PRODUCT MONOGRAPH

INCLUDING PATIENT MEDICATION INFORMATION

BAT™

Botulism Antitoxin Heptavalent (A, B, C, D, E, F, G) – (Equine)
Sterile Solution for Injection

J06AA04 Immune Sera and Immunoglobulin

"HEALTH CANADA HAS AUTHORIZED THE SALE OF THIS EXTRAORDINARY USE NEW DRUG FOR DOCUMENTED OR SUSPECTED EXPOSURE TO BOTULINUM NEUROTOXIN SEROTYPES A, B, C, D, E, F, or G BASED ON LIMITED CLINICAL TESTING IN HUMANS"

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BAT™

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PART I: HEALTH PROFESSIONAL INFORMATION

"HEALTH CANADA HAS AUTHORIZED THE SALE OF THIS EXTRAORDINARY USE NEW DRUG FOR DOCUMENTED OR SUSPECTED EXPOSURE TO BOTULINUM NEUROTOXIN SEROTYPES A, B, C, D, E, F, or G BASED ON LIMITED CLINICAL TESTING IN HUMANS"

SUMMARY PRODUCT INFORMATION

Route of Administration	Dosage Form / Strength	Clinically Relevant Nonmedicinal Ingredients
Intravenous	Sterile Solution for Injection. Each single-use vial contains a minimum 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.	10% maltose 0.03% polysorbate 80

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 a 50 milliliter (mL) vial size. 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 $F(ab')_2$ and $F(ab')_2$-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 5).

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 virus filtration step which removes viruses based on size. The virus filtration step is therefore effective for all the above lipid-enveloped viruses as well as smaller non-enveloped viruses including equine rhinovirus, equine adenoviruses and adeno-associated viruses, and equine parvovirus.

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 (MIPLD50) of botulinum neurotoxin for serotype A, B, C, D, F, and G and 1,000 $MIPLD_{50}$ of serotype E.

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

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INDICATIONS AND CLINICAL USE

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 on efficacy studies demonstrating survival benefit in animal models of botulism.

Geriatrics: No data is available.

Pediatrics: The effectiveness of BAT has not been established in pediatric patients. Limited pediatric safety data is available (for more information see **WARNINGS AND PRECAUTIONS, Special Populations, Pediatrics).**

CONTRAINDICATIONS

There is no contraindication to the use of BAT if indicated following exposure to botulinum neurotoxin.
See **WARNINGS AND PRECAUTIONS**, patients 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, and patients should be closely monitored with resuscitative measures available, during and following administration.

WARNINGS AND PRECAUTIONS

Serious Warnings and Precautions

- Prepare for monitoring and management of hypersensitivity reactions, infusion reactions or delayed allergic reactions (serum sickness)
- BAT is prepared using pools of equine plasma, therefore may carry the risk of transmitting infectious agents (see Transmission of Infectious Agents section)

Hypersensitivity

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. Medications such as epinephrine should be available for immediate 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.

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.

Infusion Rate Precautions

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.

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.

Transmission of 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 (for more information, see **DESCRIPTION**).

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 health professional to have been transmitted by BAT to Cangene Corporation (a subsidiary of Emergent BioSolutions Inc.) at 1-800-768-2304 (phone) or 1-800-768-2281 (fax).

Special Populations

Pregnant Women: There is no human or animal data to establish the presence or absence of BAT associate risk during pregnancy.

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

Pediatrics (<17 years of age): The effectiveness of BAT has not been established in pediatric patients. Limited pediatric safety data are available (see **ADVERSE REACTIONS**).

Geriatrics (> 65 years of age): The safety, pharmacokinetics, and effectiveness of BAT have not been established in geriatric subjects (see **ADVERSE REACTIONS**).

Monitoring and Laboratory Tests

Monitor vital signs for signs and symptoms of acute allergic reactions 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.

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ADVERSE REACTIONS

Adverse Drug Reaction Overview

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**)
- Delayed allergic reactions/serum sickness (see **WARNINGS AND PRECAUTIONS**)
- Infusion reactions (see **WARNINGS AND PRECAUTIONS**)

Clinical Trial Adverse Drug Reactions

Because clinical trials are conducted under very specific conditions the adverse reaction rates observed in the clinical trials may not reflect the rates observed in practice and should not be compared to the rates in the clinical trials of another drug. Adverse drug reaction information from clinical trials is useful for identifying drug-related adverse events and for approximating rates.
The safety of BAT has been tested in healthy adults and patients with suspected botulism who were treated with BAT under an expanded access clinical study.

In two 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, 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 (age 10 days to 17 years; including 1 newborn, 3 infants and toddlers, 4 children and 7 adolescents) 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 were 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.

The observed mortality rate was 11/228 (4.8%). None of these deaths were considered related to treatment with BAT.

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 serious adverse reaction of hemodynamic instability characterized by tachycardia, bradycardia and asystole during infusion of BAT.

Thirty six geriatric subjects (>65 years of age) received BAT under the CDC expanded access clinical study. One geriatric subject experienced rash as an adverse reaction following infusion of BAT.

Table 1 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
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

System Organ Class	Preferred Term	Overall (N=228)		
		No. of Events	No. of Subjects	% of Subjects
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.

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.

Post-Market Adverse Drug Reactions

Hypersensitivity/allergic reactions have been reported in patients treated with BAT, including anaphylactic shock.

DRUG INTERACTIONS

Drug-Drug Interactions

Interactions with other drugs have not been established.

Drug-Food Interactions

Interactions with foods have not been established.

Drug-Herb Interactions

Interactions with herbs have not been established.

Drug-Laboratory Interactions

BAT contains maltose which can interfere with certain types of blood glucose monitoring systems. 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.

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DOSAGE AND ADMINISTRATION

Dosing Considerations

BAT is for intravenous use only.

Recommended Dose and Dosage Adjustment

BAT is a sterile solution of purified $F(ab')_2$ and $F(ab')_2$-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 of BAT contains a minimum potency for serotypes A, B, C, D, E, F, and G antitoxin (see **Summary Product Information**).

For adult, pediatric and infant patient groups, administer a dose of BAT intravenously according to Table 2. For details on pediatric dosing by body weight see Table 3.
Administer all BAT doses after dilution 1:10 in normal saline by slow intravenous infusion according to the varying infusion rates in Table 2.

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.

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

Table 2 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 3.

Table 3 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.

Administration

1. Bring vial to room temperature prior to use.
    - 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 37 °C (98.6 °F) 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.
    - Do not shake the vial during preparation to avoid foaming.
3. 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 (see Table 3).
4. Visually inspect the product for particulate matter and discoloration prior to administration. Do not use if the solution is turbid, or contains particulates other than translucent-to-white proteinaceous particulates.
5. Use an intravenous line with constant infusion pump. Use a sterile, non-pyrogenic, low protein binding in line filter.
6. 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.

7. Discard any unused portion.

OVERDOSAGE

For management of a suspected drug overdose, contact your regional Poison Control Centre.

ACTION AND CLINICAL PHARMACOLOGY

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.

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. The primary endpoint for the study was to evaluate the percent muscle function of the EDB muscle in both feet following exposure to Botulinum toxins Type A (BOTOX®) in the left foot and Type B (MYOBLOC®) in the right foot 24 hours after intravenous administration of Botulism Antitoxin Heptavalent (Equine) Types A-G or placebo. The percent muscle function is based on the preservation of the compound muscle action potential (CMAP) wave amplitude and area of the EDB muscle measured using a reference electrode. 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.

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 4.

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 4 Pharmacokinetic Parameters (Mean) for Antitoxin Serotypes A Through G in Humans Following Intravenous Administration of either One of 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.

STORAGE AND STABILITY

Store frozen at or below -15°C until used.

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.

SPECIAL HANDLING INSTRUCTIONS

The product should be brought to room or body temperature immediately prior to use. The product should be clear or slightly opalescent. Do not use product that appears cloudy or contains particulates.

DOSAGE FORMS, COMPOSITION AND PACKAGING

Dosage Form and Packaging: BAT is supplied in 50 mL glass vials sealed 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.

Composition: BAT is a sterile solution for intravenous injection. It is made of purified antibody fragments produced from equine immune globulins (IgGs) modified by pepsin digestion. Non-medicinal ingredients include 10% maltose and 0.03% polysorbate 80. The formulated bulk material contains approximately 3 to 7 g% (30 to 70 mg/mL) protein.

PART II: SCIENTIFIC INFORMATION

PHARMACEUTICAL INFORMATION

Drug Substance

Proper name:	Botulism Antitoxin Serotype A, B, C, D, E, F or G (Equine)
Chemical name:	Botulism Antitoxin Serotype A, B, C, D, E, F or G (Equine)
Molecular formula & molecular mass:	$F(ab')_2$ of approximately 100 kDa and Fab approximately 50 kDa.
Structural formula:	Gamma immune globulin (IgG) polyclonal antibody fragments $F(ab')_2$ and Fab
Physicochemical properties:	Each BAT Drug Substance antitoxin serotype is a clear to opalescent, colorless to pale yellow liquid in an aqueous buffer (pH 5.0-6.5) containing equine derived antibody fragments that are targeted against one of the seven serotypes. The fragments are derived from digesting intact equine IgG monomers with the enzyme pepsin, resulting in $F(ab')_2$, Fab and $F(ab')_2$ related fragments

Product Characteristics

BAT™ [Botulism Antitoxin Heptavalent (A, B, C, D, E, F, G) – (Equine)] is a sterile, clear to opalescent, colorless to pale yellow liquid containing enzymatically modified and purified equine derived gamma immune globulin (gG) antibodies to the seven known botulinum toxin types (A-G).

Viral Clearance

The two manufacturing steps were implemented specifically to reduce the risk of transmission of viral disease. The solvent/detergent 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 virus filtration step which removes viruses based on size. The virus filtration step is therefore effective for all the above lipid-enveloped viruses as well as smaller non-enveloped viruses including equine rhinovirus, equine adenoviruses and adeno-associated viruses, and equine parvovirus (see Table 5).

Table 5 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	PPV	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
Virus filtration (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 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.

PPV: Porcine parvovirus

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

S/D: Solvent and detergent

n.t. – not tested

CLINICAL TRIALS

The effectiveness of BAT is based on efficacy studies demonstrating a survival benefit in animal models of botulism (see **DETAILED PHARMACOLOGY**). The safety has been tested in two clinical trials in normal healthy human subjects BT-001 and BT-002 Stage B. These studies also examined the pharmacokinetics (PK) and pharmacodynamics (PD) of the BAT product. A limited amount of safety information was also gathered from patients with suspected botulism who were treated with BAT under the CDC expanded access clinical study.

Study demographics and trial design

Table 6 Summary of subject demographics for BAT clinical trials

Study #	Trial design	Dosage, route of administration and duration	Study subjects (n = number)	Age Range	Gender
BT-001	Phase 1, single center, randomized, double blind parallel armed safety and PK study in normal healthy subjects.	Single IV dose (1 vial) or double IV doses (2 vials) of BAT (Single administration)	N=40 20 = (1 vial) 20 = (2 vials)	(19-52 years)	M = 20 F = 20
BT-002 Stage B	Phase 1a/2b, single center, randomized double blind, , parallel arm safety and PD study following IV administration of either BAT or placebo to normal healthy subjects administered BoNT serotypes A or B in the EDB muscle.	Single IV dose (one vial) of BAT or Placebo	N=26 10 = Placebo 16 = BAT (1 vial)	(19-48 years)	M = 13 F = 13
CDC expanded access program	Open label, observational expanded access clinical study for the treatment of subjects with suspected or confirmed botulism.	Single IV dose = (1 vial=143 patients Double IV doses = (2 vials= 5 patients)	N=148	46 years (10 days-88years)	M = 105 F = 43
BAT = Botulism Antitoxin Heptavalent; BoNT = Botulinum Neurotoxin; BAT AB = Antitoxin Bivalent (Equine) Types A and B (Aventis Pasteur); EDB = Extensor Digitorum Brevis; IV = Intravenous; PD = Pharmacodynamics; PK = Pharmacokinetics; CDC = Centers for Disease Control and Prevention					

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). A brief summary of the results can be found in Part I: **ACTION AND CLINICAL PHARMACOLOGY, Pharmacokinetics.**

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. A brief summary of the results can be found in Part I: **ACTION AND CLINICAL PHARMACOLOGY, Pharmacodynamics**.

To provide additional support for the efficacy demonstrated in the animal models, a preliminary analysis of data from the CDC open-label, observational expanded access clinical study for the treatment of subjects with suspected or confirmed botulism with BAT was conducted. The purpose of the CDC expanded access program was to enable the use of the investigational BAT product for treatment of individuals with botulism in the United States, as a result of naturally-occurring outbreaks or in cases of isolated, unintentional incidents. 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). The rationale behind this analysis was that early treatment with BAT would prevent symptom progression and reduce disease duration; however, later treatment would be less effective since BAT does not have an effect on BoNT once it has acted upon the cholinergic nerve endings.

Study results

Table 7 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)

In order to determine if BAT was efficacious in treating patients with botulism, duration of hospitalization was selected as the primary end point. A *post-hoc* statistical analysis of the CDC patient information to determine if treating patients early after symptom onset (≤ 2 days) versus later (> 2 days) had an effect on the duration of hospitalization. Overall the mean duration of hospitalization for patients with botulism was 23.2 days. If patients were treated with BAT within 2 days of symptom onset, the duration of hospitalization was 12.4 ± 9.28 days but if the patients were treated more than 2 days after symptom onset, the duration of hospitalization was 26.1 ± 26.37 days (Table 7). This suggests that 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 7) and is consistent with the mechanism of action (see **Part I: ACTION AND CLINICAL PHARMACOLOGY).**

DETAILED PHARMACOLOGY

Animal Studies

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 two animal models: guinea pigs (Study #1) and Rhesus macaques (Study #2).

Study demographics and trial design

Table 8 Summary of demographics for BAT therapeutic efficacy studies in animal models

Study #	Trial design	Species	Dosage, route of administration and duration	Number	Serotype	Animal Weight Range	BAT Antitoxin Dose
Study #1	Pivotal, randomized, blinded, placebo controlled GLP study	Guinea Pig (Hartley)	Single IV dose of BAT or placebo following toxin challenge (1.5xGPIMLD$_{50}$) and observation of fourth consecutive moderate/severe clinical sign	N=476 34 = Placebo (17 per sex per serotype) 34 = BAT (17 per sex per serotype)	A to G	400-500 g	1x scaled human dose
Study #2	Pivotal, randomized, blinded, placebo controlled GLP study	Rhesus Macaque	Single IV dose of BAT or placebo following toxin challenge (1.7xNHPLD$_{50}$) and observation of onset of moderate/severe clinical sign	N=60 30 = Placebo (15/sex) 30 = BAT (14 males and 16 females)	A	3.28 – 7.0 kg	1x scaled human dose
BAT = Botulism Antitoxin Heptavalent; IV = Intravenous; GPIMLD$_{50}$ = Guinea Pig Intramuscular Lethal Dose 50%; NHPLD$_{50}$ = Non-human Primate Lethal Dose 50%							

In the first pivotal study (Study #1), guinea pigs were intoxicated with one of the seven botulinum neurotoxin (BoNT) serotypes (A-G) at a dose equivalent to 1.5x guinea pig intramuscular lethal dose 50% (GPIMLD$_{50}$), which would be expected to cause death in the majority of untreated animals. The toxin was administered via intramuscular injection into the right hind limb. At the onset of four consecutive moderate or severe clinical signs (right hind

limb weakness, salivation, lacrimation, weak limbs and noticeable changes in breathing rate or pattern), groups of thirty four animals per serotype were treated with either placebo control or 1x scaled human dose of BAT (weight/weight based on an average human body weight of 70 kilograms), intravenously and observed for twenty one days. The objective of the study was to determine any statistically significant enhancement in survival of BAT treated animals, when compared to placebo controls.

In the second pivotal study (Study #2), Rhesus macaque were intoxicated intravenously with BoNT serotype A dose equivalent to 1.7x non-human primate lethal dose 50% ($NHPLD_{50/kg}$) and administered either 1x scaled human dose of BAT (n=30) or placebo control (n=30) intravenously at the onset of clinical signs (ptosis, muscular weakness, or respiratory distress). Following treatment all animals were provided supportive care (nutritional) and observed for twenty one days. The objective of this study was to confirm the therapeutic effect of a single intravenous dose of BAT when administered at the onset of clinical signs and in combination with minimal (nutritional) supportive care, in preventing mortality in BAT treated animals when compared to placebo controls.

Study Results

Guinea pig model, primary efficacy (survival)

Table 9 Summary of guinea pig survival data

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).

Treatment with a single dose of (1x scaled human dose) BAT administered to symptomatic animals resulted in a statistically significant enhancement in survival over placebo control animals, irrespective of the intoxicating serotype.

Nonhuman primate (Rhesus macaque), Primary Efficacy (Survival)

Table 10 Survival results of Study #2 and statistical significance

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

LBERI = Lovelace Biomedical and Environmental Research Institute; BAT = Botulism Antitoxin Heptavalent (A, B, C, D, E, F, G) – (Equine).

Treatment with BAT resulted in a statistically significant improvement in survival when compared to placebo controls (Table 10). None of the Rhesus macaques challenged with botulinum neurotoxin serotype A complex and treated with placebo survived to the end of the study, whereas, 14 of 30 (46.7%) nonhuman primates treated with BAT survived to the end of the study. This difference in survival rates between the two groups was statistically significant ($p<0.0001$) using the Fisher's exact test (Table 10).

TOXICOLOGY

There were no toxicity studies performed for BAT.

The pharmacokinetic/pharmacodynamic studies performed in guinea pigs and rhesus macaques in support of efficacy did not reveal toxicity concerns, when tested up to 5x scaled human dose.

REFERENCES

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

READ THIS FOR SAFE AND EFFECTIVE USE OF YOUR MEDICINE

PART III: PATIENT MEDICATION INFORMATION

BAT™

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

Read this carefully before you start taking **BAT**. This leaflet is a summary and will not tell you everything about this drug. Talk to your healthcare professional about your medical condition and treatment and ask if there is any new information about **BAT**.

"HEALTH CANADA HAS AUTHORIZED THE SALE OF THIS EXTRAORDINARY USE NEW DRUG FOR DOCUMENTED OR SUSPECTED EXPOSURE TO BOTULINUM NEUROTOXIN SEROTYPES A, B, C, D, E, F AND G BASED ON LIMITED CLINICAL TESTING IN HUMANS"

What is BAT used for?

- BAT is a botulism antitoxin made from the plasma of horses which may make the illness from botulism less severe.
- Botulism is a muscle-paralyzing disease caused by the toxin made by a bacterium called *Clostridium botulinum* which can cause the following conditions: doubled vision, blurred vision, drooping eyelids, slurred speech, difficulty swallowing, dry mouth, muscle weakness that spreads through the body and difficulty breathing. BAT can also cause paralysis and death.
- Treatment with BAT will not reverse the paralysis, but may decrease the duration and extent of paralysis.

How does BAT work?

BAT contains antibody fragments which can neutralize botulism toxins. 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 are the ingredients in BAT?

Medicinal ingredients:

Each vial of BAT contains antitoxins to serotypes A to G.

Non-medicinal ingredients:

Maltose

Polysorbate 80

BAT comes in the following dosage forms:
BAT is a sterile solution for intravenous injection provided in a single use 50 mL glass vial. Each vial 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.

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

- You have experienced allergic reactions to horses, horse blood products, asthma or hay fever in the past.
- Are pregnant or nursing.

Other warnings you should know about:
BAT is made from horse plasma and therefore may contain infectious agents such as viruses that can cause disease. This risk has been reduced by screening the horses for certain viruses and by inactivating or removing viruses during the manufacturing process.

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

The following may interact with BAT:
- Drugs that may interact with BAT have not been established.
- BAT contains maltose that can interfere with certain types of blood glucose monitoring systems (tests that check the level of sugar in your body).

How to take BAT:
BAT will be administered by a healthcare professional by an injection into your vein.

Usual dose:
Your doctor will determine the dose of BAT. The treatment may take several hours to administer.

Overdose:

If you think you have taken too much BAT, contact your healthcare professional, hospital emergency department or regional Poison Control Centre immediately, even if there are no symptoms.

What are possible side effects from using BAT?

The most common side effects of BAT are headaches, fever, rash, hives, chills, nausea and 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.

Tell your healthcare professional 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 healthcare professional 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.

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

Serious side effects and what to do about them			
Symptom / effect	Talk to your healthcare professional		Stop taking drug and get immediate medical help
	Only if severe	In all cases	
UNCOMMON Hemodynamic Instability		√	√
Serum Sickness		√	√
Anaphylaxis		√	√
Allergic Reaction (trouble breathing, swollen tongue or lips, fast heart rate)		√	√

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

Reporting Side Effects
You can help improve the safe use of health products for Canadians by reporting serious and unexpected side effects to Health Canada. Your report may help to identify new side effects and change the product safety information.
3 ways to report:

- Online at MedEffect;
- By calling 1-866-234-2345 (toll-free);
- By completing a Patient Side Effect Reporting Form and sending it by:
  - Fax to 1-866-678-6789 (toll-free), or
  - Mail to: Canada Vigilance Program
    Health Canada, Postal Locator 0701E
    Ottawa, ON
    K1A 0K9

    Postage paid labels and the Patient Side Effect Reporting Form are available at MedEffect.

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

Storage:
Store frozen at or below -15°C until used. Do not refreeze.
Keep out of reach and sight of children.

If you want more information about BAT:

- Talk to your healthcare professional
- Find the full product monograph that is prepared for healthcare professionals and includes this Patient Medication Information by visiting the Health Canada website; or by calling 1-800-768-2304

This leaflet was prepared by Cangene Corporation (a subsidiary of Emergent BioSolutions Inc.).

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