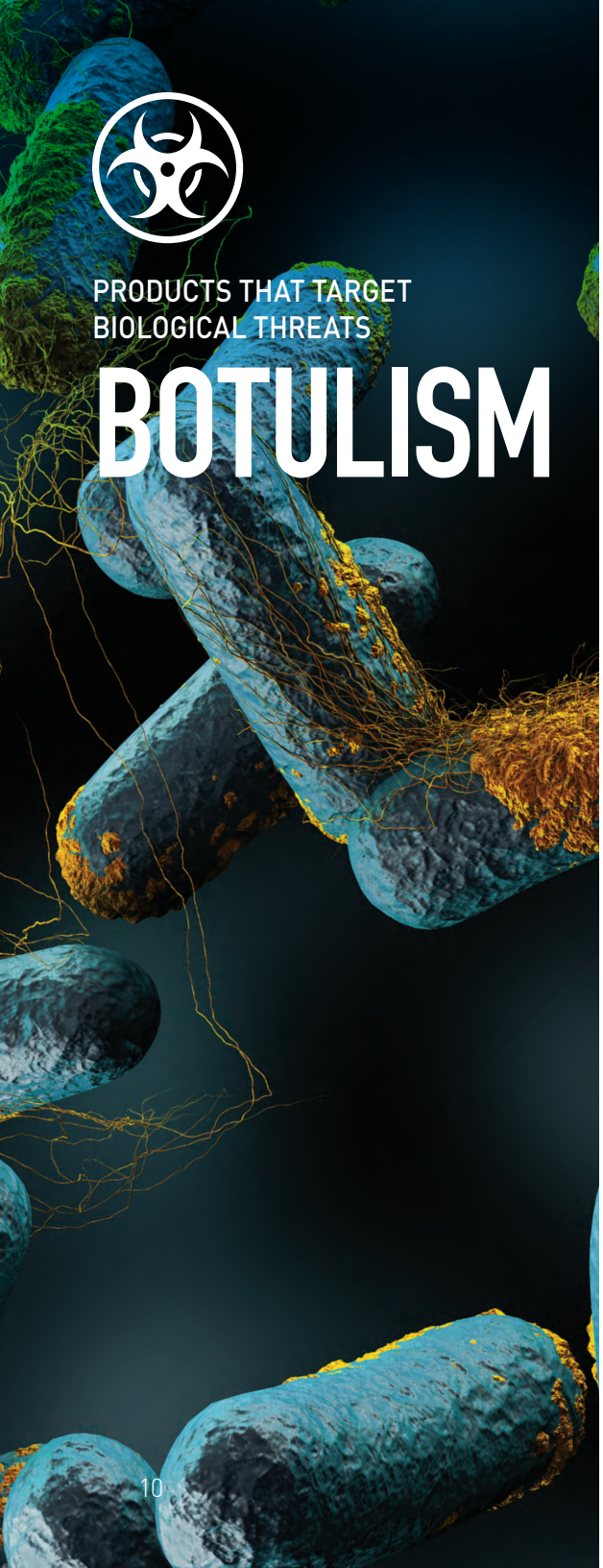
ANTHRASIL is contraindicated in patients with a history of anaphylactic or severe systemic reaction to human immune globulins and patients with IgA deficiency with antibodies against IgA and a history of IgA hypersensitivity.

Severe hypersensitivity reactions, including anaphylaxis, may occur following ANTHRASIL administration. Prepare for monitoring and management of allergic reactions. Aseptic meningitis and transfusion-related acute lung injury may occur following ANTHRASIL administration. ANTHRASIL is made from human plasma and may contain infectious agents, e.g. viruses. Patients with renal dysfunction should have their renal function and urine output monitored. Administer ANTHRASIL at the minimum infusion rate practicable in patients at risk for renal failure.

The most common adverse reactions to ANTHRASIL observed in >5% of healthy volunteers in clinical trials were headache, infusion site pain and swelling, nausea, and back pain.

Please see accompanying full U.S. Prescribing Information.

BAT, VIGIV, and ANTHRASIL are biological products shown to be effective under the animal rule and are only available in the U.S. through the CDC and Strategic National Stockpile.



PRODUCTS THAT TARGET
BIOLOGICAL THREATS

BOTULISM

BAT®

Botulism Antitoxin Heptavalent
(A, B, C, D, E, F, G) – (Equine)

BAT is a mixture of immune globulin fragments indicated for the treatment of symptomatic botulism following documented or suspected exposure to botulinum neurotoxin serotypes A, B, C, D, E, F, or G in adults and pediatric patients. The effectiveness of BAT is based solely on efficacy studies conducted in animal models of botulism.

Approvals: U.S. FDA
Customers: Over 150,000 doses sold.

IMPORTANT SAFETY INFORMATION

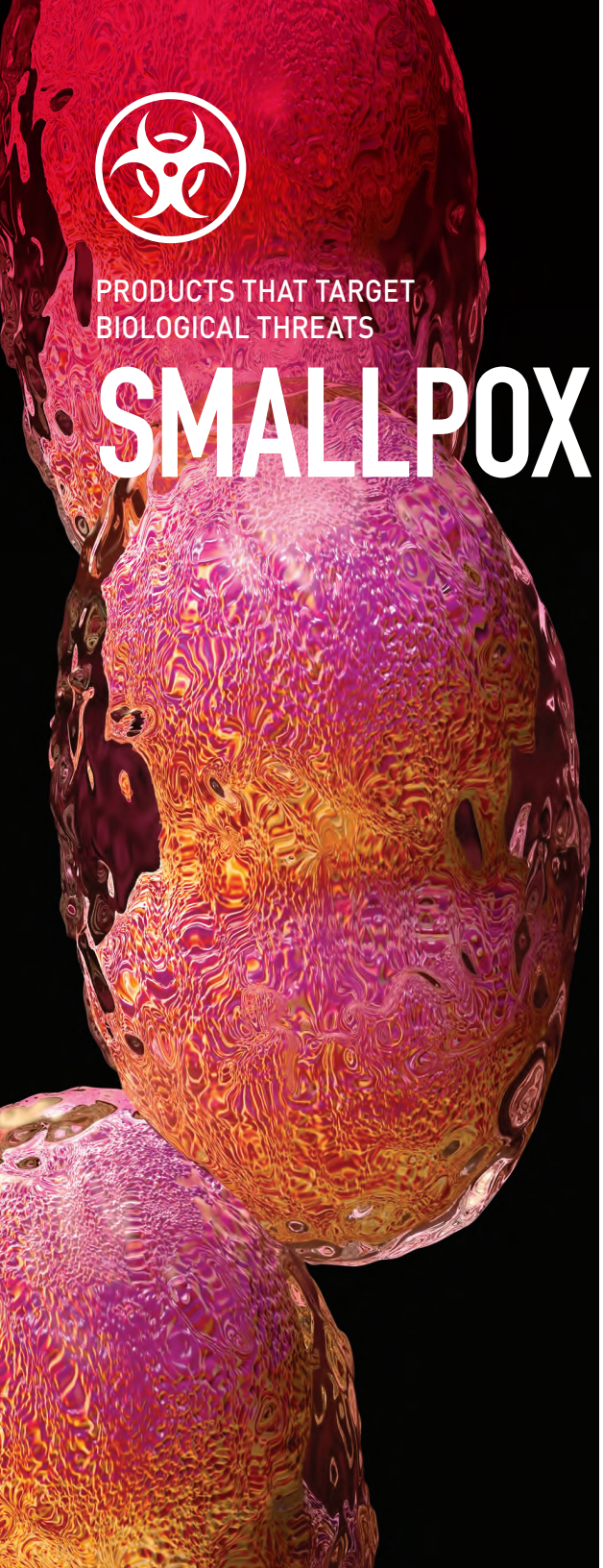
Severe hypersensitivity reactions, including anaphylaxis, as well as delayed allergic reactions, including serum sickness may occur following BAT administration. Prepare for monitoring and management of allergic reactions. Infusion reactions may be related to the infusion rate of BAT. In case of hypersensitivity reaction, discontinue BAT administration immediately and administer appropriate emergency care. Monitor and slow or interrupt the infusion and administer treatment based upon the severity of the reaction. Because BAT contains maltose, interference with non-glucose specific blood sugar testing systems can occur. Use glucose-specific testing systems. BAT is made from equine plasma and may contain infectious agents, e.g. viruses.

The most common adverse reactions observed in ≥5 % of healthy volunteers in clinical trials were headache, nausea, pruritus and urticaria. One serious adverse reaction of hemodynamic instability was observed with BAT administration.

Special Populations:
There is no human or animal data for use of BAT during pregnancy. BAT should only be given to pregnant and nursing women if the potential benefits outweigh the potential risks. It is not known whether BAT is excreted in human milk. The safety and efficacy of BAT has not been established in pediatric and geriatric populations. Only limited safety data exists for pediatric populations.

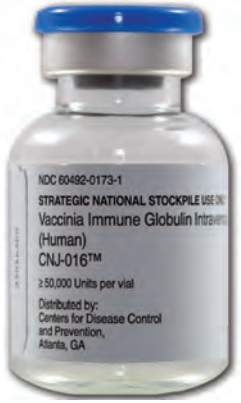
Please see accompanying full U.S. Prescribing Information.

BAT, VIGIV, and ANTHRASIL are biological products shown to be effective under the animal rule and are only available in the U.S. through the CDC and Strategic National Stockpile.



PRODUCTS THAT TARGET BIOLOGICAL THREATS

SMALLPOX



CNJ-016™

VIGIV

[Vaccinia Immune Globulin Intravenous (Human)]

VIGIV is an Immune Globulin Intravenous (Human), 5% Liquid, indicated for the treatment of complications due to vaccinia vaccination, including: • Eczema vaccinatum • Progressive vaccinia • Severe generalized vaccinia • Vaccinia infections in individuals who have skin conditions • Aberrant infections induced by vaccinia virus (except in cases of isolated keratitis)

VIGIV is not indicated for isolated vaccinia keratitis or postvaccinial encephalitis.

Approvals: U.S. FDA and Health Canada
Customers: More than 35,000 doses sold in the U.S. and other countries.

IMPORTANT SAFETY INFORMATION

WARNING: INTERACTIONS WITH GLUCOSE MONITORING SYSTEMS

Blood glucose measurement in patients receiving VIGIV must be done with a glucose-specific method (monitor and test strips) to avoid interference by maltose contained in VIGIV. Glucose dehydrogenase pyrroloquinolinequinone (GDH-PQQ) or glucose-dye-oxidoreductase method (monitor and test strips) must not be used for blood glucose testing in patients receiving VIGIV, since maltose in IGIV products has been shown to give falsely high blood glucose levels in these testing systems. This could result in the inappropriate administration of insulin, resulting in life-threatening hypoglycemia. Cases of true hypoglycemia may go untreated if the hypoglycemic state is masked by falsely elevated glucose readings.

Carefully review the production information of the blood glucose testing system, including that of the test strips, to determine if the system is appropriate for use with maltose-containing parenteral products.

VIGIV is contraindicated in patients with: isolated vaccinia keratitis; history of anaphylaxis or severe systemic reaction associated with the administration of this or other human immune globulins; and IgA deficiency with antibodies against IgA and a history of IgA hypersensitivity, as it contains trace amounts of IgA (40 mcg/mL).

Severe hypersensitivity reactions, including anaphylaxis, may occur following VIGIV administration. Prepare for monitoring and management of allergic reactions. Thrombosis, aseptic meningitis syndrome, hemolysis/hemolytic anemia, acute renal dysfunction/renal failure, and noncardiogenic pulmonary edema (Transfusion-Related Acute Lung Injury [TRALI]) may occur following VIGIV administration. For patients at risk of thrombosis, administer VIGIV at the minimum dose and infusion rate practicable. Ensure adequate hydration in patients before administration. Monitor for signs and symptoms of thrombosis and assess blood viscosity in patients at risk for hyperviscosity. Conduct confirmatory tests if hemolysis or TRALI is suspected. Monitor renal function and urine output in patients at risk of renal failure.

VIGIV is made from human plasma and may contain infectious agents, e.g. viruses.

The most common adverse drug reactions to VIGIV (>10%) are headache, nausea, rigors and dizziness.

Please see accompanying full U.S. Prescribing Information.

BAT, VIGIV, and ANTHRASIL are biological products shown to be effective under the animal rule and are only available in the U.S. through the CDC and Strategic National Stockpile.

PRODUCTS THAT TARGET
CHEMICAL THREATS

SKIN DECONTAMINATION

RSDL™
Reactive Skin
Decontamination Lotion Kit

RSDL® removes or neutralizes chemical warfare agents, including organophosphate-based pesticides from the skin, within 2 minutes.

Approvals and Clearances: U.S. FDA, EU CE Mark, Australian TGA, Health Canada, Israel Ministry of Health
Customers: More than 5 million packets sold to military, ministries of health, and first responders in over 35 countries.

IMPORTANT SAFETY INFORMATION

See full U.S. Prescribing Information for additional Important Safety Information.

Warning: Fire Hazard. Combustion may occur upon contact with strong oxidizing chemicals (e.g., HTH, super tropical bleach). Do not discard used RSDL components into strong oxidizing chemicals or their containers.

For external use only. Contact with eyes and mucous membranes should be avoided. In emergency conditions, the RSDL decontaminating solution does not require immediate removal from skin, but should be rinsed as soon as it is safe to do so. An ingredient of the RSDL decontaminating solution may be absorbed. Studies with the RSDL decontaminating solution left on the skin for 24 hours showed minimal adverse effects, however some patients have been known to experience minor skin irritation.

PRODUCTS THAT TARGET
CHEMICAL THREATS

NERVE AGENT EXPOSURE RESPONSE

Auto-Injector Platform

Ruggedized Auto-Injector Device

The Emergent Auto-Injector is designed for intramuscular rapid delivery of antidotes and other emergency response medical treatments for military use. The Emergent Auto-Injector is intended as a drug delivery component to address exposure to certain chemical agents and to other similar emerging threats. The injector can be used for both self- and buddy-injection as well as a treatment of casualties by First Responders.

Approvals: Auto-Injector is not approved by the U.S. FDA and is not marketed in the U.S.

DEVELOPMENT AND MANUFACTURING

Lansing, MI

Baltimore, MD (Camden Campus)

Lansing, MI

The Lansing facilities offer large-scale, vertically integrated manufacturing capabilities, with the capacity to produce up to 20 million doses of the only FDA-approved anthrax vaccine annually on a single manufacturing train. These capabilities support the production of multiple future vaccine and bacterial platform-based candidates.

Baltimore, MD—Camden

Emergent's sterile-injectable manufacturing facility currently produces over 20 commercial products and has contributed to the development and production of more than 200 clinical products since 1998. The Camden facility offers contract manufacturing fill and finish services for vial and syringe presentations in both liquid and lyophilized forms at clinical and commercial scale.


Baltimore, MD (Bayview Campus)


Winnipeg, Canada


Hattiesburg, MS

Baltimore, MD—Bayview

Developed in a public-private partnership, the Bayview campus is one of only three Centers for Innovation in Advanced Development and Manufacturing (CIADM) in the United States. The cutting-edge facilities allow for flexible, single use bioreactor-based development and manufacturing of critical countermeasures in support of the preparedness needs of the U.S. government and our country as a whole. The Bayview facility is poised to produce 50 million doses of pandemic flu vaccines in a 4-month period and can simultaneously support the production of viral and non-viral products.

Winnipeg, Canada

The Winnipeg manufacturing facilities have a 50-year history of manufacturing life-saving medical countermeasures, hyperimmune specialty plasma products, and products addressing serious and emerging public health threats. Experience includes recombinant and advanced product development, human and equine plasma products, and filling.

Hattiesburg, MS

State-of-the-art facility focused on manufacturing and packaging medical countermeasures addressing chemical warfare threats.

Dedicated to one simple mission:

Protect Life

"We live in a world where events that threaten public health unfold quickly and often without warning. As we have seen, these threats can be intentional, such as chemical or biological weapons, or naturally occurring emerging infectious diseases. Emergent is proud to be creating a safer world by providing specialized products and innovative preparedness solutions designed to protect individuals and communities from these public health threats. We look forward to partnering with you in protecting life."

— Daniel J. Abdun-Nabi, President and CEO of Emergent BioSolutions

emergent biosolutions®

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PROTECTING & ENHANCING
50 MILLION LIVES BY 2025

400 Professional Drive, Suite 400, Gaithersburg, Maryland 20879 USA
www.emergentbiosolutions.com

Effective October 2016

CM-AIG-0001

HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use BIOTHRAX safely and effectively. See full prescribing information for BIOTHRAX.
BIOTHRAX® (Anthrax Vaccine Adsorbed)
Suspension for Intramuscular or Subcutaneous Injection
Initial U.S. Approval: 1970

RECENT MAJOR CHANGES

INDICATIONS AND USAGE (1.1, 1.2) November/2015
DOSAGE AND ADMINISTRATION (2.1, 2.2) November/2015

INDICATIONS AND USAGE

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

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

The efficacy of BioThrax for post-exposure prophylaxis is based solely on studies in animal models of inhalational anthrax. (1)

DOSAGE AND ADMINISTRATION

For intramuscular or subcutaneous injection only.
Each dose is 0.5 mL.
Pre-Exposure Prophylaxis (2.1):

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

In persons who are at risk for hematoma formation following intramuscular injection, BioThrax may be administered by the subcutaneous route. The pre-exposure prophylaxis schedule for BioThrax administered subcutaneously is 0, 2, 4 weeks, and 6 months with booster doses 6 and 12 months after completion of the primary series, and at 12-month intervals thereafter.

Post-Exposure Prophylaxis (2.1):

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

DOSAGE FORMS AND STRENGTHS

Suspension for injection (0.5 mL dose) in 5 mL multidose vials. (3, 11)

CONTRAINDICATIONS

Severe allergic reaction (e.g. anaphylaxis) after a previous dose of BioThrax or a component of the vaccine. (4)

WARNINGS AND PRECAUTIONS

- The stopper of the vial contains natural rubber latex and may cause allergic reactions in latex sensitive individuals. (5.2)
- Pregnancy: Avoid use in pregnancy unless the potential benefit outweighs the potential risk to the fetus (5.3, 8.1)

ADVERSE REACTIONS

The most common (>10%) local (injection-site) adverse reactions observed in clinical studies were tenderness, pain, erythema, edema, and arm motion limitation. The most common (≥5%) systemic adverse reactions were muscle aches, fatigue, and headache. (6)

To report SUSPECTED ADVERSE REACTIONS, contact Emergent BioSolutions at 1-877-246-8472 or VAERS at 1-800-822-7967 or www.vaers.hhs.gov.

USE IN SPECIFIC POPULATIONS

- Pregnancy: Advise women of potential risk to the fetus. (5.3, 8.1) Pregnancy registry available, contact BioThrax (Anthrax) Vaccine in Pregnancy Registry (Phone: 1-619-553-9255). (8.1)
- Safety and effectiveness of BioThrax have not been established in pediatric or geriatric populations. (8.4, 8.5)

See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling.

Revised: November 2015

FULL PRESCRIBING INFORMATION: CONTENTS*

***Sections or subsections omitted from the full prescribing information are not listed.**

FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

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

1.1 BioThrax is approved for pre-exposure prophylaxis of disease in persons whose occupation or other activities place them at high risk of exposure.

1.2 BioThrax is approved for post-exposure prophylaxis of disease following suspected or confirmed *Bacillus anthracis* exposure, when administered in conjunction with recommended antibacterial drugs.

The efficacy of BioThrax for post-exposure prophylaxis is based solely on studies in animal models of inhalational anthrax.

2 DOSAGE AND ADMINISTRATION

For intramuscular or subcutaneous injection only.

2.1 Dose

Each dose is 0.5 mL.

Pre-Exposure Prophylaxis:

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

In persons who are at risk for hematoma formation following intramuscular injection, BioThrax may be administered by the subcutaneous route. The pre-exposure prophylaxis schedule for BioThrax administered subcutaneously is 0, 2, 4 weeks, and 6 months with booster doses at 6 and 12 months after completion of the primary series and at 12-month intervals thereafter.

The optimal schedule for catch up of missed or delayed booster doses is unknown. [See *Clinical Studies* (14)]

Post-Exposure Prophylaxis:

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

2.2 Administration

Shake the vial thoroughly to ensure that the suspension is homogeneous during withdrawal. Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit. If either of these conditions exists, do not administer the vaccine.

Administer pre-exposure prophylaxis vaccinations intramuscularly into the deltoid muscle. If pre-exposure prophylaxis requires subcutaneous administration, administer over the deltoid muscle. Administer post-exposure prophylaxis vaccinations subcutaneously over the deltoid muscle.

Do not mix with any other product in the syringe.

3 DOSAGE FORMS AND STRENGTHS

BioThrax is a suspension for injection (0.5 mL dose) in 5 mL multidose vials. See *Description* (11) for the complete listing of ingredients.

4 CONTRAINDICATIONS

Do not administer BioThrax to individuals with a history of anaphylactic or anaphylactic-like reaction following a previous dose of BioThrax or any component of the vaccine, including aluminum, benzethonium chloride, and formaldehyde. [See *Description* (11)]

5 WARNINGS AND PRECAUTIONS

5.1 Hypersensitivity Reactions

Acute allergic reactions, including anaphylaxis, have occurred with BioThrax. Appropriate medical treatment and supervision must be available to manage possible anaphylactic reactions following administration of the vaccine. [See *Contraindications* (4)]

5.2 Latex

The stopper of the vial contains natural rubber latex and may cause allergic reactions to patients with a possible history of latex sensitivity. [See *How Supplied/Storage and Handling* (16)]

5.3 Pregnancy

BioThrax can cause fetal harm when administered to a pregnant woman. If this drug is used during pregnancy, or if the patient becomes pregnant while taking this drug, the patient should be apprised of the potential hazard to a fetus. Weigh the potential benefits of vaccination against the potential risk to the fetus. [See *Use in Specific Populations* (8.1)]

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. Results of a large observational study that examined the rate of birth defects among 37,140 infants born to U.S. 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 and compared to unvaccinated women.[1] While the increased birth defect rates were not statistically significant when compared with infants born to women vaccinated outside of pregnancy, 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.

5.4 History of Anthrax Disease

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

5.5 Altered Immunocompetence

If BioThrax is administered to immunocompromised persons, including those receiving immunosuppressive therapy, the immune response may be diminished.

5.6 Limitations of Vaccine Effectiveness

Vaccination with BioThrax may not protect all individuals.

6 ADVERSE REACTIONS

The most common (≥10%) local (injection-site) adverse reactions observed in clinical studies were tenderness, pain, erythema, edema, and arm motion limitation. The most common (≥5%) systemic adverse reactions were muscle aches, headache, and fatigue.

6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a product cannot be directly compared to rates in the clinical trials of another product and may not reflect the rates observed in clinical practice.

Pre-Exposure Prophylaxis

In an open-label safety study of 15,907 doses of BioThrax administered by the subcutaneous route to approximately 7,000 textile employees, laboratory workers and other at risk individuals, local and systemic reactions were monitored. Over the course of the 5-year study the following local adverse reactions were reported: 24 (0.15% of doses administered) severe local adverse 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), 150 (0.94% of doses administered) moderate local adverse reactions (edema or induration greater than 30 mm but less than 120 mm in diameter), and 1,373 (8.63% of doses administered) mild local adverse reactions (erythema only or induration measuring less than 30 mm in diameter). Four cases of systemic adverse reactions were reported during the 5-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.

In a randomized, double-blinded, placebo-controlled, and active-controlled multi-center clinical study, 1,564 healthy subjects were enrolled. The objective of this study was to evaluate the effect of (1) changing the route of vaccine administration from subcutaneous (SC) to intramuscular (IM), and (2) of reducing the number of doses on the safety and immunogenicity of BioThrax. The dosing schedules and routes studied are provided in Table 1. [See *Clinical Studies* (14)]

Group A (8SC) (N=259) received BioThrax via the SC route of administration at Weeks 0, 2, 4, and Months 6, 12, 18 followed by 2 annual boosters (original U.S. licensed route/schedule). Group A served as the active control in this study.

Group B (8IM) (N=262) received BioThrax via the IM route of administration at Weeks 0, 2, 4, and Months 6, 12, 18 followed by 2 annual boosters.

Group C (COM) (N=782) received BioThrax via the IM route of administration at Weeks 0, 4 (no Week 2 dose), and Month 6 with various schedules thereafter. (Group C represents data from 3 randomized groups [Groups D, E, and F] combined for the analysis through Month 7 because the schedules are identical through the Month 6 dose.)

Group D (7IM) (N=256) received BioThrax via the IM route of administration at Weeks 0, 4 (no Week 2 dose), and Months 6, 12, 18 followed by 2 annual boosters.

Group E (5IM) (N=258) received BioThrax via the IM route of administration at Weeks 0, 4 (no Week 2 dose), and Months 6, 18 followed by 1 booster dose at Month 42 (2 year interval).

Group F (4IM) (N=268) received BioThrax via the IM route of administration at Weeks 0, 4 (no Week 2 dose), and Month 6 followed by 1 booster dose at Month 42 (3 year interval).

Table 1: Vaccination Schedules and Routes Evaluated

Group/Route	**Weeks**			**Months**				
	0	**2**	**4**	**6**	**12**	**18**	**30**	**42**
Group A (8SC)[a]	V	V	V	V	V	V	V	V
Group B (8IM)	V	V	V	V	V	V	V	V
Group D (7IM)	V	S	V	V	V	V	V	V
Group E (5IM)	V	S	V	V	S	V	S	V
Group F (4IM)	V	S	V	V	S	S	S	V
Placebo[b]	S	S	S	S	S	S	S	S

SC: subcutaneous; IM: intramuscular; V: vaccine, S: saline

[a] Active Control.

[b] Subjects randomized to the control group were then re-randomized (1:1) to receive saline by the IM or SC route. The IM and SC placebo groups are combined in analyses.

Subjects were instructed to complete a 14-day post-vaccination diary card after the first 2 doses and a 28 day diary card after the subsequent doses to capture solicited and unsolicited adverse reactions. Adverse reaction data were also collected from in-clinic exams, which were performed prior to, and 15 to 60 minutes after each injection, at 1 to 3 days after each injection for the first two injections, and at 28 days after injections 3 through 8. The mean age, gender ratio, and race distribution were not significantly different across treatment groups among the vaccinated cohort (N=1563). The mean age was 39 years (range 18 to 62 years). Fifty-one percent of participants were female and 49% were male. Seventy-four percent were white, 21% were black and 5% were categorized as “other”.

Shown in Table 2 are the rates (percentage) of prospectively defined local and systemic solicited adverse reactions observed in the in-clinic exams for doses 1-4 as well as the rates (percentage) of local and systemic solicited adverse reactions observed in the in-clinic exams for doses 5-8.

Analysis of injection site (local) adverse reactions by study group was performed after each dose. It was observed that groups receiving BioThrax by the IM route had a statistically significantly lower incidence ($p \leq 0.05$) of any (one or more) local adverse reactions compared to the BioThrax SC route, by dose in the in-clinic data set, in 23 out of 24 analyses. (This excludes doses where IM groups received a placebo.) Individual injection site adverse reactions occurring at statistically significantly lower frequencies ($p \leq 0.05$) in participants given BioThrax by the IM route included warmth (in all analyses), tenderness (in 19 out of 24 analyses), itching (in 22 out of 24 analyses), erythema (in all analyses), induration (in all analyses), edema (in 20 out of 24 analyses), and nodule (in all analyses). However, by dose, the incidences of arm motion limitation were comparable or higher in each BioThrax IM group compared to the 8SC group, with statistically significantly higher incidences ($p \leq 0.05$) observed in 10 out of 24 analyses. The incidence of any moderate or severe local adverse reactions was lower in BioThrax IM groups, compared to the 8SC group after each dose. Route of administration did not affect the occurrence of systemic adverse reactions, with the exception of muscle ache (increased incidence in the BioThrax IM groups after most doses). There was no pattern for differences in the incidence of any moderate or severe systemic adverse reactions for BioThrax IM groups compared to the 8SC group after each dose. The proportion of participants with severe local or systemic adverse reactions reported by adverse reaction category after each dose was very low (generally <1%).

Overall, women had a higher incidence of any local adverse reaction than did men, by dose, within BioThrax groups, regardless of the route of administration. Overall, women also had a higher incidence of any systemic adverse reaction than men, within BioThrax groups, regardless of the route of administration. A brief pain or burning sensation, felt immediately after vaccine injection, and distinct from injection site pain, was reported by 45 - 97% of all study participants receiving BioThrax. Reporting frequency and event intensity varied with route of administration and vaccine dose. Up to 11% of subjects rated the brief pain or burning they experienced immediately after vaccine injection as 8 out of 10 or greater. Female participants generally experienced a higher pain scale rating than male participants.

Eight serious adverse events (SAEs) were reported with 6 subjects and determined to be possibly related to the administration of BioThrax: (1) a case of generalized allergic reaction, (2) a case of ANA positive autoimmune disorder manifesting as a moderate bilateral arthralgia of the metacarpophalangeal (MCP) joints, (3) a right shoulder supraspinatus tendon tear, (4) a case of bilateral pseudotumor cerebri with bilateral disc edema, (5) a case of generalized seizure and hospitalization for evaluation of hydrocephalus and endoscopic fluid ventriculostomy, (6) a case of bilateral ductal carcinoma of the breast. No SAEs were determined by the investigator to be probably or definitely related to administration of BioThrax. The percent of serious adverse

events was similar between the BioThrax combined groups (193/1303 or 15%) and the placebo group (38/260 or 15%).

Fifty-one pregnancies were reported in this study, 33 of which occurred in women who received BioThrax as their last dose prior to conception and 18 in women who received placebo as their last dose prior to conception. Pregnancy outcomes where BioThrax was given within 30 days prior to conception (n=5) were 3 full-term live births (including 1 healthy term infant with a mild right clubbed foot abnormality), 1 spontaneous abortion, and 1 first trimester intra-utero fetal death. Pregnancy outcomes in the placebo group (n=5) were 4 full-term live births (including one with bilateral congenital hip dysplasia) and 1 elective abortion.

Table 2: Adverse Reactions: In-Clinic Day 0 – 3, Solicited by Dose Number[a]

	STUDY GROUP																							
	Group D BioThrax 7IM (BioThrax Doses 1, 3-8) Weeks-0-4-26[b] Months 12-18-30-42								Placebo[c] Control SC/IM (Doses 1-8) Weeks-0-2-4-26 Months 12-18-30-42								Group A BioThrax 8SC (BioThrax Doses 1-8) Weeks-0-2-4-26 Months 12-18-30-42							
Number of Subjects (N)[d]	256								260								259							
	Dose								Dose								Dose							
	1	**2[b]**	**3**	**4**	**5**	**6**	**7**	**8**	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**
	%	**%**	**%**	**%**	**%**	**%**	**%**	**%**	**%**	**%**	**%**	**%**	**%**	**%**	**%**	**%**	**%**	**%**	**%**	**%**	**%**	**%**	**%**	**%**
Local Adverse Reactions																								
Presence of any local adverse reaction	60	*23*	68	68	69	77	76	73	22	22	19	27	25	29	25	18	81	89	80	84	81	84	84	92
Warmth	4	*1*	8	10	11	13	14	19	1	0	0	0	0	0	1	1	29	41	32	39	34	40	51	49
Tenderness	46	*7*	51	47	41	44	44	48	6	8	7	10	6	7	7	4	64	72	48	65	53	57	61	63
Itching	1	*0*	2	4	7	7	7	10	0	0	0	0	1	0	0	0	3	16	23	20	17	22	25	26
Pain	16	*4*	20	15	16	13	16	15	4	2	3	4	4	2	3	2	16	22	12	19	16	14	18	20
Arm motion limitation	14	*1*	15	11	10	10	15	9	1	0	2	1	1	1	1	0	8	12	5	11	10	5	8	5
Erythema	15	*10*	20	30	35	48	40	37	11	12	7	13	14	17	14	11	53	64	57	65	64	64	68	71
Induration	7	*7*	12	16	21	23	15	17	1	3	2	3	4	4	3	3	26	35	28	40	38	36	38	35
Edema	5	*2*	11	20	15	23	30	25	3	4	4	4	4	7	8	5	17	33	31	33	31	35	37	46
Nodule	3	*0*	4	5	8	9	6	5	0	2	0	1	2	0	2	0	39	42	36	26	26	23	21	27
Bruise	5	*4*	5	3	2	4	3	2	4	5	1	4	3	5	5	4	6	7	6	6	3	6	5	6
Presence of any moderate/severe local adverse reactions[e]	5	*1*	8	7	4	5	6	4	0	0	0	0	0	0	0	0	7	16	8	13	10	7	12	14
Presence of any large local adverse reaction[f]	0	*0*	0	2	2	4	2	2	0	0	0	0	0	0	0	0	0	1	4	2	1	2	2	4
Systemic Adverse Reactions																								
Presence of any systemic adverse reaction	18	*12*	24	19	15	19	10	9	10	10	13	11	13	8	13	4	16	20	18	21	18	14	20	17
Fatigue	9	*4*	12	10	9	11	4	6	5	4	7	7	8	5	10	3	9	12	8	12	12	10	10	13
Muscle ache	8	*4*	13	6	5	5	3	5	2	2	3	4	5	3	1	1	5	8	4	5	4	3	9	5
Headache	6	*6*	9	7	8	8	5	4	4	6	5	4	7	4	6	1	7	9	8	11	7	5	9	2
Fever >100.4°F	0	*0*	0	0	0	0	0	0	0	0	0	0	1	0	0	0	0	0	0	0	0	0	0	0
Tender/painful axillary adenopathy	0	*0*	0	1	1	1	0	0	0	0	0	0	0	0	0	1	0	1	2	1	1	0	1	0
Presence of any moderate/severe systemic adverse reactions[g]	2	*2*	6	3	3	5	4	3	1	2	2	1	3	1	2	1	2	5	4	3	3	2	3	2

[a] Per-dose, statistical assessment performed on Intent-to-Treat population data. Evaluations performed at 15-60 minutes and 1-3 days following each injection and prior to the next scheduled injection.
[b] Subjects received saline (instead of BioThrax) for the Week 2 dose. Placebo dose data for 7IM group is in italics.
[c] The two saline groups (SC and IM) were combined.
[d] N is the highest number per treatment arm (received at least one dose); denominator (N) varied with dose number due to attrition over time.

[e] Moderate = causes discomfort and interferes with normal daily activities; Severe = incapacitating and completely prevents performing normal daily activities. This is based on the local AE categories of warmth, tenderness, itching, pain, and arm motion limitation.

[f] Large = an occurrence of induration, erythema, edema, nodule, and bruise with a largest diameter greater than 120 mm.

[g] Moderate = causes discomfort and interferes with normal daily activities; Severe = incapacitating and completely prevents performing normal daily activities. This is based on the systemic AE categories of fatigue, muscle ache, headache, and fever.

Solicited and unsolicited adverse reactions observed from Day 0 through month 43 at a higher frequency (by at least 5%) in the BioThrax groups (IM and SC) as compared to the placebo (P) group were: headache (70.4% IM, 78.4% SC, 68.1% P); myalgia (72% IM, 76.1% SC, 50% P); and fatigue (70.1% IM, 76.8% SC, 60.8% P).

Post-Exposure Prophylaxis

A phase 3, open-label, uncontrolled, multi-center study evaluated the three-dose post-exposure prophylaxis BioThrax schedule (Week 0, 2, and 4) in 200 healthy adult subjects. The most common solicited adverse reactions reported 7 days after each vaccination comprised local reactions, including symptoms of lump, tenderness, and erythema. The most common solicited systemic reactions comprised fatigue, headache, and myalgia. Of the subjects that reported local and systemic solicited reactions, ≥ 98% required minimal or no treatment and resulted in little to no interference 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 (3.5%), decreased joint range of motion (2.5%), myalgia (2.5%). No deaths were reported and neither of the two SAEs reported were considered to be related to vaccination. There were no pregnancies reported or subject withdrawals from the study due to adverse events.

6.2 Postmarketing Experience

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.

7 DRUG INTERACTIONS

7.1 Ciprofloxacin

Co-administration of 0.5 mL BioThrax SC with oral ciprofloxacin in human subjects did not alter the pharmacokinetics of ciprofloxacin or the immunogenicity of BioThrax as measured by the anthrax lethal toxin neutralization assay. [See *Clinical Studies* (14.3)]

7.2 Concomitant Administration with Other Vaccines

The safety and efficacy of concomitant administration of BioThrax with other licensed vaccines has not been evaluated.

BioThrax should not be mixed with any other vaccine in the same syringe or vial. If BioThrax is to be given at the same time as another injectable vaccine(s), the vaccine(s) should be administered at different injection sites.

7.3 Immunosuppressive Therapies

Immunosuppressive therapies, including chemotherapy, corticosteroids (used in high-doses longer than 2 weeks), and radiation therapy may reduce the response of BioThrax.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Category D. [See *Warnings and Precautions* (5.3)]

Healthcare practitioners are encouraged to register women who receive BioThrax during pregnancy in Emergent's vaccination pregnancy registry by calling 1-619-553-9255.

Male Fertility: A retrospective study was performed at an in-vitro fertilization clinic to evaluate whether BioThrax may impact reproductive function in men. This study compared semen parameters, embryo quality, and pregnancy outcomes in 254 male clients who stated that they had received BioThrax, with those of 791 male clients who did not.[2] Prior receipt of BioThrax did not influence semen parameters (including concentration, motility, and morphology), fertilization rate, embryo quality or clinical pregnancy rates.

8.3 Nursing Mothers

It is not known whether BioThrax is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when BioThrax is administered to a nursing woman.

8.4 Pediatric Use

Safety and effectiveness in pediatric patients have not been established for BioThrax.

8.5 Geriatric Use

BioThrax has not been approved for use in patients greater than 65 years of age.

11 DESCRIPTION

BioThrax® (Anthrax Vaccine Adsorbed) is a sterile, milky-white suspension for intramuscular or subcutaneous injections 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 (PA) protein, released during the growth period and 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 final product is formulated to contain 25 mcg/mL benzethonium chloride and 100 mcg/mL formaldehyde, added as preservatives.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Anthrax is a zoonotic disease caused by the Gram-positive, spore-forming bacterium *Bacillus anthracis*. BioThrax induces antibodies raised against PA that may contribute to protection by neutralizing the activities of the cytotoxic lethal toxin and edema toxin of *Bacillus anthracis*.[3] *Bacillus anthracis* proteins other than PA may be present in BioThrax, but their contribution to protection has not been determined.

13 NONCLINICAL TOXICOLOGY

The effect of BioThrax on embryo-fetal and pre-weaning development was evaluated in a developmental toxicity study using pregnant rabbits. One group of rabbits was administered BioThrax twice prior to gestation and during the period of organogenesis (gestation day 7). A second group of rabbits was administered BioThrax twice prior to gestation and on gestation day 17. BioThrax was administered at 0.5 ml/rabbit/occasion, by intramuscular injection. No adverse effects on mating, fertility, pregnancy, parturition, lactation, embryo-fetal or pre-weaning development were observed. There were no vaccine-related fetal malformations or other evidence of teratogenesis noted in this study.

13.2 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 aerosolized *B. anthracis* spores at a target dose exceeding the 50% lethal dose by 200-fold. 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) 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 these studies, rabbits were challenged via inhalation with 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, respectively ($p < 0.0006$ and $p < 0.004$, respectively). [See *Clinical Studies* (14.2)]

14 CLINICAL STUDIES

14.1 Pre-Exposure Prophylaxis

A controlled field study using an earlier version of a protective antigen-based anthrax vaccine developed in the 1950's and supplied by G. G. Wright and associates of the U.S. Army Chemical Corps, Fort Detrick, Frederick, MD, that consisted of an aluminum potassium sulfate-precipitated cell-free filtrate from an aerobic culture, was conducted from 1955-1959.[4] 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. The anthrax vaccine was administered subcutaneously at 0, 2, 4 weeks, 6, 12, 18 months. Prior to vaccination, the yearly average number of human anthrax cases (both cutaneous and inhalational) was 1.2 cases per 100 employees in these mills. During the trial, 26 cases of anthrax were reported across the four mills – 5 inhalation and 21 cutaneous. 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. The calculated efficacy of the vaccine to prevent all types of anthrax disease, regardless of the route of exposure or clinical manifestations, was 92.5% (lower 95% Confidence Interval (CI) = 65%).

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.[5, 6] In that time period, individuals received either BioThrax or the earlier protective antigen-based anthrax vaccine used in the field trial described above. Of the 27 reported cases of anthrax, 24 cases occurred in unvaccinated individuals. In vaccinated 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 doses of the originally licensed six-dose series of anthrax vaccine.

Between 2002 and 2007, a prospective double-blinded, randomized, placebo-controlled and active-controlled study was conducted to evaluate the impact on safety and immunogenicity on changing the administration route from SC to IM, and reducing the number of doses. This study enrolled 1,564 healthy civilian men and women between the ages of 18 and 61. A total of 1,563 subjects received at least one dose (one subject withdrew consent prior to the first injection). Subjects were randomized to one of six groups. See Table 1.

Using an Enzyme-Linked Immunosorbent Assay (ELISA), Immunoglobulin G (IgG) 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

To compare the originally licensed 6-dose SC schedule (0, 2, 4 weeks and 6, 12, and 18 months) versus a 3-dose IM primary series (at 0, 1, and 6 months), non-inferiority analyses were performed for all three primary immunogenicity endpoints. This evaluation compared the immune response at Month 7 for Group C (COM, where COM is Combined, as described in 6.1) to Month 19 for Group A (TRT-8SC, where TRT is Treatment) and Group B (TRT-8IM). Non-inferiority was demonstrated for all analyses (See Table 3). These results support a 3 dose primary series of BioThrax administered IM at 0, 1 and 6 months, followed by booster doses at 12 and 18 months and at 1-year intervals thereafter to maintain protective immunity.

The Month 7 antibody levels of Group A (TRT-8SC) were non-inferior to Month 13 and 19 antibody levels after a 0, 2, 4 week and 6 month primary SC series followed by SC booster

injections at 12 and 18 months (see Table 3). These results support a 4 dose SC primary series of BioThrax administered at weeks 0, 2, 4, and at 6 months followed by booster doses at 12 and 18 months after initiation of the series, and at 1-year intervals thereafter to maintain protective immunity.

Catch-Up Administration for Delayed or Missed Doses

In subjects who did not receive booster doses at 12, 18, and 30 months, PA antibody levels decline over time following the third dose of BioThrax administered intramuscularly at 6 months (Group F; 4IM; 0, 1, 6, and 42 months). In the absence of booster doses it is not known whether these individuals are adequately protected between 12 months and receipt of a booster dose at 42 months. One month following a dose of BioThrax at 42 months the immune response for Group F met the criteria for non-inferiority relative to Group A (8SC) for all three primary immunogenicity endpoints (see Table 3). The optimal schedule for further intramuscular booster doses among persons administered a single booster dose at 42 months following completion of a three-dose primary series at 0, 1, and 6 months is not known.

Table 3: Primary Immunogenicity Endpoints (According to Protocol[a])							
	Week 4	**Week 8**	**Month 7**	**Month 13**	**Month 19**	**Month 31**	**Month 43**
Anti-PA Specific IgG GMC, mcg/mL							
	n GMC 95%CI	n GMC 95%CI	n GMC 95%CI	n GMC 95%CI	n GMC 95%CI	n GMC 95%CI	n GMC 95%CI
TRT-8SC Group A	242 49.72 (43.32, 57.06)	235 94.29 (82.08, 108.31)	219 201.14 (174.71, 231.56)	203 201.67 (174.77, 232.71)	190 193.45 (167.29, 223.69)	167 250.07 (215.38, 290.34)	144 216.83 (185.80, 253.05)
TRT-7IM[b] Group D	723 2.63 (2.39, 2.89)	698 46.39 (42.18, 51.01)	636 206.09 (187.14, 226.96)	203 229.86 (203.20, 260.02)	192 204.95 (180.82, 232.29)	169 263.13 (231.09, 299.61)	139 254.80 (222.03, 292.40)
TRT-5IM[b] Group E				399 28.64 (25.79, 31.81)	174 293.60 (258.30, 333.73)	153 33.68 (29.48, 38.48)	141 310.02 (270.49, 355.33)
TRT-4IM[b] Group F					193 13.71 (12.11, 15.53)	179 7.80 (6.87, 8.86)	157 433.20 (379.58, 494.40)
Anti-PA Specific IgG GMT							
	n GMT 95% CI	n GMT 95% CI	n GMT 95% CI	n GMT 95% CI	n GMT 95% CI	n GMT 95% CI	n GMT 95% CI
TRT-8SC Group A	242 565.16 (492.57, 648.45)	235 1048.50 (913.05, 1204.05)	219 2211.94 (1921.78, 2545.90)	203 2184.59 (1893.62, 2520.26)	190 2080.89 (1799.87, 2405.79)	167 2677.97 (2306.82, 3108.83)	144 2282.36 (1955.79, 2663.45)
TRT-7IM[b] Group D	723 36.61 (33.32, 40.23)	698 514.57 (468.08, 565.68)	636 2257.09 (2050.12, 2484.94)	203 2546.81 (2251.11, 2881.35)	192 2254.56 (1988.85, 2555.75)	169 2867.88 (2518.14, 3266.19)	139 2760.35 (2404.66, 3168.64)
TRT-5IM[b] Group E				399 296.08 (266.67, 328.74)	174 3167.26 (2785.88, 3600.85)	153 348.89 (305.33, 398.66)	141 3286.41 (2866.50, 3767.83)
TRT-4IM[b] Group F					193 135.30 (119.44, 153.26)	179 79.63 (70.10, 90.44)	157 4683.79 (4102.99, 5346.80)
4-fold response							
	n 4-fold response 95% CI	n 4-fold response 95% CI	n 4-fold response 95% CI	n 4-fold response 95% CI	n 4-fold response 95% CI	n 4-fold response 95% CI	n 4-fold response 95% CI
TRT-8SC Group A	242 80.99 (75.47, 85.73)	235 94.89 (91.25, 97.33)	219 98.63 (96.05, 99.72)	203 99.51 (97.29, 99.99)	190 98.95 (96.25, 99.87)	167 100.00 (97.82, 100.00)	144 100.00 (97.47, 100.00)
TRT-7IM[b] Group D	723 4.15 (2.82, 5.87)	698 78.80 (75.57, 81.77)	636 97.80 (96.33, 98.79)	203 100.00 (98.20, 100.00)	192 98.96 (96.29, 99.87)	169 100.00 (97.84, 100.00)	139 100.00 (97.38, 100.00)
TRT-5IM[b] Group E				399 60.40 (55.41, 65.23)	174 99.43 (96.84, 99.99)	153 63.40 (55.24, 71.03)	141 99.29 (96.11, 99.98)

Table 3: Primary Immunogenicity Endpoints (According to Protocol[a])

	Week 4	Week 8	Month 7	Month 13	Month 19	Month 31	Month 43
TRT-4IM[b] Group F					193 37.82 (30.96, 45.07)	179 22.35 (16.47, 29.16)	157 99.36 (96.50, 99.98)

CI: Confidence Interval;

[a] According to Protocol (ATP): [NCT00119067] To be included in the ATP population at a particular timepoint, a participant must have: (a) received all injections up through that timepoint, (b) received these injections within the windows defined by protocol, (c) received the correct agent administered by the correct route according to subject's assigned study arm, (d) received the correct injection volume. A shot of 0.3 mL or greater is considered valid.

[b] Groups TRT-7IM, -5IM, and -4IM combined as group TRT-COM (combined) through Month 7 of the study, GMC: geometric mean concentration. GMT: geometric mean titer. IM: Intramuscular; SC: Subcutaneous, TRT: treatment.

14.2 Post-Exposure Prophylaxis

Based on the rabbit model-derived TNA threshold [See *Nonclinical Toxicology* (13.2)], a pivotal clinical study was conducted to evaluate the immunogenicity and safety of a post-exposure SC administration schedule of BioThrax in healthy adults following 3 doses at 0, 2, and 4 weeks. Two hundred subjects were enrolled and followed for 128 days. The primary objective was to assess immunogenicity using TNA following the completion of three SC doses of BioThrax. The primary immunogenicity endpoint was the proportion of subjects achieving a threshold TNA NF_{50} value ≥0.56 at Day 63, 5 weeks after the third vaccination. Success was concluded if the lower bound of the 2-sided 95% CI of the proportion of human subjects achieving the TNA NF_{50} threshold was ≥ 40%.

Overall, 71.2% of subjects achieved an NF_{50} value ≥0.56 on Day 63 in the pivotal study. The lower bound of the 95% CI was 64.1%. (See Table 4.)

In a separate analysis of the pivotal clinical study using the threshold associated with a 70% probability of survival in NHPs, 93.5% of subjects achieved an NF_{50} value ≥0.29 on Day 63 (Table 4). The lower bound of the 95% CI was 88.9% (Table 4). The bridging of human immunogenicity data to the NHP study was supportive of the primary analysis comparing human threshold data with rabbit survival. [See *Nonclinical Toxicology* (13.2)]

Table 4: Proportion of Subjects Achieving TNA NF_{50} Threshold[a] in the Pivotal Clinical Study (PP Population[b])

Animal Model	Time Point Human/Animal	n	Human GMT TNA NF_{50} (SD)	Animal TNA NF_{50} Threshold[c]	Number of Subjects Meeting Threshold	Proportion of Subjects Meeting Threshold (%)[d]		
						Point Est. (%)	95% CI (%)	
							Lower Bound	Upper Bound
Rabbit[e]	Day 63/Day 69	184	0.86 (2.09)	0.56	131	71.2	64.1	77.6
Non-human Primate[f]	Day 63/Day 70	184	0.86 (2.09)	0.29	172	93.5	88.9	96.6

CI = confidence interval; NF_{50} = 50% neutralization factor; PP = per protocol; SD = standard deviation; TNA = toxin neutralizing antibody.
Note: Sample size (N) and denominators used for percentages are based on the number of subjects meeting the PP criteria at specified day(s).
[a] TNA NF_{50} threshold is defined as the TNA NF_{50} value associated with 70% survival in the animal challenge studies.
[b] Human data are from the pivotal clinical study (NCT01491607).
[c] A logistic regression model with log10-transformed TNA NF_{50} values as the predictor and survival as the response is used to derive the TNA NF_{50} threshold associated with 70% probability of survival in rabbits and non-human primates, respectively.
[d] 95% CI is calculated with the exact (Clopper-Pearson) method.
[e] The proportion of subjects achieving a TNA NF_{50} response at Day 63 that met or exceeded the TNA NF_{50} threshold in the rabbit model at Day 69 comprised the primary immunogenicity endpoint.
[f] Comparison of the human TNA NF_{50} response at Day 63 with the NHP TNA NF_{50} threshold at Day 70 was defined as an immunogenicity endpoint and was supportive of the bridging of human immunogenicity data to rabbit survival.

14.3 Non-Interference of Post-Exposure Prophylaxis Vaccination and Antimicrobials When Used Concurrently

An open-label study was conducted to evaluate the potential impact 0.5 mL BioThrax administered SC at 0, 2 and 4 weeks had on the pharmacokinetics of ciprofloxacin in healthy adult male and female subjects (N=154). It also evaluated the potential impact of ciprofloxacin on immunogenicity of BioThrax two weeks following the last BioThrax dose.

Co-administration of 0.5 mL BioThrax SC with oral ciprofloxacin in human subjects did not alter the pharmacokinetics of ciprofloxacin or the immunogenicity of BioThrax as measured by the anthrax lethal toxin neutralization assay.

15 REFERENCES

1. Ryan MA, Smith TC, Sevick CJ, Honner WK, Loach RA, Moore CA, Erickson JD. 2008. Birth defects among infants born to women who received anthrax vaccine in pregnancy. Am J Epidemiol, 168:434-442.
2. Catherino WH, Levi A, Kao TC, Leondires MP, McKeeby J, Segars JH. 2005. The anthrax vaccine does not affect semen parameters, embryo quality, or pregnancy outcome in couples with a vaccinated male military service member. Fertility and Sterility, 83:480-483
3. Brachman P, Friedlander A, Grabenstein J. 2008. Anthrax Vaccine. In: Vaccines, Fifth Edition, Plotkin, S.A.: Orenstein W.A. and Offit P.A. (eds.), 111-126
4. Brachman, PS, Gold H, Plotkin SA, Fekety FR, Werrin M, Ingraham NR. 1962. Field evaluation of a human anthrax vaccine. Amer. J. Public Health, 52:632-645.
5. Food and Drug Administration, 2005, Biological Products; Bacterial Vaccines and Toxoids; Implementation of Efficacy Review; Anthrax Vaccine Adsorbed; Final Order. FDA Federal Register 2005; 70(242): 75180-75198.
6. Food and Drug Administration. Biological Products; Bacterial vaccines and toxoids; Implementation of efficacy review. Federal Register (December 13, 1985), 50(240):51002-51117.

16 HOW SUPPLIED/STORAGE AND HANDLING

BioThrax is supplied in 5 mL multidose vials containing ten 0.5 mL doses.

NDC 64678-211-05 (vial), 64678-211-01 (carton)

Store at 2 °C to 8 °C (36 °F to 46 °F). **Do not freeze**. Do not use BioThrax after the expiration date printed on the label.

The stopper of the vial contains natural rubber latex and may cause allergic reactions in latex sensitive individuals.

17 PATIENT COUNSELING INFORMATION

See FDA-approved patient labeling (Patient Information).

Advise women of the potential risk to the fetus. Encourage women who are exposed to BioThrax during pregnancy to inform their healthcare provider and enroll in the BioThrax (Anthrax) Vaccine in Pregnancy Registry (Phone: 1-619-553-9255). [See *Warnings and Precautions* (5.3) and *Use in Specific Populations* (8.1)]

Inform patients of the benefits and risks of immunization with BioThrax.

Instruct patients to report any serious adverse reaction to their health care provider.

Manufactured by:

Emergent BioDefense Operations Lansing LLC

Lansing, MI 48906

US License No. 1755

BioThrax® is a registered trademark of Emergent BioDefense Operations Lansing LLC

Information for Patients
BioThrax® (Anthrax Vaccine Adsorbed)

Please read this Patient Information summary carefully before you get this shot. This summary does not take the place of talking with your healthcare provider about BioThrax. If you have questions or would like more information, please talk with your healthcare provider.

What is BioThrax?

- BioThrax is a vaccine licensed by the FDA to protect against anthrax disease in persons 18 through 65 years of age:
  - It can be used before exposure to anthrax to protect people at high risk of getting the disease.
  - It can be used after exposure to anthrax, along with antibiotics, to protect people from getting the disease.
- BioThrax may not protect all people who get the vaccine.
- How well BioThrax works when given after exposure to anthrax has been studied only in animals. It has not been studied in humans because there are not enough people who get the disease naturally, and it is not ethical to expose people to anthrax on purpose to find out how well BioThrax works.
- The safety of BioThrax was studied in healthy adults.

Who should not get BioThrax?
You should not get BioThrax if you have a history of severe allergic reaction to any ingredient of the vaccine, including aluminum hydroxide, benzethonium chloride, and formaldehyde or had a serious reaction after getting BioThrax previously .

What should I tell my healthcare provider before getting BioThrax?

- If you may be pregnant, plan to get pregnant soon, or are nursing a baby.
- About medicines that you take, including over-the-counter medicines and supplements.
- About immune problems you have, including steroid treatments and cancer treatments.
- About blood clotting problems or if you take "blood thinners."
- If you are allergic to latex.

What if I discover I was pregnant at the time I got BioThrax?

- Inform your healthcare provider
- You can enroll in the BioThrax (Anthrax) Vaccine in Pregnancy Registry (Phone: 1-619-553-9255), if eligible

How is BioThrax given?
BioThrax is given as a shot in your arm.

After getting the first shot, you should come back for the next shots on the schedule given to you by your health care provider. It is important that you get all your shots to get the best protection.

If you get BioThrax because you may have been exposed to anthrax, it is important that you also take antibiotics for 60 days.

What are the possible or reasonably likely side effects of BioThrax?
The most common side effects of BioThrax are:

- Pain, tenderness, redness, bruising, or problems moving the arm in which you got the shot
- Muscle aches
- Headaches
- Fatigue
- Fainting

Tell your healthcare provider about any side effects that concern you. Your healthcare provider can give you a complete list of side effects available to healthcare professionals.

You may report side effects to **FDA by calling 1-800-822-7967** or to the website www.vaers.hhs.gov. You may also report side effects directly to Emergent BioSolutions at 1-877-246-8472 or at productsafety@ebsi.com.

What are the ingredients in BioThrax?
BioThrax does not contain live bacteria. BioThrax contains non-infectious proteins, aluminum hydroxide, benzothonium chloride and formaldehyde (as preservatives).

The vial stopper contains natural rubber latex.

Manufactured by Emergent BioDefense Operations Lansing LLC
Lansing, MI 48906, US
License No. 1755

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use ANTHRASIL™ safely and effectively. See full prescribing information for ANTHRASIL.

ANTHRASIL [Anthrax Immune Globulin Intravenous (Human)], sterile solution for infusion

Initial U.S. Approval: March 24, 2015

WARNING: INTERACTIONS WITH GLUCOSE MONITORING SYSTEMS AND THROMBOSIS

See full prescribing information for complete boxed warning.

• Maltose in immune globulin products, including ANTHRASIL, may give falsely high blood glucose levels with some blood point-of-care glucose testing systems (for example those based on the GDH-PQQ or glucose-dye-oxidoreductase methods) resulting in inappropriate administration of insulin and life-threatening hypoglycemia. To avoid interference by maltose contained in ANTHRASIL, perform blood glucose measurements in patients receiving ANTHRASIL with a glucose-specific method (monitor and test strips).

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

• For patients at risk of thrombosis, administer ANTHRASIL at the minimum infusion rate practicable. Ensure adequate hydration in patients before administration. Monitor for signs and symptoms of thrombosis and assess blood viscosity in patients at risk of hyperviscosity.

----------INDICATIONS AND USAGE----------

ANTHRASIL is an Anthrax Immune Globulin Intravenous (Human) indicated for the treatment of inhalational anthrax in adult and pediatric patients in combination with appropriate antibacterial drugs (1).

The effectiveness of ANTHRASIL is based solely on efficacy studies conducted in animal models of inhalational anthrax.

----------DOSAGE AND ADMINISTRATION----------

For intravenous use only.

Dosing of ANTHRASIL

Patient Group	Dose[a]	Starting Infusion Rate (first 30 min)	Incremental Infusion Rate if Tolerated (every 30 min)	Max Infusion Rate
Adults (≥17 years)	7 vials (420 units)	0.5 mL/min	1 mL/min	2 mL/min
Pediatric <1 year to ≤16 years	1–7 vials (60–420 units) based on patient weight	0.01 mL/kg/min (do not exceed the adult rate)	0.02 mL/kg/min	0.04 mL/kg/min (do not exceed the adult rate)

[a]Select initial dose based on clinical severity; severe cases may warrant use of 14 vials (840 units) in adults and 2 to 14 vials (based on weight) in pediatric patients weighing >5 kg.

Adjust dose and consider redosing based on clinical severity and response to treatment (2.1)

Weight-based Pediatric Dose

Body Weight (kg)	Vials per Dose[a]	Body Weight (kg)	Vials per Dose
<5	1	25 to <35	4
<10	1	35 to <50	5
10 to <18	2	50 to <60	6
18 to <25	3	≥60	7

[a]Select initial dose based on clinical severity. Dose may be doubled for severe cases in patients >5 kg.

Administer ANTHRASIL by slow intravenous infusion using an infusion pump (maximum 2 mL per minute).

----------DOSAGE FORMS AND STRENGTHS----------

Each single-use vial contains a minimum potency of ≥60 units by Toxin Neutralization Assay (TNA) (3).

----------CONTRAINDICATIONS----------

- History of anaphylactic or severe systemic reaction to human immune globulins (4)
- IgA deficiency with antibodies against IgA and a history of IgA hypersensitivity (4)

----------WARNINGS AND PRECAUTIONS----------

- Hypersensitivity reactions including anaphylaxis (5.1)
- Interference with blood and urine glucose testing (5.2, 5.9)
- Thrombosis may occur. Monitor patients at risk (5.3)
- Monitor renal function and urine output in patients at risk of acute renal dysfunction/failure (5.4)
- Infuse ANTHRASIL at the minimum rate practicable in patients at risk of thrombosis or renal failure (5.5)
- Monitor for clinical signs and symptoms of hemolysis and hemolytic anemia (5.6)
- Aseptic meningitis syndrome (AMS) (5.7)
- Transfusion-related Acute Lung Injury (TRALI) (5.10)
- Transmission of infectious agents from human plasma (5.11)

----------ADVERSE REACTIONS----------

The most common adverse reactions to ANTHRASIL observed in >5% of healthy volunteers in clinical trials were headache, infusion site pain and swelling, nausea, and back pain (6.1).

To report SUSPECTED ADVERSE REACTIONS, contact Cangene Corporation at 1-800-768-2304 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

----------USE IN SPECIFIC POPULATIONS----------

- Pregnancy: No human or animal data are available (8.1)

See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling.

FULL PRESCRIBING INFORMATION: CONTENTS*

*Sections or subsections omitted from the full prescribing information are not listed

FULL PRESCRIBING INFORMATION

WARNING: INTERACTIONS WITH GLUCOSE MONITORING SYSTEMS AND THROMBOSIS

• Maltose in immune globulin products, including ANTHRASIL, may give falsely high blood glucose levels with some point-of-care blood glucose testings systems (for example those based on the GDH-PQQ or glucose-dye-oxidoreductase methods) resulting in inappropriate administration of insulin and life-threatening hypoglycemia. To avoid interference by maltose contained in ANTHRASIL, perform blood glucose measurement in patients receiving ANTHRASIL with a glucose-specific method (monitor and test strips).
• Thrombosis may occur with immune globulin products, including ANTHRASIL. Risk factors may include advanced age, prolonged immobilization, hypercoagulable conditions, history of venous or arterial thrombosis, use of estrogens, indwelling vascular catheters, hyperviscosity and cardiovascular risk factors. Thrombosis may occur in the absence of known risk factors.
• For patients at risk of thrombosis, administer ANTHRASIL at the minimum infusion rate practicable. Ensure adequate hydration in patients before administration. Monitor for signs and symptoms of thrombosis and assess blood viscosity in patients at risk of hyperviscosity.

1 INDICATIONS AND USAGE

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

The effectiveness of ANTHRASIL is based solely on efficacy studies conducted in animal models of inhalational anthrax [See *13.2 Animal Toxicology and/or Pharmacology*].

Limitations:

- ANTHRASIL does not have direct antibacterial activity.
- ANTHRASIL does not cross the blood-brain barrier and does not prevent or treat meningitis.
- There have been no studies of ANTHRASIL in the pediatric, geriatric, or obese populations.

2 DOSAGE AND ADMINISTRATION

For intravenous use only.

2.1 Dose

Table 1 ANTHRASIL Dosing Guide and Intravenous Infusion Rate

Patient Group	Dose[a]	Starting Infusion Rate (first 30 minutes)	Incremental Infusion Rate if Tolerated (every 30 minutes)	Maximum Infusion Rate
Adults ≥17 years	7 vials (420 units)	0.5 mL/min	1 mL/min	2 mL/min
Pediatric <1 year to ≤16 years	1–7 vials (60–420 units) based on patient weight	0.01 mL/kg/min (do not exceed the adult rate)	0.02 mL/kg/min	0.04 mL/kg/min (do not exceed the adult rate)

[a] Select initial dose based on clinical severity; severe cases may warrant use of 14 vials (840 units) in adults and 2 to 14 vials (based on weight) in pediatric patients weighing >5 kg.

Table 2 Pediatric Dosing Guide for ANTHRASIL[a]

Body Weight (kg)	Number of ANTHRASIL Vials per Dose[b]
<5	1
<10	1
10 to <18	2
18 to <25	3
25 to <35	4
35 to <50	5
50 to <60	6
≥60	7

[a] The pediatric dosing is derived from allometric scaling based on observed adult exposure to ANTHRASIL at 420 units by Toxin Neutralization Assay (TNA) dose.

[b] Select initial dose based on clinical severity. Dose may be doubled for severe cases in patients >5 kg.

The initial dose of ANTHRASIL for the treatment of inhalational anthrax in adults in combination with appropriate antimicrobial therapy is 420 units (seven vials). Data in animal models suggest that administration of higher doses may result in improved survival [See *13.2 Animal Toxicology and/or Pharmacology*]. An initial dose of 840 units (14 vials) may be considered, depending on the clinical status of the patient.

Depending on the severity of symptoms and the response to treatment, consider an initial dose of 840 units (14 vials) and repeat dosing especially in patients experiencing substantial hemorrhage as reflected in large transfusion requirements, patients with significant compartmental fluid losses such as from large volume and/or repeated therapeutic thoracentesis and/or abdominal paracentesis, and in patients whose own immune response may be impaired/delayed. Take the magnitude of ongoing blood and fluid losses and the clinical status of the patient into account in determining the time interval between doses when repeat doses are administered. Repeated dosing and single doses greater than 840 units

in humans have not been studied. Without substantially delaying therapy, give consideration to performing therapeutic thoracentesis and/or abdominal paracentesis as indicated prior to or concurrently with administration of ANTHRASIL.

2.2 Preparation and Administration

Each vial of ANTHRASIL has a minimum potency of ≥60 units per vial [See 3 *DOSAGE FORMS AND STRENGTHS*].

1. Bring ANTHRASIL vials to room temperature.
    - Thaw frozen vials rapidly for immediate use by placing at room temperature for one hour followed by a water bath at 37°C (98.6°F) until thawed.
    - Alternatively, thaw vials by placing the required number of vials in a refrigerator at 2 to 8°C (36 to 46°F) until the vials are thawed (approximately 14 hours).
    - Do not thaw in a microwave oven. Do not refreeze vials.
    - Bring thawed vials to room temperature by letting sit on a bench for a few minutes prior to infusion.
2. Inspect vials to ensure the product is fully thawed and free from discoloration and particulate matter. The solution should be clear or slightly opalescent. Do not use solutions that are cloudy, turbid or have particulates.
3. Inspect vials to ensure there is no damage to the seal or vial. If damaged, do not use and contact the manufacturer.
4. Gently swirl upright vials by hand to ensure uniformity. Do not shake the vial during preparation to avoid foaming.
5. Follow the steps below to prepare the ANTHRASIL infusion bag:
    - Remove the protective caps from the product vials.
    - Wipe the exposed central portion of the rubber stopper with an isopropyl alcohol swab.
    - Withdraw the vial contents of ANTHRASIL into a syringe, aseptically transfer into an appropriately sized intravenous bag and label with the volume to be infused.
    - No further dilution is required.
    - Once punctured, use the vial contents to prepare the infusion bag and administer as soon as possible. ANTHRASIL contains no preservative.
6. Administer in an intravenous line with constant infusion pump. Use of an in-line filter is optional.
7. If adverse reactions occur, such as flushing, headache, nausea, changes in pulse rate or blood pressure, slow the rate of infusion or temporarily stop the infusion.

ANTHRASIL vials are for single use only. Discard any unused portion.

3 DOSAGE FORMS AND STRENGTHS

Each vial of ANTHRASIL contains a minimum potency of ≥60 units per vial.

4 CONTRAINDICATIONS

- ANTHRASIL is contraindicated in individuals with a history of anaphylaxis or prior severe systemic reaction associated with the parenteral administration of this or other human immune globulin preparations.
- ANTHRASIL is contraindicated in IgA-deficient patients with antibodies against IgA and a history of IgA hypersensitivity, as it contains trace amounts of IgA (less than or equal to 40 mcg per mL) [See *5.1 Hypersensitivity Reactions*].

5 WARNINGS AND PRECAUTIONS

5.1 Hypersensitivity Reactions

Hypersensitivity reactions may occur with ANTHRASIL.

Administer ANTHRASIL in a setting where appropriate equipment, medication (including epinephrine) and personnel trained in the management of hypersensitivity, anaphylaxis and shock are available.

Monitor all patients for signs and symptoms of acute allergic reactions (e.g. urticaria, pruritus, erythema, angioedema, bronchospasm with wheezing or cough, stridor, laryngeal edema, hypotension, tachycardia) during and following the ANTHRASIL infusion. In case of severe hypersensitivity reactions, discontinue the administration of ANTHRASIL immediately and administer appropriate emergency care.

ANTHRASIL contains trace amounts of IgA (less than or equal to 40 mcg per mL). Patients with known antibodies to IgA may have greater risk of developing severe hypersensitivity and anaphylactic reactions. ANTHRASIL is contraindicated in patients with antibodies against IgA and a history of hypersensitivity reaction [See 4 *CONTRAINDICATIONS*].

5.2 Interference with Blood Glucose Testing

ANTHRASIL contains maltose. Maltose has been shown to give falsely high blood glucose levels in certain types of blood glucose testing systems (for example, by systems based on glucose dehydrogenase pyrroloquinolinequinone (GDH-PQQ) or glucose-dye-oxidoreductase methods). Due to the potential for falsely elevated glucose readings (or falsely normal glucose readings when hypoglycemia is present), only use testing systems that are glucose-specific to test or monitor blood glucose levels in patients receiving ANTHRASIL.

Review the product information of the blood glucose testing system, including that of the test strips, to determine if the system is appropriate for use with maltose-containing parenteral products. If any uncertainty exists, contact the manufacturer of the testing system to determine if the system is appropriate for use with maltose-containing parenteral products.

5.3 Thrombosis

Thrombosis may occur following treatment with immune globulin products, including ANTHRASIL [See *BOXED WARNING*]. Risk factors include cardiovascular risk factors, advanced age, impaired cardiac output, hypercoagulable disorders, prolonged periods of immobilization, history of arterial or venous thrombosis, estrogen use, indwelling central vascular catheters, and/or known or suspected hyperviscosity. Thrombosis may occur in the absence of known risk factors. Weigh the potential risks and benefits of ANTHRASIL against those of alternative therapies for all patients for whom ANTHRASIL administration is being considered.

Because of the potentially increased risk of thrombosis, consider baseline assessment of blood viscosity in patients at risk for hyperviscosity, including those with cryoglobulins, fasting chylomicronemia/markedly high triacylglycerols (triglycerides), or monoclonal gammopathies.

In patients with risk factors where the benefits of ANTHRASIL administration out-weigh the potential risks of thrombosis, administer ANTHRASIL at the minimum rate of infusion practicable. Ensure adequate hydration in patients before administration. Monitor for signs and symptoms of thrombosis.

5.4 Acute Renal Dysfunction/Failure

Acute renal dysfunction, acute renal failure, osmotic nephropathy, acute tubular necrosis, proximal tubular nephropathy, and death may occur upon use of immune globulin intravenous products, including ANTHRASIL. Use ANTHRASIL with caution in patients with any degree of pre-existing renal insufficiency and in patients at risk of developing renal insufficiency (including, but not limited to those with diabetes mellitus, age greater than 65 years, volume depletion, paraproteinemia, sepsis, and patients receiving known nephrotoxic drugs), administering at the minimum rate of infusion practicable. Ensure that patients are not volume depleted before ANTHRASIL infusion. Do not exceed the recommended infusion rate, and follow the infusion schedule closely. Periodic monitoring of renal function and urine output is important in patients judged to be at increased risk of developing acute renal failure. Assess renal function, including measurement of blood urea nitrogen (BUN) and serum creatinine, before the initial infusion of ANTHRASIL and at appropriate intervals thereafter. If renal function deteriorates, consider discontinuing ANTHRASIL.

Most cases of renal insufficiency following administration of immune globulin products have occurred in patients receiving total doses containing 400 mg per kg of sucrose or greater. ANTHRASIL does not contain sucrose.

5.5 Infusion Rate Precautions

Adverse reactions (such as chills, fever, headache, nausea and vomiting) may be related to the rate of infusion. Follow closely the recommended infusion rate given under *2.1 Dose*. Closely monitor and carefully observe patients and their vital signs for any symptoms throughout the infusion period and immediately following an infusion.

5.6 Hemolysis

Hemolytic anemia and hemolysis may develop subsequent to ANTHRASIL administration. ANTHRASIL may contain blood group antibodies that may act as hemolysins and induce *in vivo* coating of red blood cells with immune globulin, causing a positive direct antiglobulin reaction and hemolysis. Acute hemolysis, including intravascular hemolysis, has been reported following immune globulin administration and delayed hemolytic anemia can develop due to enhanced red blood cell sequestration. Severe hemolysis may lead to renal dysfunction/failure.

The following risk factors may be associated with the development of hemolysis: high doses (e.g., >2 g per kg), given either as a single administration or divided over several days, and non-O blood group (1). Other individual patient factors, such as an underlying inflammatory state (as may be reflected by, for example, elevated C-reactive protein or erythrocyte sedimentation rate), have been hypothesized to increase the risk of hemolysis (2) but their role is uncertain.

Monitor ANTHRASIL recipients for clinical signs and symptoms of hemolysis. Consider appropriate laboratory testing in higher risk patients, including measurement of hemoglobin or hematocrit prior to infusion and within approximately 36 to 96 hours and again approximately seven to 10 days post infusion. If signs and/or symptoms of hemolysis or a significant drop in hemoglobin or hematocrit have been observed after infusion, perform additional confirmatory laboratory testing.

5.7 Aseptic Meningitis Syndrome (AMS)

AMS may occur in association with administration of immune globulin products, including ANTHRASIL. AMS usually is associated with high total doses (>2 g per kg) and begins within several hours to two days following treatment. Discontinuation of treatment has resulted in remission of AMS within several days without sequelae.

AMS is characterized by the following symptoms and signs: severe headache, nuchal rigidity, drowsiness, fever, photophobia, painful eye movements, and nausea and vomiting. Cerebrospinal fluid (CSF) studies are frequently positive with pleocytosis up to several thousand cells per cubic millimeter, predominately from the granulocytic series, and with elevated protein levels up to several hundred mg per dL, but negative culture results. Conduct a detailed neurological examination in patients exhibiting such symptoms and signs, including CSF studies, to rule out other causes of meningitis (particularly anthrax meningitis).

5.8 Monitoring: Laboratory Tests

- Consider periodic monitoring of renal function and urine output in patients judged to be at increased risk of developing acute renal failure. Assess renal function, including measurement of BUN and serum creatinine, before the initial infusion of ANTHRASIL and at appropriate intervals thereafter.

- Because of the potentially increased risk of thrombosis, consider baseline assessment of blood viscosity in patients at risk for hyperviscosity, including those with cryoglobulins, fasting chylomicronemia/markedly high triacylglycerols (triglycerides), or monoclonal gammopathies.
- If signs and/or symptoms of hemolysis are present after an infusion of ANTHRASIL, perform appropriate laboratory testing for confirmation.

If TRALI is suspected, perform appropriate tests for the presence of anti-HLA and anti-neutrophil antibodies in the product. TRALI may be managed using oxygen therapy with adequate ventilatory support.

5.9 Interference with Laboratory Testing

ANTHRASIL contains maltose, which can be misinterpreted as glucose by certain types of blood glucose testing systems (for example, those based on the GDH-PQQ or glucose-dye-oxidoreductase methods). Due to the potential for falsely elevated glucose readings, use only testing systems that are glucose-specific to test or monitor blood glucose levels in patients receiving ANTHRASIL [See *BOXED WARNING* and *5.2 Interference with Blood Glucose Testing*].

Antibodies present in ANTHRASIL may interfere with some serological tests. After administration of immune globulins like ANTHRASIL, a transitory increase of passively transferred antibodies in the patient's blood may result in positive results in serological testing (e.g. Coombs' test) [See *5.6 Hemolysis*].

Urinalysis after ANTHRASIL administration may result in elevated glucose [See *6.1 Clinical Trials Experience*]. As this is a known transient effect, testing should be repeated to determine if further action is warranted.

5.10 Transfusion-related Acute Lung Injury (TRALI)

Noncardiogenic pulmonary edema may occur in patients receiving immune globulin products, including ANTHRASIL. TRALI is characterized by severe respiratory distress, pulmonary edema, hypoxemia, normal left ventricular function, and fever and typically occurs within one to six hours after transfusion.

Monitor recipients for pulmonary adverse reactions. If TRALI is suspected, perform tests for the presence of anti-HLA and anti-neutrophil antibodies in \the product.

5.11 Transmission of Infectious Agents from Human Plasma

Because ANTHRASIL is made from human plasma, it may carry a risk of transmitting blood-borne infectious agents, e.g., viruses, the variant Creutzfeldt-Jakob disease (vCJD) agent, and, theoretically, the Creutzfeld-Jakob disease (CJD) agent. No cases of transmission of viral diseases, vCJD or CJD have been associated with the use of ANTHRASIL.

All infections thought to have been possibly transmitted by this product should be reported by the physician or other health care provider to Cangene Corporation at 1-800-768-2304.

6 ADVERSE REACTIONS

The most common adverse reactions to ANTHRASIL observed in >5% of subjects in the healthy volunteer clinical trial were headache, infusion site pain, nausea, infusion site swelling, and back pain. The safety profile of the product may be different in patients with severe inhalational/systemic anthrax from that seen in the healthy volunteer trial. The incidence and/or severity of some adverse reactions to ANTHRASIL and other intravenous immune globulin products may be related to the total protein/polyclonal antibody load administered.

6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

In a double blind, randomized, placebo-controlled study designed to assess the safety and pharmacokinetics of three doses of ANTHRASIL after a single intravenous infusion in healthy volunteers, 72 healthy adult subjects were randomized to receive a dose of 210, 420 or 840 units of ANTHRASIL by Toxin Neutralization Assay (TNA) (N=18/dosing group) or an equal volume of saline placebo (N=6/dosing group). A total of 54 healthy volunteers received one of the three ANTHRASIL doses while 18 healthy volunteers received a saline placebo.

A second stage of the study, designed only for additional safety assessment, was a randomized, open-label study in 20 healthy adult volunteers. Subjects were randomized to receive a dose of 840 units by TNA from one of two additional product lots (10 subjects per lot). There was no placebo group.

Table 1 Adverse Reactions Observed in >5% of Subjects Administered ANTHRASIL or Placebo in a Healthy Volunteer Clinical Trial

System Organ Class	Preferred Term	AIGIV Blinded Randomized Group (N=54)			Placebo (N=18)		
		No. of Events	No. of Subjects	% of Subjects	No. of Events	No. of Subjects	% of Subjects
Gastrointestinal disorders	Nausea	5	5	9.3	2	1	5.6
General disorders and administration site conditions	Infusion site pain	7	5	9.3	0	0	0.0
	Infusion site swelling	5	4	7.4	0	0	0.0
Musculoskeletal and connective tissue disorders	Back pain	2	2	3.7	1	1	5.6
Nervous system disorders	Headache	15	11	20.4	3	1	5.6

There were no serious adverse reactions reported in any of the AIGIV or saline placebo control groups in these studies. Non-serious adverse events and adverse reactions were more frequent in the active AIGIV dosage groups than in the subjects administered placebo.

Headache and back pain rates occurred in a dose-dependent fashion. Back pain was observed with 840 unit doses in five out of 74 subjects (6.8%).

Dose-related elevations in urine glucose also were noted transiently following infusion [See *5.9 Interference with Laboratory Testing*].

Infusion of ANTHRASIL was stopped for four subjects due to adverse reactions. One subject was withdrawn due to chest discomfort, flushing, tachycardia and throat tightness.

Patient Experience

Nineteen adult patients with severe systemic anthrax have been dosed with single 420 unit doses of ANTHRASIL and antimicrobial therapy through expanded access use with the Centers for Disease Control and Prevention (CDC): three patients with inhalational anthrax, 15 patients with anthrax due to injection of anthrax-contaminated heroin and one patient with gastrointestinal anthrax.

A total of 16 serious adverse reactions that began within 72 hours of infusion were reported for eight out of 19 patients (42%) as follows: acute respiratory distress syndrome (n=2), pulmonary edema, pleural effusion, acute renal insufficiency/failure (n=4), coagulopathy, cardiac arrest/death (not otherwise specified, n=2), hypotension, ascites, metabolic acidosis, hyperkalemia, and edema/perhipheral edema.

Six deaths were reported including one patient with inhalational anthrax. The cause of death in three of these six expired patients, including the patient who expired with inhalational anthrax, was consistent with progression of anthrax disease or co-morbidities and the cause of death in the remaining three patients was not determined or available.

7 DRUG INTERACTIONS

7.1 Ciprofloxacin and Levofloxacin

Based on animal studies, ANTHRASIL did not interfere with antibiotic therapy. Concomitant administration of ANTHRASIL with levofloxacin or ciprofloxacin in exposed rabbits and cynomolgus macaques, respectively, did not reduce the efficacy of antibacterial therapy.

7.2 Live, Attenuated Vaccines

Immune globulin administration may impair the efficacy of live attenuated vaccines such as measles, rubella, mumps and varicella. Defer vaccination with live virus vaccines until approximately three months after administration of ANTHRASIL. Revaccinate people who received ANTHRASIL shortly after live virus vaccination three months after the administration of the ANTHRASIL.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

There are no human data to establish the presence or absence of ANTHRASIL associated risk.

8.2 Lactation

Risk Summary

There are no data to assess the presence or absence of ANTHRASIL in human milk, the effects on the breastfed child or the effects on milk production/excretion.

8.4 Pediatric Use

Safety and effectiveness of ANTHRASIL in the pediatric population (≤16 yrs of age) have not been studied. Allometric scaling was used to derive dosing regimens to provide pediatric patients with exposure comparable to the observed exposure in adults receiving 420 units and 840 units. The dose for pediatric patients is based on body weight.

8.5 Geriatric Use

Safety and effectiveness of ANTHRASIL in the geriatric population (>65 yrs of age) have not been studied.

8.6 Renal Insufficiency

Use ANTHRASIL with caution in patients with any degree of pre-existing renal insufficiency and in patients at risk of developing renal insufficiency (including, but not limited to those with diabetes mellitus, age greater than 65 years, volume depletion, paraproteinemia, sepsis, and patients receiving known nephrotoxic drugs), administering at the minimum rate of infusion practicable. Ensure that patients are not volume depleted before ANTHRASIL infusion. Do not exceed the recommended infusion rate, and follow the infusion schedule closely.

8.7 Use in Obese Population

Safety and effectiveness of ANTHRASIL in the obese population have not been studied.

11 DESCRIPTION

ANTHRASIL, Anthrax Immune Globulin Intravenous (Human), is a sterile solution of purified human immune globulin G (IgG) containing polyclonal antibodies that bind the protective antigen (PA) component of *Bacillus anthracis* lethal and edema toxins. It is stabilized with 10% maltose and 0.03% polysorbate 80 (pH is between 5.0 and 6.5) and

contains no preservative. The product is a clear or slightly opalescent colorless liquid, free of foreign particles, supplied in a 50 mL vial with variable fill volume. The total protein concentration ranges from 40 to 70 mg per mL. An adult dosage of 420 units (seven vials) of ANTHRASIL contains up to 0.368 g protein per kg body weight, and an adult dosage of 840 units (14 vials) contains up to 0.736 g protein per kg body weight. The protein load exposure to pediatric patients due to ANTHRASIL administration may range from 0.32 to 1.26 g per kg of body weight, depending on the weight-based pediatric dose.

ANTHRASIL is prepared using plasma collected from healthy, screened donors who were immunized with BioThrax® (Anthrax Vaccine Adsorbed) to achieve high titers of anti-anthrax antibody (meeting minimum potency specifications) and purified by an anion-exchange column chromatography method. The source plasma is tested by FDA licensed nucleic acid testing (NAT) for human immunodeficiency virus 1 (HIV-1), hepatitis B virus (HBV) and hepatitis C virus (HCV). Plasma also was tested by in-process NAT for hepatitis A virus (HAV) and parvovirus B19 (B19) via minipool testing; the limit for B19 in the manufacturing pool is set not to exceed 10^4 International Units of B19 DNA per mL.

The manufacturing process contains two steps implemented specifically for virus clearance. The solvent and detergent step (using tri-n-butyl phosphate and Triton X-100) is effective in the inactivation of enveloped viruses such as HBV, HCV and HIV. Virus filtration, using a Planova 20N virus filter, is effective for the removal of viruses based on their size, including some non-enveloped viruses. These two viral clearance steps are designed to increase product safety by reducing the risk of transmission of enveloped and non-enveloped viruses. In addition to these two specific steps, the process step of anion-exchange chromatography was identified as contributing to the overall viral clearance capacity for small non-lipid enveloped viruses.

The inactivation and reduction of known enveloped and non-enveloped model viruses were validated in laboratory studies as summarized in Table 2. The viruses employed for spiking studies were selected to represent those viruses that are potential contaminants in the product, and to represent a wide range of physiochemical properties in order to challenge the manufacturing process's ability for viral clearance in general.

Table 2 Virus Reduction Values (Log_{10}) Obtained through Validation Studies

Enveloped	**Enveloped**			**Non-Enveloped**			
Genome	**RNA**		**DNA**	**RNA**		**DNA**	
Virus	**HIV-1**	**BVDV**	**PRV**	**HAV**	**EMC**	**MMV**	**PPV**
Family	Retrovirus	Flavivirus	Herpes virus	Picornavirus		Parvovirus	
Size (nm)	80–100	50–70	120–200	25–30	30	20–25	18–24
Anion Exchange Chromatography (partitioning)	Not evaluated			2.3	n.e.	3.4	n.e.
20N Filtration (size exclusion)	≥4.7	≥3.5	≥5.6	n.e.	4.8	n.e.	4.1
Solvent/Detergent (inactivation)	≥4.7	≥7.3	≥5.5	Not evaluated			
Total Reduction (log_{10})	**≥9.4**	**≥10.8**	**≥11.1**	**2.3**	**4.8**	**3.4**	**4.1**

Abbreviations:

BVDV = Bovine viral diarrhea virus; model virus for hepatitis C virus (HCV) and West Nile virus (WNV)

DNA = Deoxyribonucleic Acid

EMC = Encephalomyocarditis virus; model for HAV and for small non-enveloped viruses in general

HIV-1 = Human immunodeficiency virus-1; relevant virus for HIV-1 and model for HIV-2

HAV = Human hepatitis A virus; relevant virus for HAV and model for small non-enveloped viruses in general

MMV = Murine minute virus; model for human B19 parvovirus and for small non-enveloped viruses in general

n.e. = Not evaluated

PPV = Porcine parvovirus; model for human B19 parvovirus and for small non-enveloped viruses in general

PRV = Pseudorabies virus; model for large enveloped DNA viruses, including herpes

RNA = Ribonucleic Acid

The product potency, as determined by an *in vitro* toxin neutralization assay (TNA), is expressed in arbitrary units by comparison to a standard calibrated against the Centers for Disease Control and Prevention (CDC) Reference Serum standard. Each vial contains approximately 40 to 70 mg per mL total protein and ≥60 units of toxin neutralizing activity. The product contains ≤40 mcg per mL of immune globulin A (IgA) as well as residual amounts of solvent and detergent, which are used to inactivate lipid-enveloped viruses.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

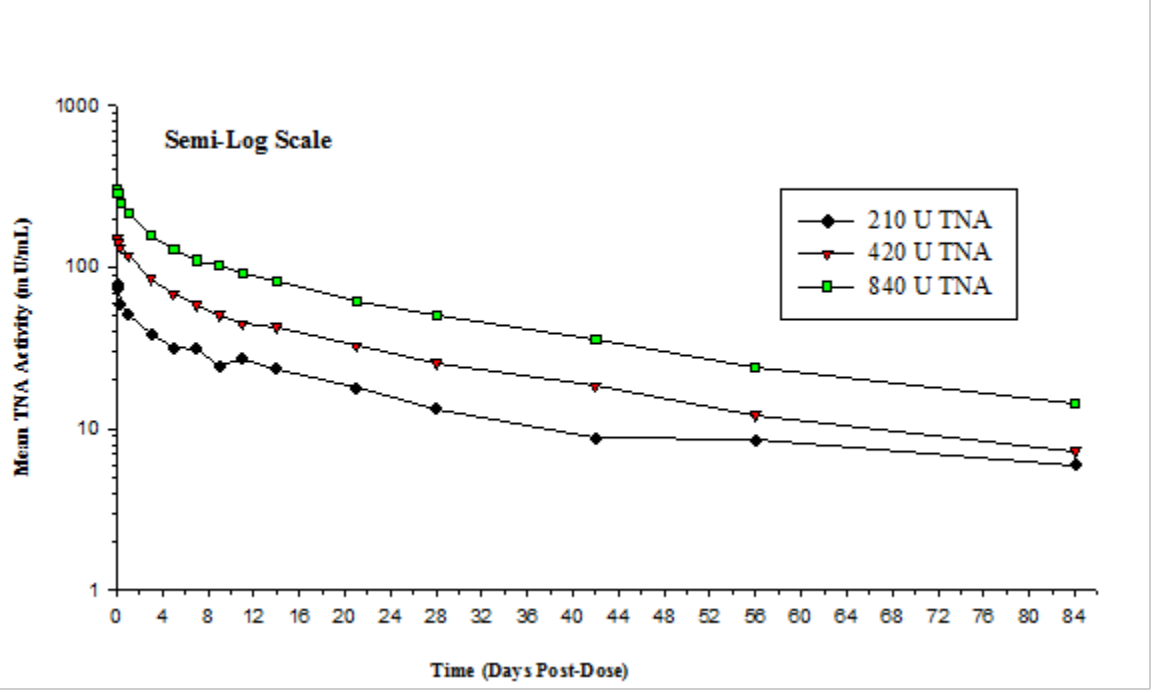
The polyclonal immune globulin G in ANTHRASIL is a passive immunizing agent that neutralizes anthrax toxin. ANTHRASIL binds to protective antigen (PA) to prevent PA mediated cellular entry of anthrax edema factor and lethal factor. ANTHRASIL is administered in combination with appropriate antibiotic therapy as the product by itself is not

known to have direct antibacterial activity against anthrax bacteria, which otherwise may continue to grow and produce anthrax toxins.

12.3 Pharmacokinetics

The mean TNA activities for three doses of ANTHRASIL (210, 420 and 840 units TNA) in the clinical trial in healthy volunteers [See *14 CLINICAL STUDIES*] are plotted on a semi-log scale in Figure 1. The pharmacokinetics of ANTHRASIL after intravenous infusion of the three dose levels were characterized; the peak levels of ANTHRASIL were reached immediately after infusion and then declined over the duration of study (84 days). The mean TNA activity remained above the lower limit of quantitation (5 milliunits per mL) over the entire 84-day post-dose period for the three doses studied.

Figure 1 Mean TNA Activities for Three Doses of ANTHRASIL



A summary of the mean pharmacokinetic results for the TNA data collected in the healthy volunteer study is presented in Table 3.

Table 3 Summary of Mean PK Results by Treatment (TNA Data)

PK Parameters	Dose Levels					
	210 U TNA	**N**	**420 U TNA**	**N**	**840 U TNA**	**N**
Arithmetic Mean (CV%)						
AUC_{0-t} (mU·d/mL)	1031.8 (23.3)	15	2176.7 (18.9)	17	4271.0 (22.3)	16
$AUC_{0-\infty}$ (mU·d/mL)	1277.5 (27.7)	7	2536.7 (14.7)	16	4788.8 (26.5)	15
C_{max} (mU/mL)	83.0 (13.4)	15	156.4 (21.7)	17	316.7 (18.3)	16
$t_{½}$ (d)	24.3 (33.3)	7	28.3 (19.9)	16	28.0 (25.2)	15
CL (mL/d)	174.2 (24.1)	7	169.7 (17.9)	16	188.6 (29.5)	15
Vd (mL)	5714.8 (11.4)	7	6837.2 (20.4)	16	7238.2 (19.4)	15
Median (Min-Max)						
T_{max} (d)	0.116 (0.109–1.068)	15	0.120 (0.120–0.412)	17	0.169 (0.165–0.459)	16

In comparison to healthy subjects, patients with inhalational anthrax are expected to initially have greater clearance of anti-PA antibodies and lower AUC from ANTHRASIL administration due to the presence of PA antigen.

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

Inhalational anthrax patients, concomitantly treated with antibiotics and a single 420 unit TNA dose of ANTHRASIL, exhibited increases in serum and pleural anti-PA levels; these levels remained at >50% of the peak anti-PA levels over the next five days. The peak serum anti-PA levels in these patients following ANTHRASIL administration (132 to 160 mcg/mL, mean 145 mcg/mL) overlapped with those obtained with the 420 unit dose in healthy volunteers (135 to 250 mcg/mL, mean 190 mcg/mL, median 192 mcg/mL), although mean levels were approximately 25% lower in the inhalational anthrax patients. In the three inhalational anthrax patients, serum and pleural levels of lethal factor declined after initiation of antibiotics and further decreased over the period of five days following ANTHRASIL administration; however, due at least in part to ANTHRASIL targeting the PA component of lethal toxin, plasma and pleural fluid lethal factor levels remained detectable when measured two to five days following ANTHRASIL administration.

Because the effectiveness of ANTHRASIL cannot ethically be tested in placebo-controlled trials in humans, a comparison of ANTHRASIL exposures achieved in healthy human subjects to those observed in animal models of inhalational anthrax in therapeutic efficacy studies was necessary to support the dosage regimen. A dose of 420 units has a similar exposure to the efficacious dose of 15 U/kg administered to New Zealand white rabbits and cynomolgus macaques. In cynomolgus macaques treated with ANTHRASIL monotherapy, a higher dose of 30 U/kg, with a similar exposure to a human dose of 840 units, may result in

improved survival [See *13.2 Animal Toxicology and/or Pharmacology*]. As a result, the initial dosing regimen is given as a range of 420 to 840 units, and the recommended regimen includes the potential for repeat dosing.

13 NONCLINICAL TOXICOLOGY

Immune globulins are normal constituents of the human body. Toxicology studies have not been performed with ANTHRASIL or its components.

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

13.2 Animal Toxicology and/or Pharmacology

Anthrax infected New Zealand white rabbits and cynomolgus macaques administered an intravenous injection of ANTHRASIL (15 units TNA per kg) that did not survive their infection showed an increase in the severity and/or incidence of central nervous system lesions (bacteria, hemorrhage and necrosis) as compared to intravenous immune globulin ("placebo") treated animals who also did not survive the infection. The mean time to death between non-surviving ANTHRASIL and placebo treated animals was comparable. Surviving rabbits had no evidence of central nervous system lesions at the end of the study. No surviving cynomolgus macaques in monotherapeutic studies were tested for central nervous system lesions.

Monotherapeutic Studies in Animal Models

In a monotherapeutic efficacy study, rabbits were exposed to a target dose of 200 x LD_{50} aerosolized anthrax spores and then administered 15 units per kg of ANTHRASIL at the onset of toxemia, as determined by the presence of PA in serum samples. Detection of PA was used as the trigger for initiation of treatment, while bacteremia status provided a retrospective confirmation of disease. Ninety-eight (98) percent of the treated animals were bacteremic prior to treatment. Of the animals that were toxemic and bacteremic prior to treatment, ANTHRASIL treatment resulted in a 26% survival in comparison to a 2% survival with IGIV placebo treatment (Table 4) over the 36 day duration of the study. ANTHRASIL treatment resulted in a significant decrease in the proportion of rabbits that were toxemic or bacteremic. The time to resolution of toxemia ($p=0.0006$) or bacteremia ($p=0.0074$) was also significantly reduced in rabbits that received ANTHRASIL.

Efficacy of ANTHRASIL was also assessed in cynomolgus macaques exposed to a target dose of 200 x LD_{50} aerosolized anthrax spores. Treatment with placebo or one of three dose levels of ANTHRASIL was initiated after animals became toxemic (positive for PA detection in serum samples), and bacteremia status provided a retrospective confirmation of disease. Survival was assessed over a period of 88 days in toxemic animals that were confirmed to be bacteremic at the time of treatment. Survival was 0% in placebo treated animals. Animals treated with 7.5 units per kg exhibited 36% survival, those treated with 15 units per kg exhibited 43% survival, and those treated with 30 units per kg exhibited 70% survival (Table

4). Compared to placebo, these survival rates were statistically significant at p=0.0451, 0.0339, and 0.0031, respectively The differences in survival between the 7.5, 15, and 30 unit per kg doses of ANTHRASIL were not statistically significant. ANTHRASIL treated animals showed a statistically significant reduction in anthrax toxin when compared to placebo treated animals.

Table 4 Survival Rates in NZW Rabbits and Cynomolgus Macaques Treated with ANTHRASIL

	NZW Rabbits at 36 Days PI		**Cynomolgus Macaques at 28 Days PI**	
	No. Survivors (%)[a]	**p-Value[b]**	**No. Survivors (%)[a]**	**p-Value[c]**
Placebo	1/48 (2)	–	0/11 (0)	–
ANTHRASIL 7.5 U/kg[d]	–	–	4/11 (36)	0.0451
ANTHRASIL 15 U/kg	13/50 (26)	0.0009	6/14 (43)	0.0339
ANTHRASIL 30 U/kg[d]	–	–	7/10 (70)	0.0031

[a] Survival among animals that were bacteremic and toxemic prior to treatment

[b] Two-sided Fisher's exact test

[c] Bonferroni-Holm adjusted one-sided Fisher's exact test

[d] Dose not evaluated in rabbits in this study

PI = Post-infection

ANTHRASIL Efficacy in Combination with Antibiotics

The efficacy of ANTHRASIL administered with levofloxacin was determined in New Zealand white rabbits with systemic disease. No significant difference between the control (normal immune globulin [IGIV] plus levofloxacin) and treatment groups (ANTHRASIL plus levofloxacin) was seen when combination treatment was delayed up to 60 hours post-challenge. There was no observed antagonism between levofloxacin and ANTHRASIL in this study. This study also supported that ANTHRASIL effectively cleared toxemia when administered with antibiotics. In ANTHRASIL treated groups, all animals cleared PA toxemia post-ANTHRASIL administration and only 4/31 (13%) of ANTHRASIL treated animals exhibited a single transient positive PA result for toxemia at the 12 or 18 hour time point post-dosing. Placebo control animals exhibited more persistent toxemia, with 26/32 (81%) having positive PA results for 18 to 90 hours post-treatment.

In a second study, treatment was delayed beyond 60 hours to simulate a clinical scenario. When combination treatment was initiated at 60, 72, 84 or 96 hours post anthrax exposure, differences in survival were seen, but no statistically significant added survival benefit was observed between groups that received placebo (IGIV plus levofloxacin) or ANTHRASIL (15 units per kg plus levofloxacin). An increase in survival was observed with ANTHRASIL when treatment was delayed to 96 hours post exposure, but was not statistically significant. When treatment was delayed to 96 hours, survival was 25% (2/8) in the antibiotic plus IGIV control group and 71% (5/7) in the ANTHRASIL plus levofloxacin group. A marginal improvement of 10 to 15% was observed at other time points, suggesting a trend in added benefit with ANTHRASIL. This study also demonstrated a significant effect of ANTHRASIL on toxemia. The majority of ANTHRASIL treated animals became negative

for PA (toxemia) within one hour post-infusion of ANTHRASIL and remained negative, even with the delayed treatment from 60 to 96 hours post-anthrax challenge and high levels of toxemia pretreatment. In contrast, placebo treated animals remained toxemic up to three days after initiating antibiotic treatment.

The efficacy of ANTHRASIL co-administered with levofloxacin was evaluated in New Zealand white rabbits when treatment was delayed to 96 hours after anthrax spore inhalation. The dose of levofloxacin was chosen to yield a comparable exposure to that achieved by the recommended dose in humans. Of the animals that survived to be treated (19% of those challenged), antibacterial drug plus ANTHRASIL (15 units per kg) resulted in 58% (18/31) survival compared to 39% (13/33) survival in rabbits treated with antibacterial drug and IGIV placebo (p=0.14, Z-test).

When animals were stratified by pre-treatment toxemia (PA) in a post hoc analysis, added benefit was observed in animals treated with ANTHRASIL and levofloxacin when they had pre-treatment PA levels between 200 and 800 ng/mL (p=0.02, Fisher's exact test). When pre-treatment toxemia was low (PA <200 ng/mL), survival was greater than 90% in all animals, regardless of treatment (Table 5). Animals with very high levels of toxemia (>800 ng/mL) did not survive irrespective of the treatment administered.

Table 5 Survival Rates in New Zealand White Rabbits Stratified by Pre-treatment PA Levels

Pre-treatment PA (ng/mL)	IGIV Placebo + Levofloxacin (%)	ANTHRASIL + Levofloxacin (%)
<200	11/12 (91.7)	8/9 (88.9)
200–800	2/11 (18.2)	10/14 (71.4)
>800	0/10 (0)	0/8 (0)
All pre-treatment PA levels	13/33 (39.4)	18/31 (58.1)

ANTHRASIL and antibiotic combination treatment was also studied in the cynomolgus macaque model of inhalational anthrax. In this study, delay of initiation of treatment to 64 hours post anthrax exposure resulted in 75% (9/12) survival in the placebo plus ciprofloxacin treatment group versus 83% (10/12) survival in the ANTHRASIL (15 units per kg) plus ciprofloxacin group (p=1).

No antagonism of ANTHRASIL when administered with antibiotic as a concomitant therapy was observed.

ANTHRASIL in Post-exposure Prophylaxis

A post exposure prophylactic study assessed the survival following aerosol exposure to a lethal dose of anthrax spores (200 x LD_{50}) in New Zealand white rabbits administered ANTHRASIL (7.5, 15 or 30 units TNA per kg) at 30 hours post-anthrax challenge compared to placebo controls. All three doses of ANTHRASIL improved survival when given 30 hours post-anthrax challenge. When animals that were both bacteremic and toxemic were treated at 30 hours following challenge, there was a 22% (2/9) survival with a dose of 15 units TNA per kg and a 33% (4/12) survival with a dose of 30 units TNA per kg. All rabbits in the placebo arm died.

14 CLINICAL STUDIES

Because it is not ethical or feasible to conduct placebo-controlled clinical trials in humans with inhalational anthrax, the effectiveness of ANTHRASIL is based on efficacy studies demonstrating a survival benefit in animal models of inhalational anthrax infection [See *13.2 Animal Toxicology and/or Pharmacology*]. The safety has been assessed in healthy adults and in a limited number of patients with anthrax who were treated with ANTHRASIL under expanded access use.

Safety and Pharmacokinetics of ANTHRASIL in Healthy Volunteers

In a double blind, randomized, placebo-controlled study designed to assess the safety and pharmacokinetics of three doses of ANTHRASIL after a single intravenous infusion in healthy volunteers, a total of 72 healthy adult subjects were randomized to receive a dose of 210, 420 or 840 units of ANTHRASIL by TNA (N=18/dosing group) or an equal volume of saline placebo (N=6/dosing group).

A second stage of this study, designed only for additional safety assessment, was a randomized, open-label study in 20 healthy adult volunteers. Subjects were randomized to receive a dose of 840 units by TNA from one of two additional product lots (10 subjects per lot). There was no placebo group [See 6 *ADVERSE REACTIONS* and *12.3 Pharmacokinetics*].

Patient Experience

Nineteen adult patients have been treated with ANTHRASIL under expanded access use, including three patients with inhalational anthrax, one patient with gastrointestinal anthrax and 15 patients with injectional anthrax due to injection of anthrax-contaminated heroin. Patients were receiving antimicrobial therapy before, during and after ANTHRASIL administration.

In patients with inhalational anthrax, two out of three patients treated with ANTHRASIL plus antimicrobial therapy survived and one died from progression of anthrax disease, systemic candidiasis and multiorgan failure. Among the 15 patients with injectional anthrax treated with ANTHRASIL plus antibiotics, 10 survived and five died (two from progression of anthrax disease; the cause of death was not determined or available for three patients). The single patient with gastrointestinal anthrax treated with ANTHRASIL survived. Therapy for these systemic anthrax cases included aggressive supportive measures including mechanical ventilation and pulmonary/abdominal fluid drainage.

In the three inhalational patients, the ANTHRASIL dose of 420 units by TNA resulted in increased anti-PA levels (correlating with increased TNA activity); these levels remained stable up to seven to 20 days post-administration, probably reflecting the rising antibody production by the patient at the same time that the exogenously-administered antibody was being cleared.

In some injectional anthrax cases, complicated by hemorrhage and pleural and/or peritoneal fluid losses from thoracentesis and/or paracentesis, serum anti-PA antibody levels fell as much as approximately 90% from their post-ANTHRASIL peak levels by 24 hours following ANTHRASIL administration. In the gastrointestinal anthrax patient, serum anti-PA levels

were observed prior to ANTHRASIL infusion with further increases in anti-PA levels post-administration and maintenance of anti-PA above pre-administration levels for 11 days was observed.

15 REFERENCES

1. Kahwaji J, Barker E, Pepkowitz S, Klapper E, Villicana R, Peng A, et al. Acute hemolysis after high-dose intravenous immunoglobulin therapy in highly HLA sensitized patients. Clin J Am Soc Nephrol. 2009 December;4;1993–97.
2. Daw Z, Padmore R, Neurath D, Cober N, Tokessy M, Desjardins D, et al. Hemolytic transfusion reactions after administration of intravenous immune (gamma) globulin: a case series analysis. Transfusion. 2008;48(8):1598-601.

16 HOW SUPPLIED/STORAGE AND HANDLING

16.1 How Supplied

NDC 60492-0249-1 for single vial

NDC 60492-0249-2 for shelf carton containing seven vials

ANTHRASIL is supplied as a 50 mL single dose vial seated with a butyl rubber stopper and an aluminum seal with a plastic flip-top cap. Each vial, regardless of fill volume, contains ≥60 units. It is packaged in a shelf carton with seven vials and a package insert.

ANTHRASIL does not contain natural rubber latex.

16.2 Storage and Handling

Store frozen at or below ≤-15°C (≤5°F) until required for use. Do not use after expiration date.

Once punctured, use the vial contents to prepare the infusion bag and infuse as soon as possible. ANTHRASIL contains no preservative.

Do not refreeze, reuse or save ANTHRASIL for future use.

Discard any partially used vials.

17 PATIENT COUNSELING INFORMATION

See FDA-approved patient labeling (Patient Information).

Discuss the risks and benefits of this product with the patient or their legally authorized representative before administering it to the patient.

- Inform patients of the potential for hypersensitivity reactions, especially in individuals with previous reactions to human immune globulin and in individuals deficient in IgA. Advise patients to be aware of the following symptoms associated with allergic reactions:

hives, rash, chest tightness, wheezing, shortness of breath, or feeling light headed or dizzy when they stand. Patients should be cautioned to seek medical attention immediately should they experience any one or more of the above mentioned symptoms, as well as other side effects including injection site pain, chills, fever, headache, nausea, vomiting, and joint pain.

- Advise patients that the maltose contained in ANTHRASIL can interfere with some types of blood glucose monitoring systems. Advise patients to use only testing systems that are glucose-specific for monitoring blood glucose levels as the interference of maltose could result in falsely elevated glucose readings that could lead to untreated hypoglycemia or to inappropriate insulin administration, resulting in life-threatening hypoglycemia.
- Inform patients that ANTHRASIL is an immune globulin product; therefore, there is the potential risk of developing other reactions observed with the immunoglobulin product class such as thrombosis, hemolysis, aseptic meningitis syndrome (AMS), transfusion-related acute lung injury (TRALI), acute respiratory distress syndrome (ARDS) and acute renal dysfunction or failure.
- Advise patients that ANTHRASIL may impair the effectiveness of certain live virus vaccines such as measles, rubella (i.e. German measles), mumps, and varicella (i.e. chickenpox).
- Inform patients that ANTHRASIL is prepared from human plasma. Products made from human plasma may contain infectious agents such as viruses that can cause disease.
- Inform patients that the efficacy of ANTHRASIL is based solely on efficacy studies demonstrating a survival benefit in animals and that the effectiveness of ANTHRASIL has not been tested in humans with anthrax. The safety of ANTHRASIL has been tested in healthy adults.

Manufactured by:

Cangene Corporation, a subsidiary of Emergent BioSolutions Inc.
155 Innovation Drive
Winnipeg, MB Canada
R3T 5Y3

PATIENT INFORMATION

ANTHRASIL [Anthrax Immune Globulin Intravenous (Human)]

What is anthrax?

Anthrax is a serious disease caused by a germ called *Bacillus anthracis*. This germ makes a poison called a toxin. People who are exposed to anthrax germs are at risk of serious illness, including death. You/your child cannot get anthrax from another person. Symptoms of anthrax disease usually start within seven days of breathing in anthrax germs, but can take up to six or seven weeks to appear.

- Early symptoms can be any of the following: fever, chills, tiredness, cough, muscle aches and headache.
- Later symptoms can be any of the following: shortness of breath, chest discomfort, confusion or nausea.

What is ANTHRASIL?

Medicines like antibiotics can kill anthrax germs. However, the anthrax poison (toxin) may continue to cause severe sickness even after the germs are gone. When someone gets the anthrax vaccine, their body's immune system makes antibodies against anthrax. Antibodies help to fight off disease and can also help to fight off the anthrax poison.

ANTHRASIL [Anthrax Immune Globulin Intravenous (Human)] is made by taking anthrax antibodies from well people who have been vaccinated. It does not contain the anthrax germ or poison. The antibodies in ANTHRASIL can then be given to someone with anthrax. This may make the sick person's disease less severe, decrease the duration of illness and increase their chance of surviving.

The effectiveness of ANTHRASIL has been studied only in animals.

The safety of ANTHRASIL was studied in healthy adults. There have been no studies of ANTHRASIL in persons less than 17 years of age.

Who should use ANTHRASIL?

Your doctor may give you ANTHRASIL if they suspect that you/your child have been exposed to anthrax and may have anthrax in your lungs.

You should get the treatment as quickly as possible to stop the progression of the illness.

Before you receive ANTHRASIL, tell your healthcare provider about all of your medical conditions, including if you are:

- Allergic to any of the ingredients in ANTHRASIL
- Deficient for immune globulin A (IgA)
- Pregnant or planning to become pregnant. It is not known if ANTHRASIL will harm your unborn baby.

- Breastfeeding or plan to breastfeed. It is not known if ANTHRASIL passes into your breast milk. You and your healthcare provider should decide if you will receive ANTHRASIL or breastfeed.
- Diabetic. ANTHRASIL contains maltose, which can give false readings on some glucose testing meters. If you are diabetic, ask your doctor what types of glucose testing meters can be used safely while you are getting ANTHRASIL.

Tell your healthcare provider about all the medicines you take, including prescription and non-prescription medicines, vitamins and herbal supplements.

How will you receive ANTHRASIL?

ANTHRASIL is given as an infusion into your vein. Your doctor will determine the dose of ANTHRASIL. The treatment may take several hours to administer. Your doctor will decide if you need more than one infusion.

What are the possible side effects of ANTHRASIL?

The most common side effects of ANTHRASIL are:

- Headache
- Pain at site of needle entry
- Nausea
- Swelling at site of needle entry
- Back pain

ANTHRASIL can cause allergic reactions. Tell your doctor right away if you have trouble breathing, swelling of your tongue or lips, a very fast heart rate, or feel very weak because these symptoms can be signs of a serious allergic reaction.

Talk to your doctor about any side effects that concern you. You can ask your doctor for additional prescribing information that is available to healthcare professionals.

What other information do you need to know about ANTHRASIL?

ANTHRASIL is made from human plasma. The plasma donors are carefully screened and the plasma is carefully cleaned, but there is a small risk that it may give you a virus. Talk to your doctor if you have any symptoms that concern you.

Tell your doctor if you have recently received a vaccine of any sort, or plan to be vaccinated. Use of ANTHRASIL may cause vaccines such as measles, rubella, mumps and varicella to not work as well. Vaccination with some vaccines may need to be delayed until approximately three months after use of ANTHRASIL. If you received ANTHRASIL shortly after a vaccination you may need to be re-vaccinated three months after the administration of the ANTHRASIL. Talk to your doctor.

You may report side effects directly to Cangene Corporation at 1-800-768-2304 or to the FDA’s MedWatch reporting system at 1-800-FDA-1088.

Manufactured by:

Cangene Corporation, a subsidiary of Emergent BioSolutions Inc.
155 Innovation Drive
Winnipeg, MB Canada
R3T 5Y3

Part No.: XXXXXXXX

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use BAT® safely and effectively. See full prescribing information for BAT®.

BAT® [Botulism Antitoxin Heptavalent (A, B, C, D, E, F, G) - (Equine)] Sterile Solution for Injection
Initial U.S. Approval: 2013

----------INDICATIONS AND USAGE----------

BAT [Botulism Antitoxin Heptavalent (A, B, C, D, E, F, G) – (Equine)] is a mixture of immune globulin fragments indicated for the treatment of symptomatic botulism following documented or suspected exposure to botulinum neurotoxin serotypes A, B, C, D, E, F, or G in adults and pediatric patients.

The effectiveness of BAT is based solely on efficacy studies conducted in animal models of botulism.

----------DOSAGE AND ADMINISTRATION----------

For intravenous use only.

Administer BAT by slow intravenous infusion after dilution 1:10 in normal saline at the dose recommended in the following table.

Patient Group	Dose	Starting Infusion Rate (first 30 minutes)	Incremental Infusion Rate if Tolerated (every 30 minutes)	Maximum Infusion Rate
Adults (≥ 17 years)	One vial	0.5 mL/min	Double the rate	2 mL/min
Pediatric (1 year to <17 years)	20 – 100% of adult dose	0.01 mL/kg/min Do not exceed the adult rate	0.01 mL/kg/min	0.03 mL/kg/min Do not exceed the adult rate
Infants (< 1 year)	10% of adult dose regardless of body weight	0.01 mL/kg/min	0.01 mL/kg/min	0.03 mL/kg/min

----------DOSAGE FORMS AND STRENGTHS----------

Each single-use vial contains a minimum potency of:

- 4,500 Units (U) for serotype A antitoxin,
- 3,300 U for serotype B antitoxin,
- 3,000 U for serotype C antitoxin,
- 600 U for serotype D antitoxin,
- 5,100 U for serotype E antitoxin,
- 3,000 U for serotype F antitoxin, and
- 600 U for serotype G antitoxin

----------CONTRAINDICATIONS----------

None.

----------WARNINGS AND PRECAUTIONS----------

- Hypersensitivity reactions including anaphylaxis. Prepare for monitoring and management of allergic reactions (5.1).
- Delayed allergic reactions (serum sickness). Patient monitoring is recommended (5.2).
- Infusion reactions. Monitor and slow or interrupt infusion and administer treatment based on the severity of the reaction (5.3).
- Interference with non-glucose specific blood sugar testing systems. Use glucose-specific testing systems (5.4).
- BAT is made from equine plasma and may contain infectious agents e.g. viruses (5.5).

----------ADVERSE REACTIONS----------

- The most common adverse reactions observed in ≥5 % of healthy volunteers in clinical trials were headache, nausea, pruritus, and urticaria (6.1).
- The most common adverse reactions reported in ≥1% of patients in a clinical study were pyrexia, rash, chills, nausea, and edema (6.1).
- One serious adverse reaction of hemodynamic instability was observed in one patient in the clinical study (6.1).

To report SUSPECTED ADVERSE REACTIONS, contact Cangene Corporation at 1-800-768-2304 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

----------USE IN SPECIFIC POPULATIONS----------

- Pediatric: Limited safety data is available in the pediatric population. Dosing in pediatric patients is based on Salisbury Rule (8.4).

See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling

Revised: 08/2015

FULL PRESCRIBING INFORMATION: CONTENTS*

*Sections or subsections omitted from the full prescribing information are not listed

FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

BAT [Botulism Antitoxin Heptavalent (A, B, C, D, E, F, G) – (Equine)] is a mixture of immune globulin fragments indicated for the treatment of symptomatic botulism following documented or suspected exposure to botulinum neurotoxin serotypes A, B, C, D, E, F, or G in adults and pediatric patients.

The effectiveness of BAT is based on efficacy studies conducted in animal models of botulism.

2 DOSAGE AND ADMINISTRATION

BAT is for intravenous use only.

2.1 Dosage and Administration

- Each vial of BAT contains a minimum potency for serotypes A, B, C, D, E, F, and G antitoxin *[see Dosage Forms and Strengths (*3*)]*.
- For adult, pediatric, and infant patient groups, administer a dose of BAT according to Table 1. For details on pediatric dosing by body weight see Table 2.
- Administer all BAT doses after dilution 1:10 in normal saline by slow intravenous infusion according to the varying infusion rates in Table 1.
- Monitor vital signs throughout the infusion. If tolerated, the infusion rate can be increased incrementally up to the maximum infusion rate, and continued for the remainder of the administration. Decrease infusion rate if the patient develops discomfort or infusion-related adverse reactions.

Table 1 BAT Dosing Guide and Intravenous Infusion Rate

Patient Group	**Dose**	**Starting Infusion Rate (first 30 minutes)**	**Incremental Infusion Rate if Tolerated (every 30 minutes)**	**Maximum Infusion Rate**
Adults (≥ 17 years)	One vial	0.5 mL/min	Double the rate	2 mL/min
Pediatric (1 year to < 17 years)	20 – 100% of adult dose	0.01 mL/kg/min Do not exceed the adult rate.	0.01 mL/kg/min	0.03 mL/kg/min Do not exceed the adult rate
Infants (< 1 year)	10% of adult dose regardless of body weight	0.01 mL/kg/min	0.01 mL/kg/min	0.03 mL/kg/min

Calculate pediatric BAT dose by body weight according to Table 2.

Table 2 Pediatric Dosing Guide for BAT Based on Salisbury Rule (1 Year to < 17 Years)

Body Weight (kg)	**Percent of Adult Dose* (%)**
10-14	20**
15-19	30
20-24	40
25-29	50
30-34	60
35-39	65
40-44	70
45-49	75
50-54	80
≥ 55	100

*Dosing guide is based on the Salisbury Rule (1):

- Body weight ≤ 30 kg: 2x weight (kg) = % adult dose to administer
- Body weight > 30 kg: weight (kg) + 30 = % adult dose to administer

Do not exceed 1 vial dose regardless of body weight.

** Minimum pediatric dose is 20% of adult dose. See Table 1 for infant dose.

2.2 Preparation

1. Bring vial to room temperature.
    - If frozen, thaw vial by placing in a refrigerator at 36 to 46 °F (2 to 8 °C) until the contents are thawed for approximately 14 hours.

- Product can be thawed rapidly by placing at room temperature for one hour followed by a water bath at 98.6 °F (37 °C) until thawed.
- Do not thaw this product in a microwave oven. Do not refreeze the vial.

2. Inspect vial to ensure there is no damage to the seal or vial. If damaged, discard the vial.
3. Do not shake the vial during preparation to avoid foaming.
4. Dilute 1:10 in 0.9% Sodium Chloride Injection, USP (saline) by adding BAT solution from the vial to the appropriate amount of saline in an IV bag. Do not use any other diluents. As the fill volume per vial varies by lot number (approximately 10 to 22 milliliters per vial), 90 to 200 milliliters of saline will be required. Withdraw the entire contents of the vial to obtain the total volume in the vial. If a partial vial is required (for pediatric dosing), the entire content of the vial should be withdrawn to ensure accurate calculation of the dosage [Table 2].
5. Visually inspect the product for particulate matter and discoloration prior to administration. Do not use if the solution is turbid, cloudy, or contains particles.
6. Use an intravenous line with constant infusion pump. Use of an in line filter is optional.
7. BAT vials are for single use only and contain no preservative. Once punctured, use the vial contents to prepare the infusion bag and administer as soon as possible.
8. Discard any unused portion.

3 DOSAGE FORMS AND STRENGTHS

BAT is a sterile solution of purified $F(ab')_2$ plus $F(ab')_2$-related immune globulin fragments derived from equine plasma, containing antitoxin activity to botulinum neurotoxins A, B, C, D, E, F, and G.

Each single-use vial, regardless of size or fill volume, contains a minimum antitoxin potency of:

- 4,500 U serotype A antitoxin,
- 3,300 U serotype B antitoxin,
- 3,000 U serotype C antitoxin,
- 600 U serotype D antitoxin,
- 5,100 U serotype E antitoxin,
- 3,000 U serotype F antitoxin, and
- 600 U serotype G antitoxin.

4 CONTRAINDICATIONS

None.

5 WARNINGS AND PRECAUTIONS

5.1 Hypersensitivity Reactions

Severe hypersensitivity reactions, including anaphylactic and anaphylactoid reactions may occur following BAT administration. Patients who have had previous therapy with an equine-derived antivenom/antitoxin, with a history of hypersensitivity to horses, asthma, or hay fever are at a greater risk for developing severe hypersensitivity reactions to BAT. Administer BAT in a setting with appropriate equipment, medication, including epinephrine, and personnel trained in the management of hypersensitivity, anaphylaxis, and shock.

Monitor all patients for signs and symptoms of acute allergic reaction (e.g. urticaria, pruritus, erythema, angioedema, bronchospasm with wheezing or cough, stridor, laryngeal edema, hypotension, tachycardia) during and following the BAT infusion. In case of hypersensitivity reaction, discontinue BAT administration immediately and administer appropriate emergency care. Have immediately available medications such as epinephrine for emergency treatment of acute hypersensitivity reactions.

For patients at risk for hypersensitivity reaction, begin BAT administration at the lowest rate achievable (< 0.01 mL/min) and monitor.

5.2 Delayed Allergic Reactions (Serum Sickness)

Delayed allergic reactions (serum sickness e.g. fever, urticarial or maculopapular rash, myalgia, arthralgia, and lymphadenopathy) may occur following BAT administration, typically 10-21 days after infusion. Monitor patients for signs and symptoms of delayed allergic reaction.

If a delayed allergic reaction (serum sickness) is suspected, administer appropriate medical care.

5.3 Infusion Reactions

Chills, fever, headaches, nausea, and vomiting can be related to the rate of infusion. Arthralgia, myalgia and fatigue or vasovagal reactions may also develop. Carefully observe patients for the onset of these infusion reactions throughout the infusion period and immediately following an infusion.

Reduce the rate of infusion if the patient experiences infusion reactions and administer symptomatic therapy. If symptoms worsen, discontinue the infusion and administer appropriate medical care.

5.4 Interference with Blood Glucose Testing

The maltose contained in BAT can interfere with some types of blood glucose monitoring systems i.e. those based on glucose dehydrogenase pyrroloquinoline-quinone (GDH-PQQ) method. This can result in falsely elevated glucose readings and inappropriate administration of insulin, resulting in life-threatening hypoglycemia. Cases of true hypoglycemia may go

untreated if the hypoglycemic state is masked by falsely elevated results *[see Drug Interactions (7)]*.

5.5 Transmissible Infectious Agents

Because BAT is made from equine plasma, it may carry the risk of transmitting infectious agents e.g. viruses. The equine plasma pools are screened for the presence of certain infectious agents and the manufacturing process for BAT includes measures to inactivate and remove certain viruses *[see Description (11)]*. Despite these measures, such products can still potentially transmit disease. No cases of transmission of viral diseases have been associated with the use of BAT.

Report all infections thought by a physician to have been transmitted by BAT to Cangene Corporation at 1-800-768-2304. Discuss the risks and benefits of this product with the patient or their legal guardian before administering it to the patient *[see Patient Counseling Information (17)]*.

6 ADVERSE REACTIONS

The most common adverse reactions observed in ≥ 5 % of healthy volunteers in clinical trials were headache, nausea, pruritus, and urticaria.

The most common adverse reactions reported in ≥ 1% of patients in a clinical study were pyrexia, rash, chills, nausea, and edema.

The following serious adverse reactions are discussed in detail in other sections of the labeling:

- Hypersensitivity reactions *[see Warnings and Precautions (5.1)]*
- Delayed allergic reactions/serum sickness *[see Warnings and Precautions(5.2)]*
- Infusion reactions *[see Warnings and Precautions (5.3)]*

6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

In a randomized, double-blind, parallel arm trial conducted to evaluate the safety of BAT in healthy subjects, and to establish the pharmacokinetic profile of the seven botulinum antitoxin serotypes contained in BAT following intravenous (IV) administration, 40 subjects were randomized to receive either one (n=20) or two vials (n=20) of BAT.

In a second parallel arm, randomized, double-blind pharmacodynamic trial, 26 healthy subjects were randomized to receive either BAT in saline (n=16) or placebo (0.9% saline; n=10).

The most common adverse reactions in all healthy subjects were headache (9%), pruritus (5%), nausea (5%), and urticaria (5%). Other adverse reactions reported in less than 4% of

subjects included pyrexia and throat discomfort. All reported adverse reactions were considered mild or moderate. No serious adverse reactions were reported. Two moderate acute allergic reactions that required premature termination of the infusion and treatment were reported. Reactions were predefined as mild if the subject was aware but could tolerate. Moderate reactions were predefined as discomfort enough to interfere with normal daily activity.

A total of 231 subjects with suspected or confirmed botulism were exposed to BAT in an open-label observational expanded access clinical study sponsored by the Centers for Disease Control and Prevention (CDC).

The majority of adult (213/216) and pediatric (13/15) subjects received one dose of BAT. Three adult subjects were exposed to a second dose of BAT, and two pediatric subjects each received two infant doses (10% of the adult dose). The administration of a second dose varied from seven hours to one month after the first dose.

Safety data was actively collected from treating physicians by the CDC. However, no on-site safety monitoring was performed, and the CDC relied on follow-up information provided by the treating physicians to determine the reporting frequencies for adverse reactions. Of the 231 subjects receiving BAT, safety information was available for 228 subjects. Adverse reactions were reported in 10% of all subjects. The most common adverse reactions were pyrexia (4%), rash (2%), chills (1%), nausea (1%), and edema (1%). Other adverse reactions were reported in less than 1% of subjects. No subject experienced anaphylaxis. One subject experienced a serious adverse reaction of hemodynamic instability characterized by bradycardia, tachycardia, and asystole during BAT administration. One subject experienced mild serum sickness (< 1%) with myalgia, arthralgia, and dark urine twelve days after BAT administration.

Table 3 Summary of Adverse Drug Reactions (ADR) Reported in Subjects that Received BAT through the CDC Expanded Access Clinical Study

System Organ Class	**Preferred Term**	**Overall (N=228)**		
		No. of Events	**No. of Subjects**	**% of Subjects**
ALL BODY SYSTEM	OVERALL	37	23	10.1
Cardiac disorders	Cardiac arrest	1	1	0.4
	Bradycardia	1	1	0.4
	Tachycardia	1	1	0.4
Gastrointestinal disorders	Vomiting	1	1	0.4
	Nausea	2	2	0.9
General disorders and administration site conditions	Pyrexia	9	9	3.9
	Chest discomfort	1	1	0.4
	Edema	2	2	0.9
	Chills	3	3	1.3
	Feeling jittery	1	1	0.4

System Organ Class	Preferred Term	Overall (N=228)		
		No. of Events	No. of Subjects	% of Subjects
Immune system disorders	Serum Sickness	1	1	0.4
Investigations	Blood pressure increased	1	1	0.4
	White blood cell count increased	1	1	0.4
Psychiatric disorders	Agitation	1	1	0.4
	Anxiety	1	1	0.4
Renal and urinary disorders	Urinary retention	1	1	0.4
Respiratory, thoracic and mediastinal disorders	Bronchospasm	1	1	0.4
Skin and subcutaneous tissue disorders	Erythema	1	1	0.4
	Hyperhidrosis	1	1	0.4
	Rash	4	4	1.8
Vascular disorders	Hemodynamic instability	1	1	0.4
	Hypotension	1	1	0.4

All adverse reactions were classified according to MedDRA Version 15.0 and are ranked according to medical significance within a given SOC.

6.2 Postmarketing Experience

The following hypersensitivity/allergic reactions have been reported in patients treated with BAT:

- Anaphylactic shock
- Angioedema
- Urticaria

6.3 Immunogenicity

As with all therapeutic proteins, there is potential for immunogenicity. All subjects from the two clinical trials were tested for immunogenicity against BAT at baseline and at the end of the studies (Day 28) using a validated assay. Eleven subjects seroconverted during the course of the two trials. One subject from each clinical trial experienced a moderate allergic reaction during the administration of BAT. Both subjects were negative for anti-BAT antibodies at baseline and at the end of their respective studies. The detection of antibody formation is highly dependent on the sensitivity and specificity of the assay. Additionally, the observed incidence of antibody (including neutralizing antibody) positivity in an assay may be influenced by several factors including assay methodology, sample handling, timing of sample collection, concomitant medications, and underlying disease. For these reasons, comparison of the incidence of antibodies to BAT with the incidence of antibodies to other products may be misleading.

7 DRUG INTERACTIONS

Drug Laboratory Interactions: Blood Glucose Testing

BAT contains maltose which can interfere with certain types of blood glucose monitoring systems *[see Warnings and Precautions (5.4)]*. Only test systems that are glucose-specific should be used in patients receiving BAT. This interference can result in falsely elevated glucose readings that can lead to untreated hypoglycemia or to inappropriate insulin administration, resulting in life-threatening hypoglycemia.

The product information of the blood glucose testing system, including that of the test strips, should be carefully reviewed to determine if the system is appropriate for use with maltose-containing parenteral systems. If any uncertainty exists, contact the manufacturer of the testing system to determine if the system is appropriate for use with maltose-containing parenteral products.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

There are no human or animal data to establish the presence or absence of BAT associated risk.

8.2 Lactation

Risk Summary

There are no data to assess the presence or absence of BAT in human milk, the effects on the breastfed child, or the effects on milk production/excretion.

Consider the developmental and health benefits of breastfeeding along with the mother's clinical need for BAT and any potential adverse effects on the breastfed child from BAT or from the underlying maternal condition.

8.4 Pediatric Use

The effectiveness of BAT has not been established in pediatric patients. Limited pediatric safety data are available.

Fifteen pediatric subjects (age 10 days to 17 years; including 1 newborn, 3 infants and toddlers, 4 children and 7 adolescents) received BAT under the CDC expanded access clinical study. A 3-year old subject and an infant received two infant doses, and 13 pediatric subjects received one pediatric dose according to Salisbury Rule [Table 2].

Two adverse reactions were reported in two pediatric subjects. One subject experienced an adverse reaction of pyrexia following infusion of BAT, while the other subject experienced a serious adverse reaction of hemodynamic instability characterized by tachycardia, bradycardia, and asystole during infusion of BAT.

Dosing in pediatric patients is based on Salisbury Rule.

8.5 Geriatric Use

The safety, pharmacokinetics, and effectiveness of BAT have not been established in geriatric subjects.

Thirty six geriatric subjects received BAT under the CDC expanded access clinical study. One geriatric subject experienced rash as an adverse reaction following infusion of BAT.

11 DESCRIPTION

BAT [Botulism Antitoxin Heptavalent (A, B, C, D, E, F, G) – (Equine)] is a sterile solution of $F(ab')_2$ and $F(ab')_2$-related antibody fragments prepared from plasma obtained from horses that have been immunized with a specific serotype of botulinum toxoid and toxin. To obtain the final heptavalent product, the seven antitoxin serotypes are blended. BAT is supplied in either a 20 or 50 milliliter vial size, with a fill volume ranging from 10 to 22 milliliters per vial. BAT is administered intravenously.

The manufacturing process for each antitoxin type includes cation-exchange chromatography to purify the immune globulin fraction, digestion with pepsin to produce $F(ab')_2$ plus $F(ab')_2$-related immune globulin fragments, anion exchange chromatography to remove the pepsin as well as other impurities and filtration. In addition, the manufacturing process includes two viral inactivation/removal steps; solvent/detergent (S/D) treatment and virus filtration [Table 4].

The S/D treatment step is effective at inactivating known lipid-enveloped viruses such as equine encephalitis, equine arteritis, West Nile virus, equine infectious anemia, equine herpes virus, rabies, and equine influenza. The BAT manufacturing process also includes a robust filtration step that is effective in reducing the levels of some lipid-enveloped viruses (listed above) as well as non-enveloped viruses including equine rhinovirus, equine adenoviruses and adeno-associated viruses, and equine parvovirus.

Table 4 Viral Clearance Capacity of the BAT Process

	Enveloped					**Non-enveloped**		
Genome	RNA	RNA	RNA	DNA	RNA	DNA	DNA	RNA
Virus	XMuLV	WNV	BVDV	PRV	PI3	Ad2	Porcine Parvovirus	EMC
Family	Retro	Flavi	Flavi	Herpes	Paramyxo	Adeno	Parvo	Picorna
Size (nm)	80-110	40-70	50-70	150-200	100-200	70-90	18-24	25-30
Nanofiltration (log_{10})	≥ 2.7	≥ 2.1	≥ 4.5	n.t	n.t.	≥ 4.7	4.5	≥ 4.5
S/D (log_{10})	≥ 4.3	≥ 5.1	n.t.	≥ 5.1	≥ 5.5	n.t.	n.t.	n.t.
Total Reduction (log_{10})	≥ 7.0	≥ 7.2	≥ 4.5	≥ 5.1	≥ 5.5	≥ 4.7	4.5	≥ 4.5

XMuLV: Xenotropic Murine Leukemia Virus; specific model for equine infectious anemia, and a model for lipid-enveloped RNA viruses

	Enveloped	Non-enveloped

of similar size, such as vesicular stomatitis virus (Rhabdo family).

WNV: West Nile Virus; relevant virus, and specific model for lipid-enveloped RNA viruses, including the arboviruses, which contains both Flavividae and Togaviridae and includes equine encephalitis viruses (Toga family) and equine viral arteritis (Arteri family, formerly a Toga virus).

BVDV: Bovine Viral Diarrhea Virus; relevant virus, and specific model for lipid-enveloped RNA viruses, including the arboviruses, which contains both Flavividae and Togaviridae and includes equine encephalitis viruses (Toga family) and equine viral arteritis (Arteri family, formerly a Toga virus).

PRV: Pseudorabies Virus; specific model for equine herpes viruses and non-specific model for lipid-enveloped viruses.

PI3: Parainfluenza III Virus; model for lipid enveloped RNA viruses, and viruses of the similar family, orthomyxo, which includes equine influenza virus.

Ad2: Adenovirus; specific model for equine adenovirus.

EMC: Encephalomyocarditis Virus; specific model for equine parvovirus and adeno-associated virus, non-specific model for small lipid and non-lipid enveloped viruses.

n.t. – not tested

BAT is formulated with 10% maltose and 0.03% polysorbate 80. The formulated bulk material contains approximately 3-7 g% (30-70 milligrams/milliliter) protein.

The product potency is expressed in units based on the mouse neutralization assay (MNA). Each unit of BAT is designed to neutralize 10,000 mouse intraperitoneal lethal dose 50% units ($MIPLD_{50}$) of botulinum neurotoxin for serotype A, B, C, D, F, and G and 1,000 $MIPLD_{50}$ of serotype E.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

The mechanism of action of BAT is through passive immunization with equine polyclonal antibody fragments (primarily $F(ab')_2$ and Fab) against botulinum neurotoxin (BoNT) A, B, C, D, E, F, and G. In the circulation the polyclonal antibody fragments bind to free BoNT. This prevents the BoNT from interacting with ganglioside anchorage sites and protein receptors on the cholinergic nerve endings. In turn this prevents BoNT internalization into the target cells. The antibody/antigen complexes are then cleared from the circulation by the organs involved in processing immune complexes.

Experimental evidence concerning the amount of circulating antitoxin needed to counteract BoNT intoxication is not fully documented. The outcome of treatment depends, as it does with other comparable conditions, largely on the time interval elapsing after the onset of symptoms and antitoxin administration.

12.2 Pharmacodynamics

A proof-of-concept clinical dose-response trial was conducted using the extensor digitorum brevis (EDB) muscle of the foot as a model for measuring muscle paralysis after exposure to botulism toxin. In this model, BAT prevented subjects from experiencing a decrease in muscle function after exposure to botulinum neurotoxin (BoNT) serotypes A and B. Subjects treated with placebo (n=10) demonstrated a loss of greater than 50% EDB muscle function within 3 days of exposure to BoNT serotypes A and B. In the BAT arm of the trial (n=16),

EDB muscle function was stable over time indicating that BAT was effective in preserving muscle function for up to 28 days following exposure to both BoNT serotype A and B.

12.3 Pharmacokinetics

The pharmacokinetics (PK) of the seven botulism antitoxin serotypes was determined in healthy human subjects following IV administration of either one (n=20) or two vials (n=20) of BAT. The various PK parameters are summarized in Table 5.

The PK parameters varied based upon the antitoxin serotype measured. Antitoxin serotypes D and E had the shortest half-lives. While antitoxin serotype B and C had the longest half-lives. The $AUC_{0-\infty}$ and C_{max} values increased in a dose proportional fashion as the BAT dose increased from one to two vials. In addition, mean clearance values appeared to be similar between both treatment groups for the seven antitoxin serotypes, suggesting dose linearity of BAT over the dose range studied.

Table 5 Pharmacokinetic Parameters (Mean) for Antitoxin Serotypes A Through G in Humans Following Intravenous Administration of either One or Two Vials of BAT

Antitoxin Serotype	Treatment Group	$AUC_{0-\infty}$ (U*hr/mL)	C_{max} (U/mL)	$t_{1/2}$ (hr)	Cl (mL/hr)	V_d (mL)
A	1 Vial	26.00	2.69	8.64	293	3637
	2 Vials	56.09	6.23	10.20	285	3993
B	1 Vial	29.30	1.90	34.20	196	9607
	2 Vials	62.55	4.28	57.10	181	14865
C	1 Vial	37.34	2.26	29.60	144	6066
	2 Vials	86.25	4.89	45.60	127	8486
D	1 Vial	7.62	0.81	7.51	137	1465
	2 Vials	14.83	1.60	7.77	151	1653
E	1 Vial	7.16	0.94	7.75	1250	14172
	2 Vials	15.66	1.75	7.32	1110	11596
F	1 Vial	31.40	2.37	14.10	169	3413
	2 Vials	63.19	4.29	18.20	168	4334
G	1 Vial	7.05	0.59	11.70	149	2372
	2 Vials	14.66	1.19	14.70	144	3063

AUC = Area Under the Concentration Curve; Cl = Clearance; C_{max} = Maximum Serum Concentration; BAT = Botulism Antitoxin Heptavalent (A, B, C, D, E, F, G) – (Equine); $t_{1/2}$ = Half-life; T_{max} = Time to Maximum Serum Concentration; U = Unit; V_d = Volume of Distribution.

13 NONCLINICAL TOXICOLOGY

13.2 Animal Toxicology and Pharmacology

Toxicological studies were not conducted for BAT or its components.

The evaluation of new treatment options for botulism using controlled human trials is unethical and infeasible. Therefore the effectiveness of BAT for treatment of botulism is based on well controlled efficacy studies conducted in guinea pigs and rhesus macaques.

Guinea Pig

In a controlled therapeutic efficacy study, guinea pigs were intoxicated with various BoNT serotypes (A, B, C, D, E, F or G) at a dose of 1.5x guinea pig intramuscular lethal dose 50% units ($GPIMLD_{50}$) via intramuscular injection into the right hind limb. The animals were then treated with either placebo control or 1x scaled human dose of BAT (weight/weight based on an average human body weight of 70 kilograms), after the onset of moderate clinical signs of botulism (right hind limb weakness, salivation, lacrimation, weak limbs and noticeable changes in breathing rate or pattern). Treatment with BAT resulted in a statistically significant improvement in the survival rate of animals across all of the serotypes tested [Table 6].

Table 6 Summary of Guinea Pig Survival Data from BAT Therapeutic Efficacy Study

Neurotoxin Serotype	Treatment Group	Survival Rate (%)	Two-sided Fisher's Exact Test (p-value)
A	1x BAT	34/34 (100%)	p<0.0001
	Placebo Control	0/34 (0%)	
B	1x BAT	34/34 (100%)	p<0.0001
	Placebo Control	1/34 (3%)	
C	1x BAT	33/34 (97%)	p<0.0001
	Placebo Control	4/34 (12%)	
D	1x BAT	33/34 (97%)	p<0.0001
	Placebo Control	5/34 (15%)	
E	1x BAT	34/34 (100%)	p<0.0001
	Placebo Control	0/34 (0%)	
F	1x BAT	34/34 (100%)	p<0.0001
	Placebo Control	4/34 (12%)	
G	1x BAT	34/34 (100%)	p<0.0001
	Placebo Control	17/34 (50%)	

BAT = Botulism Antitoxin Heptavalent (A, B, C, D, E, F, G) – (Equine).

Nonhuman Primate

In a controlled therapeutic efficacy study, rhesus macaques were intoxicated with BoNT serotype A delivered intravenously at a dose of 1.7x nonhuman primate intravenous lethal

dose 50% ($NHPLD_{50}$) units per kilogram of body weight. The animals were then treated with either placebo control or 1x scaled human dose of BAT (weight/weight based on an average human body weight of 70 kilograms), after the onset of clinical signs of botulism (ptosis, muscular weakness, or respiratory distress). Treatment with BAT resulted in a statistically significant improvement in the survival rate [Table 7].

Table 7 Summary of Rhesus macaque Survival Data from BAT Therapeutic Efficacy Study

Treatment Group	Survival Rate (%)	Two-sided Fisher's Exact Test (p-value)
1x BAT	14/30 (47%)	p<0.0001
Placebo Control	0/30 (0%)	

BAT = Botulism Antitoxin Heptavalent (A, B, C, D, E, F, G) – (Equine).

14 CLINICAL STUDIES

The effectiveness of BAT is based on efficacy studies demonstrating a survival benefit in animal models of botulism *[see Nonclinical Toxicology (13.2)]*. The safety has been tested in healthy adults and patients with suspected botulism who were treated with BAT under an expanded access clinical study.

The pharmacokinetic, pharmacodynamic, and safety profiles of BAT have been evaluated in two clinical studies. In these clinical studies, BAT was shown to have an acceptable safety profile when one or two vials of BAT were administered intravenously to healthy subjects.

In a randomized, single-center, double-blind trial the pharmacokinetics and safety of BAT was evaluated in 40 healthy subjects receiving either one (n = 20) or two (n = 20) vials of BAT by IV infusion. Serum BAT levels were measured in the subjects using the Mouse Neutralization Assay (MNA) *[see Clinical Pharmacology (12.3)]*.

In a randomized single center, double-blind trial the pharmacodynamics and safety of BAT was evaluated in 26 healthy subjects receiving either a single vial of BAT (n=16) or placebo (n=10) by IV infusion. The effects of BAT in preventing paralysis of the EDB foot muscle following administration of botulinum neurotoxin serotype A or B was determined *[see Clinical Pharmacology (12.2)]*.

To provide additional support for the efficacy demonstrated in the animal models, a preliminary analysis of data from a Centers for Disease Control and Prevention (CDC) open-label, observational expanded access clinical study for the treatment of subjects with suspected or confirmed botulism with BAT was conducted. Across the 148 subjects treated with BAT in the period analyzed, 109 subjects had a final discharge diagnosis of suspected or confirmed botulism and were included in the analysis population. The median time from the onset of botulism symptoms to treatment with BAT was 3.6 days (range: 0.25 – 38 days). Early treatment (≤ 2 days after onset of symptoms) with BAT was associated with a shorter length of hospitalization, duration in intensive care unit (ICU) and duration of mechanical ventilation compared to later treatment [Table 8] and is consistent with the mechanism of action *[see Clinical Pharmacology (12.1)]*.

Table 8 Summary of Duration of Hospitalization, ICU Stay and Mechanical Ventilation for CDC Patients Treated with BAT

	Time from Symptoms to Treatment	Number of Patients (N)	Mean Duration in Days (SD)
Hospitalization	≤ 2 Days	14	12.4 (9.28)
	> 2 Days	72	26.1 (26.37)
ICU Stay	≤ 2 Days	13	9.2 (7.40)
	> 2 Days	70	15.8 (18.76)
Mechanical Ventilation	≤ 2 Days	9	11.6 (7.83)
	> 2 Days	41	23.4 (21.11)

15 REFERENCES

1. Lack JA, Stuart-Taylor ME. Calculation of drug dosage and body surface area of children. Br J Anaesth. 1997; 78:601-605.

16 HOW SUPPLIED/STORAGE AND HANDLING

16.1 How Supplied

BAT is supplied in either 20 milliliter or 50 milliliter glass vials seated with a butyl rubber stopper and an aluminum seal with a plastic flip-top cap, with a fill volume ranging from 10 to 22 milliliters per vial. Each vial, regardless of size or fill volume contains a minimum potency of > 4,500 U serotype A antitoxin, > 3,300 U serotype B antitoxin, > 3000 U serotype C antitoxin, > 600 U serotype D antitoxin, > 5,100 U serotype E antitoxin, > 3,000 U serotype F antitoxin, and > 600 U serotype G antitoxin.

BAT is not made with natural rubber latex.

NDC Number	Product Description
60492-0075-2	A 50 milliliter single dose vial.
60492-0075-3	A 20 milliliter single dose vial.

16.2 Storage and Handling

- Store frozen at or below ≤ 5°F (≤ -15°C) until used.
- Once thawed, Botulism Antitoxin Heptavalent (A, B, C, D, E, F, G) – (Equine) may be stored at 2-8°C (36-48°F) for a maximum of 36 months or until 48 months from the date of manufacture, whichever comes first. Do not refreeze.
- Once punctured, use the vial contents to prepare the infusion bag and administer as soon as possible.

- BAT vials are for single use only and contain no preservative. Discard any unused portion.

17 PATIENT COUNSELING INFORMATION

See FDA-approved patient labeling (Patient Information).

- Inform patients of the following:
    - BAT is prepared from equine plasma and may contain infectious agents such as viruses that can cause disease.
    - The risk that such products will transmit an infectious agent has been reduced by screening the horses for prior exposure to certain viruses, by testing for the presence of certain current viral infections, and by inactivating and/or removing certain viruses during manufacturing.
    - Despite these measures, such products can still potentially transmit disease.
    - There is also the possibility that unknown infectious agents may be present in such products.
- Inform patients that persons who have received previous therapy with an equine-derived antivenom/antitoxin, have known allergies to horses, have asthma or get hay fever (seasonal allergies) may be at increased risk of hypersensitivity reactions and should only receive BAT if the benefits outweigh the risks.
- Advise patients about the potential interference with non-glucose specific monitoring systems.
    - The maltose contained in BAT can interfere with some types of blood glucose monitoring systems.
    - Only testing systems that are glucose-specific should be used in patients receiving BAT.
    - This interference can result in falsely elevated glucose readings that can lead to untreated hypoglycemia or to inappropriate insulin administration, resulting in life-threatening hypoglycemia.

Manufactured By:

Cangene Corporation, a subsidiary of Emergent BioSolutions Inc.

Winnipeg, Manitoba

Canada, R3T 5Y3

U.S. License No. 1201

PATIENT INFORMATION

BAT® [Botulism Antitoxin Heptavalent (A, B, C, D, E, F, G) – (Equine)]

What is botulism?

Botulism is a muscle-paralyzing disease caused by a toxin made by a bacterium called *Clostridium botulinum*.

Botulism can cause the following conditions:

- Double vision,
- Blurred vision,
- Drooping eyelids,
- Slurred speech,
- Difficulty swallowing,
- Dry mouth,
- Muscle weakness that spreads through the body,
- Difficulty breathing.

Botulism can also cause paralysis and death. After a person is exposed to the toxin, problems can start as early as three hours or as late as a few days. It can take weeks or months to get better. During that time, many people need special care in the hospital.

The effectiveness of BAT has been studied in animals with botulism.

What is BAT?

BAT is a botulism antitoxin made from the plasma of horses. It contains antibody fragments which can neutralize botulism toxins. BAT may make the illness from botulism less severe. Treatment with BAT will not reverse the paralysis, but may decrease the duration and extent of paralysis.

Who should use BAT?

Your doctor may give you BAT if they suspect that you have been exposed to botulism toxin. You should get the treatment as quickly as possible to stop the progression of the illness.

Unless the benefits outweigh the risks, you should not receive BAT if you have a known history of allergies to horses or horse blood products, asthma or hay fever (seasonal allergies).

How will you receive BAT?

BAT is given as an injection into your vein. Your doctor will determine the dose of BAT. The treatment may take several hours to administer. Your doctor will decide if you need more than one injection.

What are the possible or reasonably likely side effects of BAT?

The most common side effects of BAT are:

- Headache
- Fever
- Rash
- Hives
- Chills
- Nausea
- Swelling

Some people have a chilly feeling, difficulty breathing, and have a quick rise in body temperature within the first 20 to 60 minutes after getting BAT. This can be managed by your doctor.

BAT can cause allergic reactions. Tell your doctor or go to the emergency department right away if you have trouble breathing, swelling of your tongue or lips, or a very fast heart rate because this can be signs of a serious allergic reaction.

Tell your doctor if you get pains in your joints and back, fever, and a rash within one to three weeks after getting BAT. These can be signs of "serum sickness" and can last for a few weeks. Your doctor can give you medicine to help with serum sickness.

Talk to your doctor about any side effects that concern you. You can ask your doctor for additional prescribing information that is available to healthcare professionals.

What other information do you need to know about BAT?

BAT is made from horse plasma. The horses are carefully screened and the plasma is carefully cleaned, but there is a small risk that it may give you a virus. Talk to your doctor if you have any symptoms that concern you.

You may report side effects directly to Cangene Corporation at 1-800-768-2304 or to the FDA's MedWatch reporting system at 1-800-FDA-1088.

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HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use CNJ-016 safely and effectively. See full prescribing information for CNJ-016.

CNJ-016, Vaccinia Immune Globulin Intravenous (Human), sterile solution

Initial U.S. Approval: 2005

WARNING: INTERACTIONS WITH GLUCOSE MONITORING SYSTEMS

See full prescribing information for complete boxed warning.

Blood glucose measurement in patients receiving Vaccinia Immune Globulin Intravenous (Human) (VIGIV) must be done with a glucose-specific method (monitor and test strips) to avoid interference by maltose contained in VIGIV. Maltose in IGIV products may give falsely high blood glucose levels in certain types of blood glucose testing systems (for example those based on the GDH-PQQ or glucose-dye-oxidoreductase methods) resulting in inappropriate administration of insulin and life-threatening hypoglycemia. Cases of true hypoglycemia may go untreated if the hypoglycemic state is masked by falsely elevated glucose readings.

----------RECENT MAJOR CHANGES----------

----------INDICATIONS AND USAGE----------

CNJ-016 is an Immune Globulin Intravenous (Human), 5% Liquid, indicated for the treatment of complications due to vaccinia vaccination (1), including:

- Eczema vaccinatum
- Progressive vaccinia
- Severe generalized vaccinia
- Vaccinia infections in individuals who have skin conditions
- Aberrant infections induced by vaccinia virus (except in cases of isolated keratitis)

CNJ-016 is not indicated for isolated vaccinia keratitis or postvaccinial encephalitis (1).

----------DOSAGE AND ADMINISTRATION----------

- For intravenous use.
- CNJ-016 is administered at a dose of 6,000 Units per kg, as soon as symptoms for complication(s) due to vaccinia vaccination appear (2.1).
- Higher doses (e.g. 9,000 Units per kg or 24,000 Units per kg) may be considered in the event that the patient does not respond to the initial dose of 6,000 Units per kg (2.1).
- For patients with risk factors for thrombosis, the maximum daily dose of VIGIV should not exceed 12,000 Units per kg (2.3).

----------DOSAGE FORMS AND STRENGTHS----------

Sterile solution available as 20 mL single-use vial containing a dose of ≥50,000 Units per vial (3).

----------CONTRAINDICATIONS----------

- Isolated vaccinia keratitis (4)
- History of anaphylactic or severe systemic reaction to human globulins (4)
- IgA deficiency with antibodies against IgA and a history of IgA hypersensitivity (4)

----------WARNINGS AND PRECAUTIONS----------

- Hypersensitivity to human immune globulin (acute anaphylaxis) (5.1)
- Thrombosis may occur with immune globulin products, including VIGIV. For patients at risk of thrombosis, administer VIGIV at the minimum dose and infusion rate practicable. Ensure adequate hydration in patients before administration. Monitor for signs and symptoms of thrombosis and assess blood viscosity in patients at risk for hyperviscosity. (5.3)
- Aseptic meningitis syndrome (AMS) (5.4)
- Hemolysis or hemolytic anemia (5.5)
- Noncardiogenic pulmonary edema [Transfusion-Related Acute Lung Injury (TRALI)] (5.6)
- Infusion rate precautions (5.7)
- Acute renal dysfunction/failure (5.8)
- Transmission of infectious agents from human plasma (5.9)
- Monitor renal function and urine output in patients at risk of renal failure; check baseline blood viscosity in patients at risk of hyperviscosity; and conduct confirmatory tests if hemolysis or TRALI is suspected (5.10)

----------ADVERSE REACTIONS----------

The most common adverse drug reactions to CNJ-016 (>10%) are headache, nausea, rigors and dizziness.

To report SUSPECTED ADVERSE REACTIONS, contact Cangene Corporation at 1-800-768-2304 or FDA at 1-800-FDA-1088 or *www.fda.gov/medwatch*.

----------DRUG INTERACTIONS----------

- Efficacy of live attenuated virus vaccines may be impaired by immune globulin administration; revaccination may be necessary (7.1)
- Antibodies in CNJ-016 may interfere with some serological tests (7.2)

----------USE IN SPECIFIC POPULATIONS----------

See 17 for PATIENT COUNSELING INFORMATION

Revised: [12/2015]

FULL PRESCRIBING INFORMATION: CONTENTS*

*Sections or subsections omitted from the full prescribing information are not listed

FULL PRESCRIBING INFORMATION

WARNING: INTERACTIONS WITH GLUCOSE MONITORING SYSTEMS

Blood glucose measurement in patients receiving VIGIV must be done with a glucose-specific method (monitor and test strips) to avoid interference by maltose contained in VIGIV. Glucose dehydrogenase pyrroloquinolinequinone (GDH-PQQ) or glucose-dye-oxidoreductase method (monitor and test strips) must not be used for blood glucose testing in patients receiving VIGIV, since maltose in IGIV products has been shown to give falsely high blood glucose levels in these testing systems. This could result in the inappropriate administration of insulin, resulting in life-threatening hypoglycemia. Cases of true hypoglycemia may go untreated if the hypoglycemic state is masked by falsely elevated glucose readings.

Carefully review the product information of the blood glucose testing system, including that of the test strips, to determine if the system is appropriate for use with maltose-containing parenteral products [see *5.2 Interference with Blood Glucose Testing*].

1 INDICATIONS AND USAGE

CNJ-016® [Vaccinia Immune Globulin Intravenous (Human)] (VIGIV) is indicated for the treatment and/or modification of the following conditions:

- Eczema vaccinatum
- Progressive vaccinia
- Severe generalized vaccinia
- Vaccinia infections in individuals who have skin conditions such as burns, impetigo, varicella-zoster, or poison ivy; or in individuals who have eczematous skin lesions because of either the activity or extensiveness of such lesions
- Aberrant infections induced by vaccinia virus that include its accidental implantation in eyes (except in cases of isolated keratitis), mouth, or other areas where vaccinia infection would constitute a special hazard.

Exercise caution when using VIGIV in the treatment of patients having complication due to vaccinia vaccination that include concomitant vaccinia keratitis, since a single study in rabbits has demonstrated increased corneal scarring upon intramuscular vaccinia immune globulin administration in vaccinia keratitis (1).

VIGIV is not considered to be effective in the treatment of postvaccinial encephalitis.

2 DOSAGE AND ADMINISTRATION

For intravenous use only.

2.1 Dosage for Treatment of Severe Complications of Vaccinia Vaccination

VIGIV should be administered at a dose of 6,000 Units per kg, as soon as symptoms appear and are judged to be due to severe vaccinia-related complication. Consideration may be given to repeat dosing, depending on the severity of the symptoms and response to treatment; however, clinical data on repeat doses are lacking. The administration of higher doses (e.g. 9,000 Units per kg) may be considered in the event that the patient does not respond to the initial 6,000 Units per kg dose. In clinical trials, doses of up to 24,000 Units per kg administered to healthy volunteers were well tolerated [see *14 CLINICAL STUDIES*].

2.2 Preparation

- Visually inspect parenteral products for particulate matter and discoloration prior to administration, whenever solution and container permit. Do not use CNJ-016 if the solution is turbid.
- DO NOT SHAKE VIAL. SHAKING VIAL MAY CAUSE FOAMING.
- Remove the entire contents of the vial to obtain the labeled dosage of CNJ-016. If partial vials are required for the dosage calculation, the entire contents of the vial should be withdrawn to ensure accurate calculation of the dosage requirement.
- CNJ-016 is compatible with 0.9% Sodium Chloride USP. No other drug interactions or compatibilities have been evaluated. If a pre-existing catheter must be used, the line should be flushed with 0.9% Sodium Chloride USP before use. Do not dilute more than 1:2 (v/v).
- CNJ-016 vial is for single use only. Do not reuse or save CNJ-016 for future use.
- CNJ-016 contains no preservatives. Discard partially used vials.

2.3 Administration

- Parenteral products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit. CNJ-016 should not be used if the solution is turbid.
- Administer CNJ-016 intravenously through a dedicated intravenous line with the rate of infusion of no greater than 2 mL/min.
- The maximum rate of infusion utilized for CNJ-016 is 4 mL/min [see *6.1 Clinical Trials Experience*].
- For patients weighing less than 50 kg, infuse the product at a rate no greater than 0.04 mL/kg/minute (133.3 Units per kg/minute).
- Slower infusion rate may be needed for patients who develop a minor adverse reaction (e.g. flushing) or for patients with risk factors for thrombosis/thromboembolism.
- For patients with pre-existing renal insufficiency, or at increased risk of acute kidney injury, thrombosis, or volume overload, do not exceed the recommended infusion rate and follow the infusion schedule closely.

- For patients with risk factors for thrombosis, the maximum daily dose of VIGIV should not exceed 12,000 Units per kg [see *5.3 Thrombotic Events*].

3 DOSAGE FORMS AND STRENGTHS

- Solution of gamma globulin (5% or 50 mg/mL)
- 20 mL single-dose vial containing antibodies to vaccinia virus at ≥50,000 Units per vial

4 CONTRAINDICATIONS

- VIGIV is contraindicated in *isolated* vaccinia keratitis.
- VIGIV is contraindicated in individuals with a history of anaphylaxis or prior severe systemic reaction associated with the parenteral administration of this or other human immune globulin preparations.
- VIGIV is contraindicated in IgA-deficient patients with antibodies against IgA and a history of IgA hypersensitivity, as it contains trace amounts of IgA (40 mcg/mL).

5 WARNINGS AND PRECAUTIONS

5.1 Hypersensitivity

Severe immediate hypersensitivity reactions to plasma-derived products may occur, for example, in patients with IgA deficiency or hypersensitivity to human globulin. Although acute systemic allergic reactions were not seen in clinical trials with VIGIV [see *6.1 Clinical Trials Experience*], administer the product only in a setting where appropriate equipment and personnel trained in the management of acute anaphylaxis are available. In case of hypotension, allergic or anaphylactic reaction, discontinue the administration of VIGIV immediately and give supportive care as needed. In case of shock, observe the current medical standards for shock treatment.

5.2 Interference with Blood Glucose Testing

Some types of blood glucose testing systems (for example those based on the glucose dehydrogenase pyrroloquinolinequinone (GDH-PQQ) or glucose-dye-oxidoreductase methods) could falsely interpret the maltose contained in VIGIV as glucose [see *BOXED WARNING*]. This could result in falsely elevated glucose readings and, consequently, in the inappropriate administration of insulin, resulting in life-threatening hypoglycemia. Also, cases of true hypoglycemia may go untreated if the hypoglycemic state is masked by falsely elevated glucose readings. Accordingly, when administering VIGIV or other parenteral maltose-containing products, measure blood glucose with a glucose-specific method.

Carefully review the product information of the blood glucose testing system, including that of the test strips, to determine if the system is appropriate for use with maltose-containing parenteral products. If any uncertainty exists, contact the manufacturer of the testing system to determine if the system is appropriate for use with maltose-containing parenteral products.

5.3 Thrombotic Events

Thrombotic events may occur in association with IGIV treatment. Patients at risk include those with a history of cardiovascular risk factors, advanced age, impaired cardiac output, hypercoagulable disorders, prolonged periods of immobilization, history of arterial or venous thrombosis, estrogen use, indwelling central vascular catheters, and/or known or suspected hyperviscosity. Weigh the potential risks and benefits of VIGIV against those of alternative therapies for all patients for whom VIGIV administration is being considered.

Because of the potentially increased risk of thrombosis, consider baseline assessment of blood viscosity in patients at risk for hyperviscosity, including those with cryoglobulins, fasting chylomicronemia/markedly high triacylglycerols (triglycerides), or monoclonal gammopathies.

In patients where the benefits of VIGIV administration out-weigh the potential risks of thrombotic and thromboembolic events, administer VIGIV at the minimum concentration available and at the minimum rate of infusion practicable. While there are currently no prospective data in patients with thrombosis/thromboembolism to identify a maximum safe dose, concentration, and/or rate of infusion for VIGIV, the maximum daily dose of VIGIV should not exceed 12,000 Units per kg in patients with thrombotic risk factors.

5.4 Aseptic Meningitis Syndrome (AMS)

AMS may occur in association with IGIV administration. AMS usually begins within several hours to two days following IGIV treatment. Discontinuation of IGIV treatment has resulted in remission of AMS within several days without sequelae.

AMS is characterized by the following symptoms and signs: severe headache, nuchal rigidity, drowsiness, fever, photophobia, painful eye movements, and nausea and vomiting. Cerebrospinal fluid (CSF) studies are frequently positive with pleocytosis up to several thousand cells per cubic millimeter, predominately from the granulocytic series, and with elevated protein levels up to several hundred mg/dL, but negative culture results. Conduct a thorough neurological examination in patients exhibiting such symptoms and signs, including CSF studies, to rule out other causes of meningitis.

AMS may occur more frequently in association with high total doses (2 g/kg) of IGIV treatment. For VIGIV, at the recommended dosage of 6,000 Units per kg, a patient may be exposed to up to 0.12 g/kg protein after VIGIV administration.

5.5 Hemolysis

VIGIV may contain blood group antibodies which may act as hemolysins and induce *in vivo* coating of red blood cells with immune globulin, causing a positive direct antiglobulin reaction and hemolysis. Acute hemolysis, consistent with intravascular hemolysis, has been reported and hemolytic anemia can develop subsequent to IGIV therapy due to enhanced red blood cell sequestration.

The following risk factors may be associated with the development of hemolysis following Immune Globulin Intravenous (Human) (IGIV) products: high doses, given either as a single administration or divided over several days, and non-O blood group (2). Other individual

patient factors, such as an underlying inflammatory state (as may be reflected by, for example, elevated C-reactive protein or erythrocyte sedimentation rate), have been hypothesized to increase the risk of hemolysis following administration of IGIV (3), but their role is uncertain. Closely monitor VIGIV recipients for clinical signs and symptoms of hemolysis, particularly patients with risk factors noted above. Consider appropriate laboratory testing in higher risk patients, including measurement of hemoglobin or hematocrit prior to infusion and within approximately 36 to 96 hours post infusion. If signs and/or symptoms of hemolysis or a significant drop in hemoglobin or hematocrit have been observed after VIGIV infusion, perform additional confirmatory laboratory testing. If transfusion is indicated for patients who develop hemolysis with clinically compromising anemia after receiving VIGIV, perform adequate cross-matching to avoid exacerbating on-going hemolysis.

5.6 Transfusion-related Acute Lung Injury (TRALI)

Noncardiogenic pulmonary edema may occur in patients administered IGIV. TRALI is characterized by severe respiratory distress, pulmonary edema, hypoxemia, normal left ventricular function, and fever and typically occurs within 1 to 6 hours after transfusion. Patients with TRALI may be managed using oxygen therapy with adequate ventilatory support.

Monitor VIGIV recipients for pulmonary adverse reactions. If TRALI is suspected, perform appropriate tests for the presence of anti-neutrophil antibodies in both the product and patient serum.

5.7 Infusion Rate Precautions

Adverse drug reactions may be related to the rate of infusion. Follow closely the recommended infusion rate given under *2.3 Administration*. Closely monitor and carefully observe patients and their vital signs for any symptoms throughout the infusion period and immediately following an infusion.

5.8 Acute Renal Dysfunction/Failure

Renal dysfunction, acute renal failure, osmotic nephropathy, proximal tubular nephropathy, and death may occur upon use of immune globulin intravenous (Human) (IGIV) products. Use VIGIV with caution in patients with pre-existing renal insufficiency and in patients at risk of developing renal insufficiency (including, but not limited to those with diabetes mellitus, age greater than 65 years, volume depletion, paraproteinemia, sepsis, and patients receiving known nephrotoxic drugs), and administer VIGIV at the minimum rate of infusion practicable. In these cases, it is important to ensure that patients are not volume depleted before VIGIV infusion. Do not exceed the recommended infusion rate, and follow the infusion schedule closely [see *2.3 Administration*]. Periodic monitoring of renal function and urine output is particularly important in patients judged to be at increased risk of developing acute renal failure. Assess renal function, including measurement of blood urea nitrogen (BUN) and serum creatinine, before the initial infusion of VIGIV and at appropriate intervals thereafter. If renal function deteriorates, consider discontinuing VIGIV.

Most cases of renal insufficiency following administration of IGIV have occurred in patients receiving total doses containing 400 mg/kg of sucrose or greater. VIGIV does not contain sucrose. No prospective data are currently available in patients with risk factors for renal insufficiency to identify a maximum safe dose, concentration, and/or rate of infusion for VIGIV.

5.9 Transmission of Infectious Agents from Human Plasma

VIGIV is prepared from human plasma and carries the possibility of blood-borne viral agents and, theoretically, the Creutzfeld Jakob disease agent. The risk of transmission of recognized blood-borne viruses has been reduced by screening plasma donors for prior exposure to certain viruses, by testing for the presence of certain current viral infections, and by implementing process steps for the inactivation and/or removal of certain potential viruses during manufacturing [see *11 DESCRIPTION*]. Despite these measures, VIGIV can still potentially transmit disease as some as yet unknown infectious agents may not be removed by the manufacturing process. Therefore VIGIV should be given only if a benefit is expected.

All infections thought to have been possibly transmitted by this product should be reported by the physician or other health care provider to Cangene Corporation at 1-800-768-2304.

5.10 Monitoring: Laboratory Tests

- Periodic monitoring of renal function and urine output is particularly important in patients judged to be at increased risk of developing acute renal failure. Assess renal function, including measurement of BUN and serum creatinine, before the initial infusion of VIGIV and at appropriate intervals thereafter.
- Because of the potentially increased risk of thrombosis, consider baseline assessment of blood viscosity in patients at risk for hyperviscosity, including those with cryoglobulins, fasting chylomicronemia/markedly high triacylglycerols (triglycerides), or monoclonal gammopathies.
- If signs and/or symptoms of hemolysis are present after an infusion of VIGIV, perform appropriate laboratory testing for confirmation.
- If TRALI is suspected, perform appropriate tests for the presence of anti-neutrophil antibodies in both the product and patient’s serum.

6 ADVERSE REACTIONS

Drug exposure to date has primarily been evaluated in healthy volunteers. The most common adverse reactions to VIGIV treatment (>10%) include headache, nausea, rigors and dizziness in clinical trials involving VIGIV. Although there were no serious adverse events reported in VIGIV clinical trials, there has been a post-marketing case of severe vaccinia infection that developed intravascular hemolysis, leukopenia and thrombocytopenia during VIGIV treatment.

6.1 Clinical Trials Experience

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.

In a safety/pharmacokinetics study, 60 healthy male and female volunteers received a single intravenous dose of either 6,000 Units per kg or 9,000 Units per kg VIGIV. The population consisted of vaccinia vaccination-naïve subjects, ages 18 to 32, with both males and females enrolled in an approximate 50:50 ratio.

In a pharmacodynamic study, 32 healthy male and female volunteers were randomized to receive vaccinia vaccination (n=10), VIGIV (9,000 Units per kg) 4 days prior to vaccinia vaccination (n=10), or VIGIV (9,000 Units per kg) concurrent with vaccinia vaccination (n=12). The population consisted of vaccinia vaccination-naïve subjects, ages 18 to 32, with both male and female enrolled in a 75:25 ratio. The ethnic background of patients included those of Caucasian, African American, Asian and Hispanic descent, with the majority of them being Caucasian.

In an additional pharmacodynamic clinical study, 50 healthy male and female volunteers were randomized to receive VIGIV at 9,000 Units per kg (n=20) or at 24,000 Units per kg (n=20) or placebo (n=10) 4 days prior to vaccinia vaccination (n=30) or placebo (n=20). The population consisted of vaccinia vaccination-naïve male and female subjects, ages 18 to 33, in a 60:40 ratio. The ethnic background of patients included those of Caucasian, African American, and Hispanic descent, with the majority of them being African American.

The most frequently reported adverse reactions related to VIGIV administration in all three clinical studies were headache, nausea, rigors, and dizziness. Table 1 describes the adverse reactions that were temporally related to VIGIV or placebo administration that occurred during or within three days of product infusion with a frequency of 5% or higher in any one treatment group.

Table 1 Adverse Drug Reactions that Occurred Temporally* During or Following VIGIV Administration (≥5%)

SYSTEM ORGAN CLASS	PREFERRED TERM	CNJ-016 (%)				PLACEBO[a] N=32 (%)
		6,000 U/kg[b] N=31	9,000 U/kg[c] N=39	9,000 U/kg[d] N=20	24,000 U/kg[d] N=20	
All Body System	All Preferred Terms	19 (61.3)	30 (76.9)	2 (10.0)	5 (25.0)	4 (12.5)
Gastrointestinal Disorders	Nausea	4 (12.9)	11 (28.2)	0 (0.0)	0 (0.0)	1 (3.1)
	Vomiting NOS	1 (3.2)	3 (7.7)	0 (0.0)	0 (0.0)	0 (0.0)
General Disorders and Administration Site Conditions	Rigors	7 (22.6)	7 (17.9)	0 (0.0)	0 (0.0)	0 (0.0)
	Feeling cold	4 (12.9)	6 (15.4)	0 (0.0)	0 (0.0)	0 (0.0)
	Pain NOS	1 (3.2)	5 (12.8)	0 (0.0)	0 (0.0)	0 (0.0)
	Feeling hot	3 (9.7)	1 (2.6)	0 (0.0)	0 (0.0)	0 (0.0)
	Asthenia	2 (6.5)	2 (5.1)	0 (0.0)	0 (0.0)	1 (3.1)
	Pyrexia	2 (6.5)	1 (2.6)	0 (0.0)	0 (0.0)	0 (0.0)

SYSTEM ORGAN CLASS	PREFERRED TERM	CNJ-016 (%)				PLACEBO[a] N=32 (%)
		6,000 U/kg[b] N=31	9,000 U/kg[c] N=39	9,000 U/kg[d] N=20	24,000 U/kg[d] N=20	
	Fatigue	0 (0.0)	2 (5.1)	0 (0.0)	0 (0.0)	1 (3.1)
	Edema peripheral	0 (0.0)	0 (0.0)	0 (0.0)	1 (5.0)	0 (0.0)
Metabolism and Nutrition Disorders	Appetite decreased NOS	2 (6.5)	2 (5.1)	0 (0.0)	0 (0.0)	0 (0.0)
Musculoskeletal and Connective Tissue Disorders	Muscle spasm	2 (6.5)	2 (5.1)	0 (0.0)	1 (5.0)	0 (0.0)
	Back pain	2 (6.5)	2 (5.1)	0 (0.0)	0 (0.0)	0 (0.0)
Nervous System Disorders	Headache	17 (54.8)	23 (59.0)	1 (5.0)	4 (20.0)	3 (9.4)
	Dizziness	5 (16.1)	7 (17.9)	1 (5.0)	0 (0.0)	1 (3.1)
	Paraesthesia	2 (6.5)	1 (2.6)	0 (0.0)	0 (0.0)	0 (0.0)
	Tremor	1 (3.2)	2 (5.1)	0 (0.0)	0 (0.0)	0 (0.0)
Skin and Subcutaneous Tissue Disorders	Sweating increased	3 (9.7)	2 (5.1)	0 (0.0)	0 (0.0)	0 (0.0)
Vascular Disorders	Pallor	1 (3.2)	3 (7.7)	0 (0.0)	0 (0.0)	0 (0.0)

*Adverse events that occurred during or within 3 days of VIGIV or placebo administration.

[a] 0.9% NaCl infused at 2 mL/min.

[b] Infusion rate: 4 mL/min; subjects were fasted.

[c] Infusion rate: 4 mL/min or 2 mL/min; subjects were fasted.

[d] Infusion rate: 2 mL/min; subjects were not fasted.

Most adverse reactions were of mild intensity (defined in study protocols as awareness of a sign or symptom but subject can tolerate). One subject in the 9,000 Units per kg dosage group experienced syncope.

There was a lower incidence of adverse reactions when VIGIV (9,000 Units per kg) was infused at 2 mL/min than 4 mL/min. There was a higher incidence of adverse reactions after administration of VIGIV in fasted subjects compared to subjects that were not fasted overnight.

There were no serious adverse reactions or adverse reactions of severe intensity in the clinical studies. There were no instances of VIGIV discontinuation due to an adverse event, or reduction in dose or infusion rate.

6.2 Post-marketing Experience

Because post-marketing adverse reactions 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 exposure to the product. This is also the case with literature reports authored independently.

There has been a case of severe vaccinia infection that developed intravascular hemolysis, leukopenia and thrombocytopenia while receiving VIGIV. However, the hemolysis did not reoccur with continued VIGIV dosing.

The following is a list of adverse reactions that have been identified and reported during the post-approval use of other IGIV products:

- *Infusion reactions*: Hypersensitivity (e.g., anaphylaxis), headache, diarrhea, tachycardia, fever, fatigue, dizziness, malaise, chills, flushing, urticaria or other skin reactions, wheezing or other chest discomfort, nausea, vomiting, rigors, back pain, myalgia, arthralgia, and changes in blood pressure
- *Renal*: Acute renal dysfunction/failure, osmotic nephropathy
- *Respiratory*: Apnea, Acute Respiratory Distress Syndrome (ARDS), TRALI, cyanosis, hypoxemia, pulmonary edema, dyspnea, bronchospasm
- *Cardiovascular*: Cardiac arrest, thromboembolism, vascular collapse, hypotension
- *Neurological*: Coma, loss of consciousness, seizures, tremor, aseptic meningitis syndrome
- *Integumentary*: Stevens-Johnson syndrome, epidermolysis, erythema multiforme, dermatitis (e.g., bullous dermatitis)
- *Hematologic*: Pancytopenia, leukopenia, hemolysis, positive direct antiglobulin (Coombs') test
- *Gastrointestinal*: Hepatic dysfunction, abdominal pain
- *General/Body as a Whole*: Pyrexia, rigors

7 DRUG INTERACTIONS

7.1 Live, Attenuated Vaccines

Immune globulin administration may impair the efficacy of live attenuated vaccines such as measles, rubella, mumps and varicella. Defer vaccination with live virus vaccines until approximately three months after administration of VIGIV. Revaccinate people who received VIGIV shortly after live virus vaccination three months after the administration of the VIGIV.

7.2 Drug/Laboratory Interactions

- VIGIV contains maltose, which can be misinterpreted as glucose by certain types of blood glucose testing systems (for example, those based on the GDH-PQQ or glucose-dye-oxidoreductase methods). Due to the potential for falsely elevated glucose readings, only testing systems that are glucose-specific should be used to test or monitor blood glucose levels in patients receiving VIGIV [see *BOXED WARNING* and *5.2 Interference with Blood Glucose Testing*].

- Antibodies present in VIGIV may interfere with some serological tests. After administration of immune globulins like VIGIV, a transitory increase of passively transferred antibodies in the patient's blood may result in positive results in serological testing (e.g. Coombs' test) [see *5.5 Hemolysis*].

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Category C. Animal reproduction studies have not been conducted with VIGIV; therefore, it is not known whether VIGIV can cause fetal harm when administered to a pregnant woman or whether it can affect reproduction capacity. However, immune globulins have been widely used during pregnancy for many years without any apparent negative reproductive effects (4). The risk/benefit of VIGIV administration should be assessed for each individual case.

8.3 Nursing Mothers

It is not known whether VIGIV is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when VIGIV is administered to a nursing mother.

8.4 Pediatric Use

Safety and effectiveness in the pediatric population (<16 yrs of age) has not been established for VIGIV.

8.5 Geriatric Use

Safety and effectiveness in the geriatric population (>65 yrs of age) has not been established for VIGIV.

8.6 Renal Insufficiency

Use VIGIV with caution in patients with pre-existing renal insufficiency and in patients at increased risk of developing renal insufficiency [see *5.8 Acute Renal Dysfunction/Failure*].

11 DESCRIPTION

VIGIV is a solvent/detergent-treated, filtered sterile solution of purified gamma globulin (IgG) fraction of human plasma containing antibodies to vaccinia virus. It is stabilized with 10% maltose and 0.03% polysorbate 80 (pH is between 5.0 and 6.5) and contains no preservative. The product is a clear to opalescent liquid.

VIGIV is manufactured from plasma collected from healthy, screened donors with high titers of anti-vaccinia antibody (meeting minimum potency specifications) that is purified by an anion-exchange column chromatography method (5, 6). The plasma donors were boosted with vaccinia vaccine prior to donating plasma used in the production of the product. Each

plasma donation used for the manufacture of VIGIV is tested for the presence of hepatitis B virus (HBV) surface antigen (HBsAg) and antibodies to human immunodeficiency viruses (HIV) 1/2 and hepatitis C virus (HCV) using FDA-licensed serological tests.

Plasma used in the manufacture of this product was tested by FDA licensed Nucleic Acid Testing (NAT) for HIV-1 and HCV and found to be negative. A NAT for HBV was also performed on all Source Plasma used and found to be negative; however, the significance of a negative result has not been established. The Source Plasma has also been tested by NAT for hepatitis A virus (HAV) and parvovirus B19 and the limit for B19 in the manufacturing pool is set not to exceed 10^4 IU of B19 DNA per mL.

The manufacturing process contains two steps implemented specifically for virus clearance. The solvent and detergent step (using tri-n-butyl phosphate and Triton X-100) is effective in the inactivation of enveloped viruses, such as HBV, HCV and HIV (7). Virus filtration, using a Planova 20N virus filter, is effective for the removal of viruses based on their size, including some non-enveloped viruses (8). In addition to the two specific steps, the anion-exchange chromatography step contributes to the removal of small non–lipid enveloped viruses.

The inactivation and reduction of known enveloped and non-enveloped model viruses were validated in laboratory studies as summarized in Table 2.

Table 2 Virus Reduction Values (Log_{10}) Obtained through Validation Studies

Enveloped	**Enveloped**				**Non-Enveloped**			
Genome	**RNA**		**DNA**		**RNA**		**DNA**	
Virus	**HIV-1**	**BVDV**	**PRV**	**Vaccinia**	**HAV**	**EMC**	**MMV**	**PPV**
Family	retro	flavi	herpes	pox	picorna		parvo	
Size (nm)	80–100	50–70	120–200	220–450 long x 140–260 wide	25–30	30	20–25	18–24
Anion Exchange Chromatography (partitioning)	Not evaluated				2.3	n.e.	3.4	n.e.
20N Filtration (size exclusion)	≥4.7	≥3.5	≥5.6[a]	n.e.	n.e.	4.8	n.e.	4.1
Solvent/Detergent (inactivation)	≥4.7	≥7.3	≥5.5	≥3.7	Not evaluated			
Total Reduction (log_{10})	**≥9.4**	**≥10.8**	**≥11.1**	**≥3.7**	**7.1**		**7.5**	

[a]The PRV was retained by the 0.1 μm pre-filter during the virus validation. Since manufacturing employs a 0.1 μm pre-filter before the 20N filter, the claim of ≥5.6 reduction is considered applicable.

Abbreviations:

HIV-1: human immunodeficiency virus-1; relevant virus for human immunodeficiency virus-1 and model for HIV-2

BVDV: bovine viral diarrhea virus; model virus for hepatitis C virus (HCV) and West Nile virus (WNV)

PRV: pseudorabies virus; model for large enveloped DNA viruses, including herpes

HAV: human hepatitis A virus; relevant virus for HAV and model for small non-enveloped viruses in general
EMC: encephalomyocarditis virus; model for HAV and for small non-enveloped viruses in general
MMV: murine minute virus; model for human parvovirus B19 and for small non-enveloped viruses in general
PPV: porcine parvovirus; model for human parvovirus B19 and for small non-enveloped viruses in general
n.e.: not evaluated

The product potency (as determined by a plaque reduction neutralization test) is expressed in arbitrary units (U) by comparison to the FDA reference standard. Each vial contains approximately 40 to 70 mg/mL total protein and ≥50,000 units of vaccinia antibody neutralizing activity. The product contains ≤40 mcg/mL of Immune globulin A (IgA).

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

VIGIV provides passive immunity for individuals with complications to vaccinia virus vaccination. The exact mechanism of action is not known.

12.2 Pharmacodynamics

Two phase 2, double-blind pharmacodynamic studies were conducted in which 82 healthy volunteers were randomized to receive vaccinia vaccination with or without VIGIV.

In the first study, the efficacy of 9,000 Units per kg of VIGIV on the immunologic and local response to Dryvax was evaluated. A total of 32 healthy subjects were randomized to receive single IV infusions of either VIGIV (9,000 Units per kg) or Placebo (0.9% Sodium Chloride Injection USP) on Day 0, and either Placebo or VIGIV (9,000 Units per kg) concurrently with vaccinia (Dryvax) vaccination on Day 4.

In a second study, 50 healthy subjects were randomized to receive a single IV infusion of either VIGIV (9,000 Units per kg), VIGIV (24,000 Units per kg), or Placebo (0.9% Sodium Chloride Injection USP) on Day 0, and either placebo or vaccinia (Dryvax) vaccination on Day 4.

The effect of VIGIV on the immunologic response to Dryvax was determined by measuring vaccinia antibody titer (vaccinia IgG) in plasma and comparing titer levels across all three treatment arms. In addition, the effect of VIGIV on the local response (tissue) to Dryvax was assessed by evaluating the size of the pox reaction, as well as the area of erythema and induration following vaccination.

VIGIV (9,000 Units per kg and 24,000 Units per kg) reduced the local and immunological response to vaccinia vaccination when it was administered 4 days prior to vaccination compared to vaccination alone. This is consistent with the hypothesis that VIGIV can neutralize vaccinia virus *in vivo* [see *14 CLINICAL STUDIES*]. In addition, infusions of VIGIV of up to 24,000 Units per kg were well tolerated [see *6.1 Clinical Trials Experience*].

12.3 Pharmacokinetics

A phase 1, double-blind study was conducted in which 60 healthy subjects were randomized to receive either 6,000 Units per kg or 9,000 Units per kg VIGIV. After intravenous administration of 6,000 Units per kg to 31 healthy subjects, a mean peak plasma concentration of 161 Units per mL was achieved within 2 hours. The half-life of VIGIV was 30 days (range of 13 to 67 days) and the volume of distribution was 6630 mL. Pharmacokinetic parameters were calculated based on antibody levels determined by an ELISA.

The levels of vaccinia immune globulin remained in circulation for a prolonged period of time, with a mean half-life ranging from approximately 26 to 30 days. Maximum plasma concentrations (C_{max}) of VIGIV reached levels ranging from approximately 160 to 232 Units per mL in 1.8 to 2.6 hours. In addition, the drug had a large volume of distribution, as demonstrated by both non-compartmental and compartmental analyses.

Non-compartmental analyses demonstrated that at the two dose levels studied, the drug exhibited dose-proportionality (AUC and C_{max} values) (Table 3). The pharmacokinetic parameters estimated by compartmental analysis were similar to those calculated by non-compartmental methods.

Table 3 Non-compartmental Pharmacokinetic Parameters (mean (±SD)) of Vaccinia Immune Globulin Intravenous (Human)

VIGIV (6,000 U/kg or 9,000 U/kg) from Measured Data Arithmetic Mean (±SD)		
Parameter	**6,000 U/kg**	**9,000 U/kg**
$AUC_{0-\infty}$ (U*h/mL)	58521 (16079)	78401 (17502)
AUC_{0-t} (U*h/mL)	49405 (13246)	71541 (13173)
C_{MAX} (U/mL)	161 (40.0)	232 (40.9)
T_{MAX} (h)	1.84 (1.12)	2.61 (2.41)
$T_{½}$ (days)	30.0 (10.0)	26.2 (5.08)

The plasma concentration of circulating VIGIV was also compared to a theoretical value obtained from a model of previously licensed Baxter Vaccinia Immune Globulin (VIG) product at day 5 after IV administration of VIGIV. Since Baxter VIG was administered IM and VIGIV is to be administered IV, the comparison was made at approximately five days to account for equilibration between the extravascular and intravascular compartments following IM injection.

The binding capacity and neutralizing antibody activity of anti-vaccinia antibody in these subjects five days after intravenous administration of VIGIV (both 6,000 Units per kg and 9,000 Units per kg dosages) were at least as high as the theoretical values that would be achieved following the intramuscular administration of the comparator VIG (see Table 4). Five days represents the approximate time of peak serum anti-vaccinia antibody concentration following intramuscular administration of other Immune Globulin (Human)

products. No historical pharmacokinetic data are available for the theoretical intramuscular comparator VIG.

Table 4 Test of Non-inferiority

Dose VIGIV (U/kg)	Plasma Levels, U/mL (Range[a])		Ratio of Means % (97.5% Lower Confidence Interval Bound)[d]
	VIGIV[b]	VIGIM[c]	
6,000	60.1 (36.1–84.6)	66.2 (42.3–94.9)	90.82 (86.94)
9,000	90.3 (63.4–133.8)	64.8 (47.6–87.2)	139.40 (135.27)

[a] Geometric mean (range)

[b] Observed levels

[c] Simulated levels

[d] Expressed as a percentage relative to the geometric mean of the simulated concentrations at Day 5 after 6,000 U/kg intramuscular administration

13 NONCLINICAL TOXICOLOGY

Immune globulins are normal constituents of the human body. Toxicology studies have not been performed with VIGIV as the product has been formulated with ingredients that are known to be non-toxic at the levels present in the final product.

13.2 Animal Toxicology and/or Pharmacology

The efficacy of VIGIV against vaccinia virus in a mouse-tail lesion model was assessed. A range of doses of VIGIV and a previously licensed VIG were compared for their ability to reduce pox formation in this model.

Using this model, it was demonstrated that VIGIV exerted an *in vivo* protective effect against vaccinia infection when compared to a negative control. In addition, when using the mouse-tail lesion model with two different strains of vaccinia virus, it was observed that the protective effect of VIGIV appeared similar to that of the previously licensed VIG and a CBER reference standard.

Since VIGIV is a product of human origin, secondary pharmacodynamics, safety pharmacology and pharmacodynamic drug interactions were not investigated in animals.

14 CLINICAL STUDIES

The pharmacokinetic, pharmacodynamic and safety profiles of VIGIV were evaluated in three clinical trials. In these clinical studies, VIGIV was shown to have an acceptable safety profile when administered as single infusions of 6,000 Units per kg, 9,000 Units per kg or 24,000 Units per kg to healthy subjects. For the phase 1 safety/pharmacokinetics study, see *12.3 Pharmacokinetics*.

14.1 Pharmacodynamic Effect of VIGIV on Immune and Local Responses to Dryvax

- In a phase 2, randomized, single center, double-blind study with three parallel treatment arms, the efficacy of 9,000 Units per kg of VIGIV on the immunologic and local

response to the smallpox vaccine Dryvax was evaluated. Thirty-two healthy female and male subjects were randomized to receive single IV infusions of either VIGIV (9,000 Units per kg) or Placebo (0.9% Sodium Chloride Injection USP) on Day 0, and either Placebo or VIGIV (9,000 Units per kg) concurrently with vaccinia (Dryvax) vaccination on Day 4.

In this study, the curves for antibody titre vs. time were similar between administration of VIGIV four days prior to vaccination with Dryvax and concurrent administration of VIGIV with Dryvax.

Based on area under the effective time curve from Day 4 to 32 ($AUEC_{4-32}$) results, the administration of VIGIV four days prior to vaccination with Dryvax slightly reduced the pox reaction and erythema area by 4 to 9% and 8 to 12%, respectively, as compared to the concurrent administration of VIGIV with the Dryvax vaccine, or with Dryvax alone.

- In an additional phase 2, randomized, single center, double-blind, study with five parallel treatment arms, the efficacy of two different doses of VIGIV (9,000 Units per kg and 24,000 Units per kg) on the immunologic and local response to Dryvax was evaluated.

  Fifty healthy subjects were randomized to receive a single IV infusion of either VIGIV (9,000 Units per kg), VIGIV (24,000 Units per kg), or Placebo (0.9% Sodium Chloride Injection USP) on Day 0, and either placebo or vaccinia (Dryvax) vaccination on Day 4.

  The administration of VIGIV four days prior to vaccinia vaccination decreased the endogenous immune response to Dryvax in a dose-dependent manner. In addition, the mean pox reaction and erythema area diameters were smaller in size when 24,000 Units per kg of VIGIV was administered prior to vaccination with Dryvax compared to those when 9,000 Units per kg of VIGIV was administered prior to vaccination with Dryvax or to those from administration of Dryvax alone. These data are consistent with the hypothesis of vaccinia virus neutralization *in vivo* by VIGIV.

15 REFERENCES

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16 HOW SUPPLIED/STORAGE AND HANDLING

16.1 How Supplied

NDC 60492-0173-1

The product is supplied as a 20 mL single dose vial containing ≥50,000 Units per vial. It is packaged in a shelf carton with 24 vials and a package insert.

VIGIV does not contain latex.

16.2 Storage and Handling

Product may be stored frozen at or below 5°F (≤-15°C) or refrigerated at 36 to 46°F (2 to 8°C); refer to label for appropriate storage conditions. Do not use after expiration date.

If product is received frozen, use within 60 days of thawing at 2 to 8°C. Intravenous infusion should begin within 4 hours after entering the vial.

Do not reuse or save VIGIV for future use. This product contains no preservative; therefore, partially used vials should be discarded.

17 PATIENT COUNSELING INFORMATION

Discuss the risks and benefits of VIGIV with the patient before prescribing or administration.

- Inform patients of the potential for hypersensitivity reactions, especially in individuals with previous reactions to human immune globulin and in individuals deficient in IgA [see 4 *CONTRAINDICATIONS* and *5.1 Hypersensitivity*]. Advise patients to be aware of the following symptoms associated with allergic reactions: hives, rash, chest tightness, wheezing, shortness of breath, or feeling light headed or dizzy when they stand. Patients should be cautioned to seek medical attention immediately should they experience any one or more of the above mentioned symptoms, as well as other side effects including injection site pain, chills, fever, headache, nausea, vomiting, and joint pain.
- Advise patients that the maltose contained in VIGIV can interfere with some types of blood glucose monitoring systems. They must use only testing systems that are glucose-specific for monitoring blood glucose levels as the interference of maltose could result in falsely elevated glucose readings. This could lead to untreated hypoglycemia or

to inappropriate insulin administration, resulting in life-threatening hypoglycemia [see *5.2 Interference with Blood Glucose Testing*].

- Advise patients that VIGIV may impair the effectiveness of certain live virus vaccines such as measles, rubella (i.e. German measles), mumps, and varicella (i.e. chickenpox). Should the patient have been recently vaccinated, they should notify their treating physician [see *7.1 Live, Attenuated Vaccines*].
- Inform patients that VIGIV is prepared from human plasma. Products made from human plasma may contain infectious agents such as viruses that can cause disease. The risk that such products will transmit an infectious agent has been reduced by screening plasma donors for prior exposure to certain viruses, by testing for the presence of certain current virus infections, and by inactivating and/or removing certain viruses during manufacturing. Despite these measures, such products can still potentially transmit disease. There is also the possibility that unknown infectious agents may be present in such products [see *5.9 Transmission of Infectious Agents from Human Plasma*].

Manufactured by:

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