# INSTRUCTIONS FOR RECEIVING BAT™ ANTITOXIN

**Alaska Division of Public Health, Section of Epidemiology (SOE) Vaccine Depot**

**9210 Vanguard Dr, Suite 102, Anchorage, AK 99507**

**Important Notice: Please store enclosed BAT™ in a monitored FREEZER (≤ -20°C +/- 5°C ).**

**Do not re-freeze BAT™ once it has thawed!**

- ☐ Upon receiving immediately check the TempTale Temperature Monitor display. If the TempTale display indicates that a shipping temperature deviation occurred, contact SOE immediately at the number below.
- ☐ Visually inspect vial(s). The contents should be completely frozen.
- ☐ If vial is completely frozen and the TempTale display confirmed no temperature deviation during shipment, place the kit in an alarmed monitored **FREEZER (-20 °C +/- 5 °C).** If vial is partially or completely thawed, place the kit in an alarmed monitored **refrigerator (2-8 °C)** and contact SOE ASAP.
- ☐ Return the TempTale Monitor and shipping container to the SOE Vaccine Depot ASAP using a priority, tracked shipping method.
- ☐ **For problems or other questions call 907-341-2209 or 907-341-2207.**

## CONFIRMATION OF RECEIPT OF BAT™:

Date/Time BAT™ Received: _____Time:_____

Kit Number Received: _____Lot No:_____Exp Date:_____

Kit Number Received: _____Lot No:_____Exp Date:_____

Received Frozen ☐Yes ☐No (if No, call the above number)

BAT™ Received and Visually Inspected by:_____

Facility Name: _____Phone: _____

**Fax this completed confirmation sheet to 907-341-2249**

Revised 4/12/2013

# BAT™ (Botulinum Antitoxin) Kit CHECKLIST

| UPON RECEIPT OF KIT/PRIOR TO USE | DATE COMPLETED |
|---|---|
| 1. Fill out the bottom portion of the coversheet, titled "Instructions for Receiving BAT™ Antitoxin," **[page AK:1]**. Fax this back to the Section of Epidemiology Depot at 341-2249. | |
| 2. Store the BAT™ in the freezer; monitor freezer temperatures. **Store frozen at or below ≤ 5°F (≤ -15°C) until used.** | |
| | |
| **IMMEDIATELY UPON USE** | **DATE COMPLETED** |
| 1. **If botulism is suspected, call Epidemiology immediately: 907-269-8000 business hours OR 800-478-0084 after-hours**. | |
| 2. Provide patients or their guardians with the Patient Information Guide **[AK: 26-27].** | |
| 3. Prepare for BAT™ administration; using the guidance in the package insert [**AK:10-25].** If product is frozen, bring vial to room temperature using guidance on **pages AK:12-13.** | |
| 4. Administer BAT™. | |
| 5. Report any adverse reactions to the FDA as described in the Treatment Instructions **[AK:5].** | |
| | |
| **WITHIN 48 HOURS OF USE** | **DATE COMPLETED** |
| 1. Notify the Section of Epidemiology Vaccine Depot of the Kit # used and order replacement stock. Phone: 907-341-2207 or 341-2209. | |
| 2. Complete the "Botulism Case Report Form" **[pages AK:6-8]**. | |
| 3. Fax completed "Botulism Case Report Form" back to the Section of Epidemiology at 563-7868. | |
| | |
| **UPON PATIENT DISCHARGE OR DEATH** | **DATE COMPLETED** |
| 1. Complete "Clinical Outcome Report" **[AK:9]**. | |
| 2. Fax "Clinical Outcome Report" back to the Section of Epidemiology at 563-7868. | |

## Report all suspected cases of botulism immediately to:
## Section of Epidemiology
## 907-269-8000 during business hours OR 1-800-478-0084 after hours
## Epidemiology main fax: 563-7868
## Depot fax: 341-2249

***NOTE: The Botulism Case Report and Clinical Outcome Report Forms are available online at***
http://www.epi.alaska.gov/id/botulism/resources.htm

# BAT™ (Botulinum Antitoxin) Kit Packing List

I. New Treatment Instructions for BAT™ (Botulinum Antitoxin) **[pages AK:4-5]**

II. Botulism Case Report Form **[pages AK:6-8]**
***Return completed form to the Section of Epidemiology***

III. Clinical Outcome Report Form to be completed by clinician administering BAT™ and to be accompanied by a copy of the discharge summary **[page AK:9]**
***Return completed form to the Section of Epidemiology***

IV. Package Insert **[pages AK:10-25]**.

V. Patient Information Guide **[pages AK:26-27]**.

VI. One vial of BAT™ (Botulinum Antitoxin) product

**Report all suspected cases of botulism immediately to:**
**Section of Epidemiology**
**907-269-8000 during business hours**
**1-800-478-0084 after hours**

*****Please return completed forms to Section of Epidemiology*****
by fax 907-563-7868;
or mail to
Infectious Diseases Program / Section of Epidemiology
3601 C Street, Suite 540, Anchorage, AK 99503

# Treatment Instructions for use of BAT™ (Botulinum Antitoxin)

**Botulism is both a medical and public health emergency. As soon as patients are stable, any suspected case of botulism should be immediately reported to the Alaska Section of Epidemiology: call 907-269-8000 during business hours or 1-800-478-0084 after hours.**

In March 2013, FDA licensed the use of BAT™ for use in managing cases of suspected botulism. Prior to this, the product (H-BAT) was under an investigational new drug (IND) protocol for treatment of suspected cases. BAT™ contains antitoxins to treat botulism types A-G, including E, which is the most common type in Alaska. One vial of BAT™ is supplied in this botulism treatment kit. This document contains specific instructions for using BAT™.

**Overview of treatment plan**

1. Obtain clinical specimens (blood, stool, vomitus) for botulinum toxin testing.
2. Save suspected food.
3. Administer BAT™ per package insert instructions **page AK:12**. **Closely monitor patient for any symptoms of anaphylactic symptoms; have resuscitative measures available.**

**Detailed, step-by-step instructions**

1. PRIOR to administration of BAT™, draw 15-20 cc of whole blood; enough to result in 10cc of serum. Ask your laboratory to separate off the serum and hold the serum in the refrigerator pending instructions from the Section of Epidemiology (SOE).

2. Whenever possible, obtain stool, vomitus, and gastric contents for botulism testing. Send these clinical specimens to your laboratory and ask them to be held pending instructions from SOE.

3. Save any suspect food items brought to the hospital by the patient/family member(s). Food should be refrigerated, sent to your laboratory, and held pending instructions from SOE.

4. If BAT™ is received frozen, it can be thawed expeditiously at 37°C (99°F) in a warm water bath (instead of in a refrigerator at 2°C−8°C [36°F−46°F]). See package insert **[pages AK:11-13]** for specific details on storage, handling and dilution into 0.9% Sodium Chloride Injection (USP) for infusion.

5. Sensitivity testing is no longer required; however, skin sensitivity testing should be considered for those patients at risk of acute hypersensitivity reaction. See **page AK:14**] of the package insert.

6. Administer the BAT™ according to the package insert; procedures are summarized on the following page in Tables 1 and 2 [**page AK:12]**. One 20 ml vial of BAT™ is considered an adult dose. **Children ≥17 years of age** should receive an adult dose. For **children <17 years,** consult **page AK:12** of the package insert for weight-based scaling of dose. In general for very young children (0-3 years old), it is advisable to consult a CDC botulism officer at 770-488-7100 (24/7 hotline); or for **infants (less than 1 year old)** consult the California Infant Botulism Program (510-231-7600).

**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**

| 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 dose is 20% of adult dose.

7. **Report all adverse reactions and medication errors to Cangene (doing business as Emergent BioSolutions) the manufacturer of BAT™**. Please report adverse events to Cangene Corporation (Phone: 1-800-768-2304; Fax: 1-800-768-2281; pharmacovigilance@ebsi.com). Please do not contact CDC to report adverse events associated with BAT.

   In order to further assess safety, clinical benefit, and pediatric dosing of BAT, Cangene must comply with FDA's post-marketing requirements.[1] Please be informed that CDC will share with Cangene contact information of treating physicians and certain information about treated patients to help facilitate Cangene meet the FDA requirements. For more information on Cangene's postmarketing patient registry (BT-010), visit http://www.clinicaltrials.gov/show/NCT02055183. Cangene will be contacting you about your voluntary participation in Cangene's patient registry.

8. Fax completed forms within 7 days of completion of BAT™ therapy (or hospital discharge) to the Alaska Section of Epidemiology at **907-563-7868 ATTN: Infectious Diseases Program**
   Botulism Case Report Form **pages AK:6-8**
   Clinical Outcome Report Form **page AK:9**

[1] www.fda.gov/BiologicsBloodVaccines/BloodBloodProducts/ApprovedProducts/LicensedProductsBLAs/FractionatedPlasmaProducts/ucm345137.htm

Centers for Disease Control and Prevention
1600 Clifton Road, MS C09, Atlanta, GA 30333
Fax: 404-639-2205

# BOTULISM CASE REPORT

## REPORTING AGENCY

| *Officer Releasing Antitoxin* | *Health Agency* | *Telephone Number* | *Today's Date* |
|---|---|---|---|
| | | | ___ ___ _____ |

| *Date of First Report* | *First Reported By* | *State Contact (if applicable)* |
|---|---|---|
| ___ ___ _____ | | |

| *Treating Physician/Contact for H-BAT Release Name-* *Last Name, First Name* | *Telephone Number* | *Fax Number* / *Email* | *Specialty* ☐Internist ☐Intensivist ☐Neurologist ☐Infectious Disease ☐Pediatrician ☐Other _____ |
|---|---|---|---|
| *Attending Physician Name - Last Name, First Name* | *Telephone Number* | *Fax Number* / *Email* | *Specialty* ☐Internist ☐Intensivist ☐Neurologist ☐Infectious Disease ☐Pediatrician ☐Other _____ |

## DEMOGRAPHIC INFORMATION

| *Patient Name - Last Name, First Name, Middle Initial:* | *Patient's Telephone Number* | *Patient's E-mail Address* |
|---|---|---|
| | | |

| *Patient's Street Address* | *City* | *State* | *Zip Code* |
|---|---|---|---|
| | | | |

| *Date of Birth* | *Age* | *Sex* | *Ethnicity* | *Race (check all that apply)* | | |
|---|---|---|---|---|---|---|
| ___ ___ _____ | _____ ☐Months ☐Years | ☐Male ☐Female | ☐Non-Hispanic/Non-Latino ☐Hispanic/Latino ☐Unknown | ☐African-American/Black ☐American Indian | ☐Asian ☐Pacific Islander ☐White | ☐Alaska Native ☐Other_____ ☐Unknown |

## CLINICAL INFORMATION

| *Symptomatic?* ☐Yes ☐No ☐Unk | *Onset Date of First Botulism Symptom* | *Onset Hour (military)* | *Onset Date of Neurologic Symptoms* | *Date First Sought Medical Care* | *Currently Hospitalized?* ☐Yes ☐No ☐Unk | *If yes, Admit date* |
|---|---|---|---|---|---|---|
| | | ___ ___ | | | | |

| *Hospital Name* | *City* | *State* | *Zip Code* | *Telephone Numbers* |
|---|---|---|---|---|
| | | | | |

| *Admitted to ICU?* ☐Yes ☐No ☐Unk *If yes, date* | *Placed on Ventilator?* ☐Yes ☐No ☐Unk *If yes, date* ___ ___ _____ | *Additional Hospital Phone Numbers (e.g., Pharmacy and ICU)* |
|---|---|---|
| | | |

## CLINICAL PRESENTATION

*Vital Signs (upon presentation)*

Temperature (°F) _____ Blood Pressure (mmHg) _____/_____ Heart Rate (beats/min.) _____ Respiration Rate (breaths/min.) _____

| **Symptoms** | Yes | No | Unk | **Physical Exam Findings** | Yes | No | Unk |
|---|---|---|---|---|---|---|---|
| Nausea | | | | Alert and Oriented | | | |
| Vomiting | | | | Extraocular Palsy (paralysis of eye muscles) | | | |
| Abdominal Pain | | | | If yes, is it bilateral? | | | |
| Diarrhea | | | | If bilateral, is it symmetric? | | | |
| Constipation | | | | Ptosis (drooping eyelids) | | | |
| Blurred Vision | | | | If yes, is it bilateral? | | | |
| Diplopia (double vision) | | | | If bilateral, is it symmetric? | | | |
| Dizziness | | | | Pupils dilated (mm= ) | | | |
| Slurred Speech | | | | If yes, is it bilateral? | | | |
| Thick tongue | | | | Pupils constricted (mm= ) | | | |
| Change in sound of voice | | | | If yes, is it bilateral? | | | |
| Hoarseness | | | | Pupils non-reactive | | | |
| Dry mouth | | | | If yes, is it bilateral? | | | |
| Dysphagia (difficulty swallowing) | | | | Facial Paralysis | | | |
| Shortness of breath | | | | If yes, is it bilateral? | | | |
| Subjective weakness | | | | If bilateral, is it symmetric? | | | |
| Fatigue | | | | Palatal weakness | | | |
| Paresthesia (abnormal sensation, e.g. numbness) | | | | If yes, is it bilateral? | | | |
| Urinary Retention | | | | Impaired gag reflex | | | |
| Other Symptoms (specify): | | | | Sensory deficit(s) If yes, specify | | | |
| | | | | Other (specify): | | | |

*Comments / Remarks:*

COMPLETE & RETURN ALL 3 PAGES OF THIS FORM BY FAX TO SOE 907-563-7868

**Musculoskeletal Exam:** (*0=no evidence of contractility; 1=slight contractility, no movement; 2=full range of motion, gravity eliminated; 3=full range of motion w/ gravity; 4=full range of motion against gravity, some resistance; 5=full range of motion against gravity, full resistance*)

| Proximal Upper Extremity | Distal Upper Extremity | Proximal Lower Extremity | Distal Lower Extremity |
|---|---|---|---|
| R:__/5 L:__/5 ☐Unk | R:__/5 L:__/5 ☐Unk | R:__/5 L:__/5 ☐Unk | R:__/5 L:__/5 ☐U |

**Deep Tendon Reflexes:** (*0=No response; 1=sluggish or diminished; 2=active or expected response; 3=more brisk than expected, slightly hyperactive; 4=brisk, hyperactive, with intermittent or transient clonus*)

| Biceps/Triceps | Brachial | Patellar | Ankle |
|---|---|---|---|
| R:__/4 L:__/4 ☐Unk | R:__/4 L:__/4 ☐Unk | R:__/4 L:__/4 ☐Unk | R:__/4 L:__/4 ☐Unk |

**If muscle weakness/paralysis present, describe progression.**

☐Ascending, ending with cranial nerves ☐Descending, beginning with cranial nerves ☐Other: _____

| ***Clinical Tests*** | Yes | No | Unk | If yes, specify as noted |
|---|---|---|---|---|
| Lumbar puncture CSF analysis | | | | Date ____ ____ _____ WBC count _____ RBC_____ Glucose _____ Protein _____ |
| *Repeat Lumbar puncture?* ☐Yes ☐No ☐Unk If yes, specify as noted | | | | Date ____ ____ _____ WBC count _____ RBC_____ Glucose _____ Protein _____ |
| EMG | | | | Date ____ ____ _____ Done with rapid, repetitive stimulation ☐Yes ☐No ☐Unk If yes, at what hertz? _____ Check one: ☐Suggestive of/consistent with botulism ☐Not consistent with botulism ☐Unk |
| Edrophonium (Tensilon) | | | | Date ____ ____ _____ Describe test results: |
| CT scan or MRI scan | | | | ☐Head ☐Spine ☐Other _____ Suggestive of diagnosis other than botulism ☐Yes ☐ No ☐Unk Describe:_____ |

***Past Medical History***

*Prior Botulism Diagnosis?* ☐Yes ☐No ☐Unk — *If yes, date*

*Medications that could cause neuromuscular paralysis used within 30 days before illness onset (check all that apply).*
☐Myobloc (toxin type B) ☐Aminoglycoside (e.g. gentamicin,tobramycin) ☐Other _____
☐Botox (toxin type A) ☐Anticholinergic ☐Other _____

*Prior Neurologic Impairment?* ☐Yes ☐No ☐Unk — *If yes, specify* _____

*Does the patient have an allergy to equine products?* ☐Yes ☐No ☐Unk — *If yes. describe*

***Differential Diagnosis per attending MD*** *(Please place a 1 for the most likely diagnosis, 2 for the second most likely, and 3 for the third most likely)*

____Botulism ____Tick paralysis ____Paralytic shellfish poisoning
____Myasthenia gravis ____Eaton-Lambert syndrome ____Other_____
____Guillain-Barré syndrome ____Stroke or central nervous system mass or lesion ____Other_____

## EPIDEMIOLOGIC INFORMATION

***Travel History***

*Did patient travel **outside county of residence** within 15 days prior to illness onset?* ☐Yes ☐No ☐Unk
*If yes, specify all locations and dates below.*

| *Location (city, county, state, country)* | *Dates of Travel* |
|---|---|
| | to ___ ___ _____ |
| | ___ ___ _____ to ___ ___ _____ |
| | ___ ___ _____ to ___ ___ _____ |

## Contacts/ Other Ill Persons

*Any contacts with similar illness?* ☐Yes ☐No ☐Unk — *If yes, complete table below*:

| *Name* | *Age* | *City, State* | *Onset Date* | *Relationship* |
|---|---|---|---|---|
| | *Sex* | *Telephone Number* | *Date Reported to Public Health* | *Nature of Contact* |
| *Name* | *Age* | *City, State* | *Onset Date* | *Relationship* |
| | *Sex* | *Telephone Number* | *Date Reported to Public Health* | *Nature of Contact* |

*Comments / Remarks:*

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## Exposures / Risk Factors

*Provide information about the patient's wound and drug use in the table below.*

| | Yes | No | Unk | *If yes, specify as noted* |
|---|---|---|---|---|
| Wound or Abscess | ☐ | ☐ | ☐ | Location(s):<br>Description:<br>Date of injury: ___ ___ ____<br>How wound occurred:<br>Did/does wound appear infected? ☐Yes ☐No ☐Unk |
| Injects Black Tar Heroin (Chiba) | ☐ | ☐ | ☐ | Date last used: ___ ___ ____<br>Injection method (check all that apply): ☐Intravenous ☐Intramuscular<br>☐Subcutaneous (skin-pop) ☐Other: _____ ☐Unk |
| Injects other drugs | ☐ | ☐ | ☐ | Drugs injected (check all that apply): ☐Heroin ☐Cocaine ☐Methamphetamine<br>☐Other: _____ ☐Unk<br>Injection method (check all that apply): ☐Intravenous ☐Intramuscular<br>☐Subcutaneous (skin-pop) ☐Other: _____ ☐Unk |
| Sniffs/snorts drugs | ☐ | ☐ | ☐ | Drugs sniffed/snorted (check all that apply): ☐Heroin ☐Cocaine<br>☐Methamphetamine ☐Other: _____ ☐Unk |
| Uses other drugs | ☐ | ☐ | ☐ | Types: |

*Provide information regarding any suspect food items consumed prior to illness in the table below. If more than three items, append pages; please ask about high risk foods even if wound botulism is suspected. Please pay special attention to fish or seafood exposures.*

| | *Suspect Food 1* | *Suspect Food 2* | *Suspect Food 3* |
|---|---|---|---|
| Food item | | | |
| Date and time eaten | Date:___ ___ ___ Time:___ ___am/pm | Date:___ ___ ___ Time:___ ___am/pm | Date:___ ___ ___ Time:___ ___am/pm |
| Type of item (check one) | ☐Homemade<br>☐Commercial product<br>• Brand: _____<br>• Lot number: _____<br>☐Restaurant-associated<br>☐Unk | ☐Homemade<br>☐Commercial product<br>• Brand: _____<br>• Lot number: _____<br>☐Restaurant-associated<br>☐Unk | ☐Homemade<br>☐Commercial product<br>• Brand: _____<br>• Lot number: _____<br>☐Restaurant-associated<br>☐Unk |
| How item preserved | ☐Canned ☐Dried ☐Fermented<br>☐Salted ☐Pickled ☐No preservation<br>☐Other: _____<br>☐Unk | ☐Canned ☐Dried ☐Fermented<br>☐Salted ☐Pickled ☐No preservation<br>☐Other: _____<br>☐Unk | ☐Canned ☐Dried ☐Fermented<br>☐Salted ☐Pickled ☐No preservation<br>☐Other: _____<br>☐Unk |
| How item stored | ☐Unrefrigerated ☐Refrigerated<br>☐Frozen ☐Unk<br>☐Other:_____ | ☐Unrefrigerated ☐Refrigerated<br>☐Frozen ☐Unk<br>☐Other:_____ | ☐Unrefrigerated ☐Refrigerated<br>☐Frozen ☐Unk<br>☐Other:_____ |
| How item served | ☐Heated ☐Only warmed ☐Unheated<br>☐Fried ☐Boiled<br>☐Other: _____<br>☐Unk | ☐Heated ☐Only warmed ☐Unheated<br>☐Fried ☐Boiled<br>☐Other: _____<br>☐Unk | ☐Heated ☐Only warmed ☐Unheated<br>☐Fried ☐Boiled<br>☐Other: _____<br>☐Unk |
| # persons sharing item | | | |
| # persons ill | | | |
| Samples of food available | ☐Yes ☐No ☐Unk | ☐Yes ☐No ☐Unk | ☐Yes ☐No ☐Unk |
| Samples submitted for botulism testing | ☐Yes ☐No ☐Unk | ☐Yes ☐No ☐Unk | ☐Yes ☐No ☐Unk |
| Foods of same lot/batch recovered or recalled | ☐Yes ☐No ☐Unk | ☐Yes ☐No ☐Unk | ☐Yes ☐No ☐Unk |

*Provide information regarding any other exposures of interest in the table below.*

| *Exposure* | *Description* |
|---|---|
| | |
| | |
| | |

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Centers for Disease Control and Prevention
1600 Clifton Road, MS C09
Atlanta, GA 30333
Fax: 404-639-2205



# Clinical Outcome Report*

***Please include copy of discharge summary***

**Please complete upon discharge or death and fax to 907-563-7868 ATTN: Botulism Surveillance**

## REPORTING AGENCY

| *Treating Physician - Last Name, First Name* | *Telephone Number* | *Fax Number* | *Today'sDate* ___ ___ _____ |
|---|---|---|---|
| *Attending Physician Name - Last Name, First Name* | *Telephone Number* | *Fax Number* | *Speciality* |
| *Hospital Name* | *City* | *State* | *Zip Code* |

## DEMOGRAPHIC INFORMATION

| *Patient Name - Last Name, First Name, Middle Initial* | *City* | *State* | *Zip Code* |
|---|---|---|---|

*Date of Birth* ___ ___ _____

*Sex*
□Male
□Female

## CLINICAL OUTCOME INFORMATION

How many days was patient hospitalized? _____days

How many days was patient in intensive care? _____days

Did patient require mechanical ventilation? □Yes □No □Unk

If yes, how many days was patient on a ventilator? _____days

Did patient require a a tracheostomy? □Yes □No □Unk

If yes, when was the tracheostomy done? ___ ___ _____

Did the patient develop pneumonia? □Yes □No □Unk

What was the final diagnosis? (*please check one)*

□Botulism □Tick paralysis □Paralytic shellfish poisoning
□Myasthenia gravis □Eaton-Lambert syndrome □Other_____
□Guillain-Barre syndrome □Stroke or central nervous system mass or lesion

Was treatment given for any of the above diagnosis (even if it wasn't the final diagnosis)? □Yes □No □Unk

If yes, specify type
□Botulism Antitoxin □Plasmapheresis □Neostigmine/Physostigmine □Other Immunoglobulin therapy_____

Did the patient develop an adverse event after botulism antitoxin administration? □Yes □No □Unk

If yes, specify adverse event _____

Did the patient die? □Yes □No □Unk

**If yes,**

When did patient die? ___ ___ _____

What was the cause of death? _____

**If no,**

Where was patient discharged?
□Home □Nursing home □ Physical therapy/rehabilitation facility □Other (specify)_____

Did patient have residual disability upon discharge? □Yes □No □Unk

**If yes, please specify types below (check as many as apply)**

□Proximal Upper Extremity Weakness □Diminshed deep tendon reflexes □Other_____
□Distal Upper Extremity Weakness □Fatigue □Other_____
□Proximal Lower Extremity Weakness □Stroke or central nervous system mass or lesion
□Distal Lower Extremity Weakness □Other_____

## ADDITIONAL INFORMATION

*Comments / Remarks:*

## 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----------**

- Pregnancy: No human or animal data. Use only if clearly needed (8.1).
- 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: 03/2013**

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**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 [3 DOSAGE FORMS AND STRENGTHS].
- 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.
- Consider skin sensitivity testing for patients at risk of acute hypersensitivity reactions [5.1 Hypersensitivity Reactions].

  *Skin Sensitivity Test*

  Administer of 0.02 milliliters of 1:1000 saline-diluted BAT (enough to raise a small wheal) intradermally on the volar surface of the forearm. If the test is negative, repeat the test using a 1:100 dilution. Perform concurrent positive (histamine) and negative (saline) control tests. A positive test is a wheal with surrounding erythema at least 3 millimeters larger than the negative control test; read at 15-20 minutes. The histamine control must be positive for valid interpretation.
- 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**

| 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 dose is 20% of adult 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.
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 with a history of hypersensitivity to horses or equine blood products, asthma, and hay fever are at a greater risk for developing severe hypersensitivity reactions to BAT. To ascertain risk of allergic reactions in these cases, consider performing a skin sensitivity test [see 2.1 Dosage and Administration].

Administer BAT in a setting with appropriate equipment, medication, 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.

## 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 [7 DRUG INTERACTIONS].

### 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 [11 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 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 [17 PATIENT COUNSELLING INFORMATION].

## 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 [5.1]
- Delayed allergic reactions/serum sickness [5.2]
- Infusion reactions [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 |
| Immune system disorders | Serum Sickness | 1 | 1 | 0.4 |
| Investigations | Blood pressure increased | 1 | 1 | 0.4 |

| System Organ Class | Preferred Term | Overall (N=228) | | |
|---|---|---|---|---|
| | | No. of Events | No. of Subjects | % of Subjects |
| | 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 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 [5.4 Interference with Blood Glucose Testing]. 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

Pregnancy Category C. Animal reproduction studies have not been conducted with BAT. It is not known whether BAT can cause fetal harm when administered to a pregnant woman or can affect reproductive capacity. BAT should only be given to pregnant women if the benefits outweigh the risks.

### 8.3 Nursing Mothers

It is not known whether BAT is excreted in human milk. Caution should be exercised when BAT is administered to a nursing mother since many drugs are excreted in human milk.

### 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 using tri-n-butyl phosphate (TnBP) and triton X-100 (TX-100) 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 adeno- 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 | RNA | RNA |
| Virus | XmuLV | WNV | BVDV | PRV | PI3 | Ad2 | EMC | Porcine Parvovirus |
| Family | Retro | Flavi | Flavi | Herpes | Paramyxo | Adeno | Picorna | Parvo |
| Size (nm) | 80-110 | 40-70 | 50-70 | 150-200 | 100-200 | 70-90 | 25-30 | 18-24 |
| Nanofiltration ($log_{10}$) | ≥ 2.7 | ≥ 2.1 | ≥ 4.5 | | | ≥ 4.7 | ≥ 4.5 | 4.5 |
| S/D ($log_{10}$) | ≥ 4.3 | ≥ 5.1 | | ≥ 5.1 | ≥ 5.5 | | | |
| 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.

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

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; Tmax = 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, salvation, 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).

*Non-human 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 [13.2 Animal Toxicology and Pharmacology]. 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). A brief summary of the results can be found in [12.3 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 [12.2 Pharmacodynamics].

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 [12.1 Mechanism of Action].

**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 for a maximum of 36 months at 2-8 $^{o}$C (36-48 $^{o}$F) or until 48 months from the date of manufacture, whichever comes first. Do not refreeze.

# 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 known to have allergies to horses or other allergies such as seasonal allergies or hay fever, or asthma 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.

## 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.

**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.

**Manufactured By:**

Cangene Corporation

Winnipeg, Manitoba

Canada, R3T 5Y3