衛生福利部疾病管制署專案進口肉毒桿菌抗毒素申請及使用注意事項

110 年 2 月 9 日修訂

一、為應國內疑似肉毒桿菌中毒患者治療之需要，衛生福利部疾病管制署（下稱疾管署）專案進口七價肉毒桿菌抗毒素〔BAT, Botulism Antitoxin Heptavalent(A, B, C, D, E, F, G）—（Equine）〕，儲備於 6 區管制中心（下稱區管中心），供醫療院所申請提供予有使用需求之疑似肉毒桿菌中毒病例。

二、肉毒桿菌中毒為法定傳染病，醫療院所發現疑似肉毒桿菌中毒病例，須依法通報。如研判病患有抗毒素使用需求[1,2]，請依下列流程申請及回報相關資料（申請流程圖示如附件一）：

（一）洽疾管署區管中心（聯繫窗口請參循附件二）或撥打 1922 專線。為評估病患使用抗毒素之必要性及瞭解其預後，請病患之主治醫師就個案病況與疾管署防疫醫師聯繫討論。

（二）如經評估同意醫療院所領用，請填妥「肉毒桿菌抗毒素使用申請表暨病患（代理人）同意書」（附件三）及上傳個案病歷摘要。疾管署會將藥物送達。

（三）使用抗毒素之前，須先採取患者血液檢體 40 毫升（血清 20 毫升）送疾管署檢驗，以研判是否為肉毒桿菌中毒病例及鑑定中毒之毒素型別[3]。

（四）病人用藥完成後，請依追蹤時程填寫「肉毒桿菌抗毒素使用追蹤調查表」（附件四）。相關文件皆需上傳至疾管署傳染病個案通報系統中傳染病個案病歷資料彙集平台。

三、為緊急救治考量，國人或非本國籍之疑似肉毒桿菌中毒者均可申請使用本項抗毒素。惟因人為因素注射肉毒桿菌素（如：醫學美容）之疑似肉毒桿菌中毒個案或無居留證之外籍人士等，需自費使用，請醫療院所於申請藥品領用時填具「肉毒桿菌抗毒素付費使用同意書」（附件五），並檢具相關申請文件。

四、使用七價肉毒桿菌抗毒素，請遵循以下事項：

（一）抗毒素須經 0.9%生理食鹽水 10 倍稀釋後，搭配具 15 微米過濾膜的無菌輸液套，始能進行靜脈輸液且須階段性調整輸注速率。

（二）一瓶（vial）為成人標準用量，未滿 17 歲者請依年齡及體重調整劑量，使用前務必詳閱「七價肉毒桿菌抗毒素使用說明」（附件六）及「仿單」（附件七）。

（三）此抗毒素屬專案進口藥品，並未取得衛生福利部藥物許可證，具引發過敏反應或其他傳染性疾病感染風險，另可能干擾血糖檢測值等，須先向病患或其家屬詳細說明。

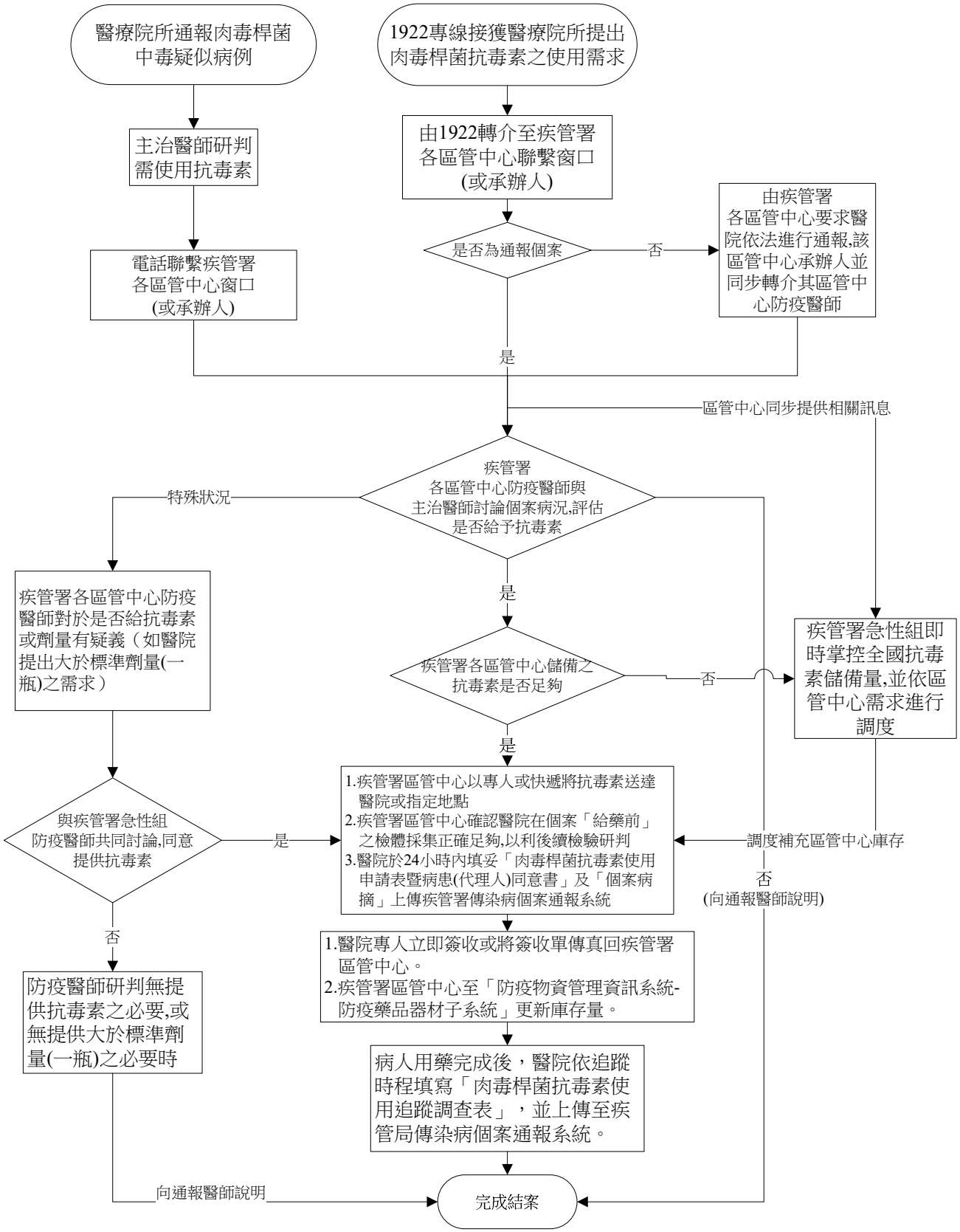
（四）醫療院所使用時若發現不良反應，須通報至「全國藥物不良反應通報中心」，以保障病人權益。

備註：

1. 肉毒桿菌抗毒素僅避免血液中游離的毒素繼續傷害神經肌肉接合處，無法移除已與神經肌肉接合處連結的毒素，因此無法立即緩解症狀。病患需經數週至數月的時間，待已經受損的末梢神經恢復後才能逐漸復原。臨床上除了給予抗毒素外，維持患者換氣功能等支持性療法更為重要。
2. 創傷型肉毒桿菌中毒除給予抗毒素外，傷口處應予以擴創及引流，並以抗生素治療。

3. 未給予血液檢體送驗以一次為原則。

附件一　　肉毒桿菌抗毒素申請流程圖



附件二、衛生福利部疾病管制署各區管制中心聯繫窗口

儲備單位	聯絡人	上班時間 聯絡電話	非上班時間 值班電話	傳真	轄區範圍
臺北區管制中心	蔡宇婷	（02）85905000 轉 5006	（02）25509831 或 1922	（02）25505876	基隆市、臺北市、新北市、宜蘭縣、連江縣、金門縣
北區管制中心	楊景婷	（03）3982789 轉 132	（03）3983647 或 1922	（03）3931723	桃園市、新竹縣、新竹市、苗栗縣、
中區管制中心	張智凱	（04）24739940 轉 215	（04）24725110 或 1922	（04）24739774	臺中市、彰化縣、南投縣
南區管制中心	郭柏伸	（06）2696211 轉 202	（06）2906684 或 1922	（06）2906714	雲林縣、嘉義縣、嘉義市、臺南市
高屏區管制中心	鄭琴怡	（07）5570025 轉 632	0912204709 或 1922	（07）5574664 （07）5574544	高雄市、屏東縣、澎湖縣
東區管制中心	鄭騫琳	（03）8223106 轉 226	（03）8222690 或 1922	（03）8224732	臺東縣、花蓮縣

附件三、肉毒桿菌抗毒素使用申請表暨病患（代理人）同意書

A. 基本資料

1.個案姓名：_____

2.國籍：□本國籍　□非本國籍：_____（加入全民健康保險□有□無）

3.性別：□男　　□女

4.出生日期：_____年_____月_____日

5.居住地：_____縣（市）_____鄉鎮市區

6.體重：_____公斤

B. 發病及暴露史

1.發病時間：_____年____月_____日_____時

2.攝食時間：_____年_____月_____日_____時

3.疑似中毒食物：_____

4.共 食 者：_____人，出現疑似症狀者_____人

5.其他：_____

C. 臨床評估及檢查

1.症狀：意識狀態：E_____V_____M_____（必填）；

神經症狀：□1.視覺模糊（複視）；□2.眼皮下垂；□3.瞳孔放大；□4.口乾；□5.吞嚥困難；□6.說話困難；□7.呼吸困難；□8.排尿困難；□9.感覺異常；□10.近端肢體無力（10-1□上肢、10-2□下肢）；□11.遠端肢體無力（11-1□上肢、11-2□下肢）

腸道症狀：□12.嘔吐；□13.腹瀉；□14.便秘；□15.腹脹

其他症狀：□16.發燒____℃；□17.其他：_____（請填寫）

2.插管治療：□1.否；□2.是（插管日期____年____月____日）

3.相關檢查：□1.EMG_____；□2.CSF_____；□3.MRI_____；□4.其他：_____

_____

_____

D. 就醫過程

1.初診醫院：_____醫院，就診時間：____年____月____日____時，主治醫師：_____

2.轉診醫院 A：_____醫院，就診時間：____年____月____日____時，主治醫師：_____

3.轉診醫院 B：_____醫院，就診時間：____年____月____日____時，主治醫師：_____

E. 檢 附 文 件

□病歷摘要（必備）

□「使用專案進口肉毒桿菌抗毒素同意書」

□如為因人為因素注射肉毒桿菌素或未加入全民健康保險之外籍人士等個案，請填具「肉毒桿菌抗毒素付費使用同意書」。

F. 申請醫師

□已詳閱「衛生福利部疾病管制署專案進口肉毒桿菌抗毒素申請及使用注意事項」

□已詳閱「七價肉毒桿菌抗毒素使用說明」及「仿單」

□已向病患詳細說明下列事項**並獲得病患同意書**如附頁。

一、需實施此項治療的原因

二、可能發生之併發症及危險

申請數量：_____瓶，申請日期：_____年_____月_____日　　申請醫師：_____(簽名或蓋章)

醫療機構名稱：_____醫院_____科　主治醫師：_____

疾病管制署

審核紀錄

審核意見：

審核結果：□同意，核定數量：_____瓶；　□不同意

審 核 者：_____　　提 供 者：_____

審核日期：_____　　提供日期：_____

使用專案進口肉毒桿菌抗毒素同意書

Patient Consent Form for Botulism Antitoxin Use

本人（病患或代理人）經處方醫師之說明，已充分瞭解注射「七價肉毒桿菌抗毒素」可能引起之副作用及需注射的原因，並同意使用本抗毒素；若注射後發生不適或緊急之情況，應立刻向醫師諮詢或接受必要之處置。

I (or the representative) am fully informed and understand the botulism antitoxin therapy [Botulism Antitoxin Heptavalent (A, B, C, D, E, F, G) – (Equine), BAT] and the possible side effects associated with this therapy. I (or the representative) agree to receive the antitoxin therapy. Should any discomfort or side effect develops after injection of Botulism antitoxin, I (or the representative) will immediately seek medical attention.

*病患本人簽名（Signature of the patient）: _____

如果病患本人無法簽名，請代理人簽名

If the patient is unable to sign the consent form, the agreement should be signed from the representative.

與病患之關係（The representative: Please select the relationship with the patient）:

☐法定代理人或監護人（Legally Authorized Representative or Guardian)

☐配偶（Husband or Wife）

☐親屬，稱謂：_____（Relative: _____）

☐其他關係人_____（Others: _____）

代理人簽名（Signature of the representative）:_____

代理人身分證字號(護照號碼)/I.D. (or Passport no.) of the representative：_____

日期（Date）：中華民國　　年　　月　　日;_____ (mm/dd/yyyy)

病人資訊 (Basic information of the patient):

1. 姓名：_____
2. 身分證字號(護照號碼)/I.D. (or Passport no.)：_____
3. 連絡電話或手機/Contact TEL (or Mobile phone)：_____

*註：使用者為未成年、無行為能力或限制行為能力者，應得其法定代理人（或監護人）同意。

*Note: The consent form must be signed by a legally authorized representative (or guardian) if the drug (antitoxin) is to be given to a minor, or an individual with no or limited capacity to make juridical acts.

附件四、肉毒桿菌抗毒素使用追蹤調查表

一、個案基本資料

1.個案姓名：_____	4.發病日：_____年_____月_____日
2.性別：□男□女	5.醫院名稱：_____醫院_____科　聯絡醫師：_____
3.出生日期：_____年_____月_____日	6.個案聯絡人：_____ 聯絡電話：_____

二、申請抗毒素時臨床症狀評估

1.意識狀態	E_____V_____M_____（必填）
2.神經症狀	□1.視覺模糊（複視）；□2.眼皮下垂；□3.瞳孔放大；□4.口乾；□5.吞嚥困難；□6.說話困難；□7.呼吸困難；□8.排尿困難；□9.感覺異常；□10.近端肢體無力（10-1□上肢、10-2□下肢）；□11.遠端肢體無力（11-1□上肢、11-2□下肢）
3.腸道症狀	□12.嘔吐；□13.腹瀉；□14.便秘；□15.腹脹
4.其他症狀	□16.發燒____℃；□17.其他：_____（請填寫）
5.插管治療	□1.否；□2.是（插管日期____年____月____日）
6.相關檢查	□1.EMG_____；□2.CSF_____；□3.MRI_____；□4.其他_____

三、抗毒素使用劑量

1.病患體重：_____公斤

2.標準用量（1 瓶）　　時間：____年____月____日____時____分～____年____月____日____時____分

3.特殊或追加用量（1 瓶）時間：____年____月____日____時____分～____年____月____日____時____分

四、抗毒素使用後不良反應（adverse reactions）評估

1.Hypersensitivity reaction（可能發生在數分鐘或數小時）	□無；□蕁麻疹；□噁心；□頭痛；□支氣管痙攣；□休克；□其他___	出現時間：___年___月___日___時___分
2.Infusion reactions（可能發生在 1～2 小時）	□無；□發燒；□寒顫；□血壓升高；□其他____	出現時間：___年___月___日___時___分
3.Serum sickness（可能發生在 5～24 天）	□無；□搔癢；□蕁麻疹；□發燒；□關節痛；□其他_____	出現時間：___年___月___日___時___分

五、抗毒素使用後臨床症狀評估

評估日期	病人狀況評估	
第一次評估： **使用後 6~12 小時內** 日期：____年____月___日 ____時____分 住院：□1.一般病房； □2.加護病房	1.意識狀態	E_____V_____M_____（必填）；
	2.神經症狀	□1.視覺模糊（複視）；□2.眼皮下垂；□3.瞳孔放大；□4.口乾；□5.吞嚥困難；□6.說話困難；□7.呼吸困難；□8.排尿困難；□9.感覺異常；□10.近端肢體無力（10-1□上肢、10-2□下肢）；□11.遠端肢體無力（11-1□上肢、11-2□下肢）
	3.其他症狀	□16.發燒____℃；□17.其他：_____（請填寫）
	4.插管治療	□1.否；□2.是（插管日期__年__月__日）
第二次評估： **使用後 3～7 天內**	1.意識狀態	E_____V_____M_____（必填）；

評估日期	病人狀況評估	
日期：____年____月___日 ____時____分 住院：□1.一般病房； □2.加護病房	2.神經症狀	□1.視覺模糊（複視）；□2.眼皮下垂；□3.瞳孔放大； □4.口乾；□5.吞嚥困難；□6.說話困難；□7.呼吸困難； □8.排尿困難；□9.感覺異常； □10.近端肢體無力（10-1□上肢、10-2□下肢）； □11.遠端肢體無力（11-1□上肢、11-2□下肢）
	3.其他症狀	□16.發燒____℃；□17.其他：_____（請填寫）
	4.插管治療	□1.否（拔管日期____年____月____日）； □2.是（插管日期____年____月____日）
第三次評估： **使用後 8～14 天內** 日期：___年____月____日 住院：□1.一般病房； □2.加護病房	1.意識狀態	E_____V_____M_____（必填）
	2.神經症狀	□1.視覺模糊（複視）；□2.眼皮下垂；□3.瞳孔放大； □4.口乾；□5.吞嚥困難；□6.說話困難；□7.呼吸困難； □8.排尿困難；□9.感覺異常； □10.近端肢體無力（10-1□上肢、10-2□下肢）； □11.遠端肢體無力（11-1□上肢、11-2□下肢）
	3.其他症狀	□16.發燒____℃；□17.其他：_____（請填寫）
	4.插管治療	□1.否（拔管日期____年____月____日）； □2.是（插管日期____年____月____日）
第四次評估： **使用後 15～28 天內** 日期：____年____月___日 住院：□1.一般病房； □2.加護病房	1.意識狀態	E_____V_____M_____（必填）
	2.神經症狀	□1.視覺模糊（複視）；□2.眼皮下垂；□3.瞳孔放大； □4.口乾；□5.吞嚥困難；□6.說話困難；□7.呼吸困難； □8.排尿困難；□9.感覺異常； □10.近端肢體無力（10-1□上肢、10-2□下肢）； □11.遠端肢體無力（11-1□上肢、11-2□下肢）
	3.其他症狀	□16.發燒____℃；□17.其他：_____（請填寫）
	4.插管治療	□1.否（拔管日期____年____月____日）； □2.是（插管日期____年____月____日）
第五次評估： **出院** 日期：____年____月___日 住院：□1.一般病房； □2.加護病房	1.意識狀態	E_____V_____M_____（必填）
	2.神經症狀	□1.視覺模糊（複視）；□2.眼皮下垂；□3.瞳孔放大； □4.口乾；□5.吞嚥困難；□6.說話困難；□7.呼吸困難； □8.排尿困難；□9.感覺異常； □10.近端肢體無力（10-1□上肢、10-2□下肢）； □11.遠端肢體無力（11-1□上肢、11-2□下肢）
	3.其他症狀	□16.發燒____℃；□17.其他：_____（請填寫）
	4.插管治療	□1.否（拔管日期____年____月____日）； □2.是（插管日期____年____月____日）

※第二次評估至第四次評估，請儘可能選擇病人病情較有變化的一天填寫，如無明顯變化仍須填寫。
※第二次以後之評估，僅需填寫此頁上傳至本署傳染病個案通報系統即可。

附件五、肉毒桿菌抗毒素付費使用同意書[1]

因臨床需要，經病患_____(簽名)〔或其代理人_____(簽名) （與病患之關係：_____)〕同意後[2]，本院（所）同意以自行付費方式使用由衛生福利部疾病管制署提供之肉毒桿菌抗毒素_____瓶。

本院瞭解並同意於簽署本同意書一個月內，匯款支付前述_____瓶抗毒素之費用共計

新台幣___拾___萬___仟___佰___拾___元整（NT＄_____）[3]至衛生福利部疾病管制署[4]，並傳真匯款收據至衛生福利部疾病管制署所轄區管中心。

此致衛生福利部疾病管制署

立書醫療院所：_____醫療院所代號：_____

代表人：_____

開業執照字號：_____

地址：_____

聯絡電話：_____

中華民國_____年_____月_____日

註 1：本同意書由收治因人為因素注射肉毒桿菌素（如：醫學美容）之疑似肉毒桿菌中毒個案以及無全民健康保險卡之外籍人士等之醫療院所填寫。

註 2：如果病患本人無法簽名，請代理人簽名，如果使用者為未成年、無行為能力或限制行為能力者，應取得其法定代理人（或監護人）同意。

註 3：費用以**最新乙批**專案進口之每瓶實際單價計算，以 109 年為例，約新臺幣 26 萬元／每瓶，實際價格請洽詢衛生福利部疾病管制署。

註 4：費用請匯款至以下銀行帳戶，匯入銀行：中央銀行國庫局（代號：0000022），帳號：267863，戶名：衛生福利部疾病管制署 301 專戶

附件六、七價肉毒桿菌抗毒素〔BAT, Botulism Antitoxin Heptavalent （A, B, C, D, E, F, G）–（Equine）〕使用說明

衛生福利部疾病管制署（下稱疾管署）依傳染病防治法第 20 條第 1 項儲備防疫藥物，專案進口肉毒桿菌抗毒素，提供疑似肉毒桿菌中毒者經醫療院所通報與疾管署評估後領用。此七價肉毒桿菌抗毒素〔BAT, Botulism Antitoxin Heptavalent（A, B, C, D, E, F, G）—（Equine）〕尚未經衛生福利部核發藥物許可證，本說明係參考美國食品藥物管理局核准之肉毒桿菌抗毒素英文仿單內容，摘要說明抗毒素之劑量及使用方式，以利醫事人員快速瞭解重點。有關詳細使用方式及注意事項，請詳閱該藥品仿單內容。仿單下載網址如下：
https://www.fda.gov/downloads/BiologicsBloodVaccines/BloodBloodProducts/ApprovedProducts/LicensedProductsBLAs/FractionatedPlasmaProducts/UCM345147.pdf

一、用途：

用於治療經醫師評估診斷為疑似或確診肉毒桿菌中毒之成人及兒童等病患。

二、劑型及體積：

此注射劑須經稀釋才能使用，每瓶（1 vial）為一成人使用劑量，須以0.9%生理食鹽水注射液（0.9% sodium chloride或0.9% normal saline）以 1:10 稀釋（藥品體積為1，生理食鹽水體積為9）後，以靜脈輸注方式使用。

三、抗毒素單位：

每瓶含A型抗毒素4,500單位、B型抗毒素3,300單位、C型抗毒素3,000單位、D型抗毒素600單位、E型抗毒素5,100單位、F型抗毒素3,000單位及G型抗毒素600單位，為一成人使用劑量。

四、每瓶（vial）容量：

可能因批次而異（範圍：10－22 ml），107年購入批號為23001123A的每瓶原液容量為15.6 ml。

五、用法及劑量：

採靜脈輸液，依年齡層及體重給予不同劑量及輸注速率，如**表一**及**表二**所列：

表一、劑量及輸注速率

年齡層	劑量	起始輸注速率（Starting Infusion Rate）（開始輸液 30 分鐘）	病患耐受下，每 30 分鐘調升輸液速率（Incremental Infusion Rate, if Tolerated）	最大輸注速率（Maximum Infusion Rate）
17 歲以上（含）	1 瓶	0.5 ml/分鐘	開始輸液後的第二個 30 分鐘起：每 30 分鐘可調升一倍輸	2 ml/分鐘

年齡層	劑量	起始輸注速率（Starting Infusion Rate）（開始輸液 30 分鐘）	病患耐受下，每 30 分鐘調升輸液速率（Incremental Infusion Rate, if Tolerated）	最大輸注速率（Maximum Infusion Rate）
			注速率，至最大輸注速率為止	
1 歲以上（含），未滿 17 歲	20－100%的成人劑量（即兒童劑量，請依下表二給予）	0.01 ml/公斤/分鐘（起始輸注速率不得快於 0.5 ml/分鐘）	0.01 ml/公斤/分鐘	0.03 ml/公斤/分鐘（但不得快於成人的 2 ml/分鐘）
未滿 1 歲	10%的成人劑量	0.01 ml/公斤/分鐘	0.01 ml/公斤/分鐘	0.03 ml/公斤/分鐘

表二、1 歲以上（含），未滿 17 歲者所給予的兒童劑量（以每瓶 15.6 ml 為舉例）

體重（公斤）	劑量（以成人劑量的百分比%呈現）*	肉毒桿菌抗毒素原液容量（ml）
10－14	20**	3.1
15－19	30	4.7
20－24	40	6.2
25－29	50	7.8
30－34	60	9.4
35－39	65	10.1
40－44	70	10.9
45－49	75	11.7
50－54	80	12.5
≧55	100=1 vial	15.6

*上表係依據 Salisbury Rule 換算劑量，公式請見仿單。

**兒童劑量至少需 20%的成人劑量，未滿 1 歲嬰兒劑量請見表一。

六、使用前注意事項〔請參考仿單第2點（DOSAGE AND ADMINISTRATION）及第5點（WARNINGS AND PRECAUTIONS）相關內容〕：

（一）抗毒素無色透明，如抗毒素使用前出現顆粒、混濁或變色，請避免使用；並請勿搖晃抗毒素，以避免形成泡沫。

（二）抗毒素請冷藏（2－8℃）保存。

（三）少數接受此肉毒桿菌抗毒素治療之個案，可能發生對馬血漿製劑或馬源性蛋白過敏反應（hypersensitivity），若有急用，需經臨床醫師審慎評估可能風險後再申請。

（四）由於此肉毒桿菌抗毒素製造原料為馬血漿，製造過程雖已進行傳染性疾病致病源去除或去活化，惟仍無法完全排除傳染性疾病致病原殘留之可能性，具有可能傳播其他感染性疾病之風險。

（五）本肉毒桿菌抗毒素含麥芽糖（maltose）成分，可能干擾某些血糖監測儀器檢測結果，以致高估血糖值。因此，注射肉毒桿菌抗毒素的患者，請採用具葡萄糖特異

性（glucose-specific）的血糖測量方式，以獲取實際血糖值。

七、使用方法〔請參考仿單第2點（DOSAGE AND ADMINISTRATION）相關內容〕：

（一）肉毒桿菌抗毒素原液 10 倍稀釋：

1.先準備相當於肉毒桿菌抗毒素原液 9 倍容量的 0.9%生理食鹽水注射液（0.9% sodium chloride 或 0.9% normal saline）。再將肉毒桿菌抗毒素加入其中混合，即完成肉毒桿菌抗毒素稀釋液配製。

2.參考範例：**以每瓶 15.6 ml 為例**，配製成人劑量，請先準備約 140 ml（15.6 x 9=140.4）的 0.9%生理食鹽水注射液作為稀釋使用，再將整瓶肉毒桿菌抗毒素原液加入混合及稀釋。實務操作上，提供以下稀釋方法供參考：

（1）自 500 ml 袋裝（或瓶裝）的 0.9%生理食鹽水注射液，以無菌針具取出其中約 360 ml（500-140=360）並丟棄。

（2）再將一整瓶肉毒桿菌抗毒素原液（以每瓶 15.6 ml 為例）以無菌針具加入袋（瓶）中，與袋（瓶）中約 140 ml 的 0.9%生理食鹽水注射液混合，完成約 156 ml 的肉毒桿菌抗毒素稀釋液配製。

（3）最後將前述裝有肉毒桿菌抗毒素稀釋液的袋（瓶）子，接上輸液套，並依照表一之輸注速率注意病患耐受反應與小心評估使用。

3.未滿 17 歲者給予劑量，請依上表一及表二或仿單所詳述內容調整。

（二）輸液套的規格：請選擇具過濾器且其過濾孔徑為 15 微米（15 micrometer）的無菌輸液套，作為輸注使用，以濾除可能的混濁物或顆粒。

八、可能產生之副作用〔請參考仿單第6點（ADVERSE REACTIONS）相關內容〕：依臨床實證研究，少數使用者可能出現的副作用為發熱、皮膚紅疹、寒顫、噁心及浮腫等輕度或中度不良反應。如於輸液治療期間出現過敏或身體不適等症狀，請調降肉毒桿菌抗毒素輸注速率，並給予症狀治療；如症狀持續惡化，應暫停輸注肉毒桿菌抗毒素。

九、肉毒桿菌抗毒素請於開封後儘快使用，如抗毒素於提供病患治療後仍有剩餘，請將其丟棄，勿再保留剩餘抗毒素作為日後治療其他病患使用〔**請參考仿單第2點（DOSAGE AND ADMINISTRATION）相關內容**〕。

附件七　　七價肉毒桿菌抗毒素

〔BAT, Botulism Antitoxin Heptavalent（A, B, C, D, E, F, G）－（Equine）〕仿單

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

----------RECENT MAJOR CHANGES----------
Dosage and Administration, Preparation (2.2) [09/2016]

----------INDICATIONS AND USAGE----------
BAT [Botulism Antitoxin Heptavalent (A, B, C, D, E, F, G) – (Equine)] is a mixture of immune globulin fragments indicated for the treatment of symptomatic botulism following documented or suspected exposure to botulinum neurotoxin serotypes A, B, C, D, E, F, or G in adults and pediatric patients.
The effectiveness of BAT is based solely on efficacy studies conducted in animal models of botulism.

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

For intravenous use only.

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

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

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

Each single-use vial contains a minimum potency of:

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

----------CONTRAINDICATIONS----------
None.

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

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

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

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

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

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

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

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

Revised: 03/2017

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FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

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

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

2 DOSAGE AND ADMINISTRATION

BAT is for intravenous use only.

2.1 Dosage and Administration

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

Table 1 BAT Dosing Guide and Intravenous Infusion Rate

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

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

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

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

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

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

Do not exceed 1 vial dose regardless of body weight.

** **Minimum pediatric dose is 20% of adult dose. See**

Table 1 for infant dose.

2.2 Preparation

1. Bring vial to room temperature.

- If frozen, thaw vial by placing in a refrigerator at 36 to 46 °F (2 to 8 °C) until the contents are thawed for approximately 14 hours.
- Product can be thawed rapidly by placing at room temperature for one hour followed by a water bath at 98.6 °F (37 °C) until thawed.
- Do not thaw this product in a microwave oven. Do not refreeze the vial.

2. Inspect vial to ensure there is no damage to the seal or vial. If damaged, discard the vial.
3. Do not shake the vial during preparation to avoid foaming.
4. Dilute 1:10 in 0.9% Sodium Chloride Injection, USP (saline) by adding BAT solution from the vial to the appropriate amount of saline in an IV bag. Do not use any other diluents. As the fill volume per vial varies by lot number (approximately 10 to 22 milliliters per vial), 90 to 200 milliliters of saline will be required. Withdraw the entire contents of the vial to obtain the total volume in the vial. If a partial vial is required (for pediatric dosing), the entire content of the vial should be withdrawn to ensure accurate calculation of the dosage [Table 2].
5. Visually inspect the product for particulate matter and discoloration prior to administration. Do not use if the solution is turbid, cloudy, or contains particles other than a few translucent-to-white proteinaceous particulates.
6. Use an intravenous line with constant infusion pump. Use a 15 micron sterile, non-pyrogenic, low protein binding in-line filter.
7. BAT vials are for single use only and contain no preservative. Once punctured, use the vial contents to prepare the infusion bag and administer as soon as possible.
8. Discard any unused portion.

3 DOSAGE FORMS AND STRENGTHS

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

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

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

4 CONTRAINDICATIONS

None.

5 WARNINGS AND PRECAUTIONS

5.1 Hypersensitivity Reactions

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

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

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

5.2 Delayed Allergic Reactions (Serum Sickness)

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

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

5.3 Infusion Reactions

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

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

5.4 Interference with Blood Glucose Testing

The maltose contained in BAT can interfere with some types of blood glucose monitoring systems i.e. those based on glucose dehydrogenase pyrroloquinoline-quinone (GDH-PQQ) method. This can result in falsely elevated glucose readings and inappropriate administration of insulin, resulting in life-threatening hypoglycemia. Cases of true hypoglycemia may go untreated if the hypoglycemic state is masked by falsely elevated results *[see Drug Interactions (7)]*.

5.5 Transmissible Infectious Agents

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

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

6 ADVERSE REACTIONS

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

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

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

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

6.1 Clinical Trials Experience

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

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

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

The most common adverse reactions in all healthy subjects were headache (9%), pruritus (5%), nausea (5%), and urticaria (5%). Other adverse reactions reported in less than 4% of subjects included pyrexia and throat discomfort. All reported adverse reactions were considered mild or moderate. No serious adverse reactions were reported. Two moderate acute allergic reactions that required premature termination of the infusion and treatment were reported. Reactions were predefined as mild if the subject was aware but could tolerate. Moderate reactions were predefined as discomfort enough to interfere with normal daily activity.

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

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

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

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

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

System Organ Class	Preferred Term	Overall (N=228)		
		No. of Events	No. of Subjects	% of Subjects
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
Skin and subcutaneous tissue disorders	Erythema	1	1	0.4
	Hyperhidrosis	1	1	0.4
	Rash	4	4	1.8
Vascular disorders	Hemodynamic instability	1	1	0.4
	Hypotension	1	1	0.4

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

6.2 Postmarketing Experience

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

- Anaphylactic shock
- Angioedema
- Urticaria

6.3 Immunogenicity

As with all therapeutic proteins, there is potential for immunogenicity. All subjects from the two clinical trials were tested for immunogenicity against BAT at baseline and at the end of the studies (Day 28) using a validated assay. Eleven subjects seroconverted during the course of the two trials. One subject from each clinical trial experienced a moderate allergic reaction during the administration of BAT. Both subjects were negative for anti-BAT antibodies at baseline and at the end of their respective studies. The detection of antibody formation is highly dependent on the sensitivity and specificity of the assay. Additionally, the observed

incidence of antibody (including neutralizing antibody) positivity in an assay may be influenced by several factors including assay methodology, sample handling, timing of sample collection, concomitant medications, and underlying disease. For these reasons, comparison of the incidence of antibodies to BAT with the incidence of antibodies to other products may be misleading.

7 DRUG INTERACTIONS

Drug Laboratory Interactions: Blood Glucose Testing

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

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

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

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

8.2 Lactation

Risk Summary

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

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

8.4 Pediatric Use

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

Fifteen pediatric subjects (age 10 days to 17 years; including 1 newborn, 3 infants and toddlers, 4 children and 7 adolescents) received BAT under the CDC expanded access

clinical study. A 3-year old subject and an infant received two infant doses, and 13 pediatric subjects received one pediatric dose according to Salisbury Rule [Table 2].

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

Dosing in pediatric patients is based on Salisbury Rule.

8.5 Geriatric Use

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

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

11 DESCRIPTION

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

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

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

Table 4 Viral Clearance Capacity of the BAT Process

	Enveloped					**Non-enveloped**		
Genome	RNA	RNA	RNA	DNA	RNA	DNA	DNA	RNA
Virus	XMuLV	WNV	BVDV	PRV	PI3	Ad2	Porcine Parvovirus	EMC
Family	Retro	Flavi	Flavi	Herpes	Paramyxo	Adeno	Parvo	Picorna

	Enveloped					Non-enveloped		
Size (nm)	80-110	40-70	50-70	150-200	100-200	70-90	18-24	25-30
Nanofiltration (log_{10})	≥ 2.7	≥ 2.1	≥ 4.5	n.t	n.t.	≥ 4.7	4.5	≥ 4.5
S/D (log_{10})	≥ 4.3	≥ 5.1	n.t.	≥ 5.1	≥ 5.5	n.t.	n.t.	n.t.
Total Reduction (log_{10})	≥ 7.0	≥ 7.2	≥ 4.5	≥ 5.1	≥ 5.5	≥ 4.7	4.5	≥ 4.5

XMuLV: Xenotropic Murine Leukemia Virus; specific model for equine infectious anemia, and a model for lipid-enveloped RNA viruses of similar size, such as vesicular stomatitis virus (Rhabdo family).

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

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

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

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

Ad2: Adenovirus; specific model for equine adenovirus.

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

n.t. – not tested

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

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

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

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

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

12.2 Pharmacodynamics

A proof-of-concept clinical dose-response trial was conducted using the extensor digitorum brevis (EDB) muscle of the foot as a model for measuring muscle paralysis after exposure to botulism toxin. In this model, BAT prevented subjects from experiencing a decrease in muscle function after exposure to botulinum neurotoxin (BoNT) serotypes A and B. Subjects treated with placebo (n=10) demonstrated a loss of greater than 50% EDB muscle function within 3 days of exposure to BoNT serotypes A and B. In the BAT arm of the trial (n=16), EDB muscle function was stable over time indicating that BAT was effective in preserving muscle function for up to 28 days following exposure to both BoNT serotype A and B.

12.3 Pharmacokinetics

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

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

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

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

Antitoxin Serotype	Treatment Group	$AUC_{0-\infty}$ (U*hr/mL)	C_{max} (U/mL)	$t_{1/2}$ (hr)	Cl (mL/hr)	V_d (mL)
G	1 Vial	7.05	0.59	11.70	149	2372
	2 Vials	14.66	1.19	14.70	144	3063

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

13 NONCLINICAL TOXICOLOGY

13.2 Animal Toxicology and Pharmacology

Toxicological studies were not conducted for BAT or its components.

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

Guinea Pig

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

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

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

Neurotoxin Serotype	Treatment Group	Survival Rate (%)	Two-sided Fisher's Exact Test (p-value)
G	1x BAT	34/34 (100%)	p<0.0001
	Placebo Control	17/34 (50%)	

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

Nonhuman Primate

In a controlled therapeutic efficacy study, rhesus macaques were intoxicated with BoNT serotype A delivered intravenously at a dose of 1.7x nonhuman primate intravenous lethal dose 50% ($NHPLD_{50}$) units per kilogram of body weight. The animals were then treated with either placebo control or 1x scaled human dose of BAT (weight/weight based on an average human body weight of 70 kilograms), after the onset of clinical signs of botulism (ptosis, muscular weakness, or respiratory distress). Treatment with BAT resulted in a statistically significant improvement in the survival rate [Table 7].

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

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

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

14 CLINICAL STUDIES

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

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

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

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

To provide additional support for the efficacy demonstrated in the animal models, a preliminary analysis of data from a Centers for Disease Control and Prevention (CDC) open-

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

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

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

15 REFERENCES

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

16 HOW SUPPLIED/STORAGE AND HANDLING

16.1 How Supplied

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

BAT is not made with natural rubber latex.

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

16.2 Storage and Handling

- Store frozen at or below ≤ 5°F (≤ -15°C) until used.
- Once thawed, Botulism Antitoxin Heptavalent (A, B, C, D, E, F, G) – (Equine) may be stored at 2-8°C (36-48°F) for a maximum of 36 months or until 48 months from the date of manufacture, whichever comes first. Do not refreeze.
- Once punctured, use the vial contents to prepare the infusion bag and administer as soon as possible.
- BAT vials are for single use only and contain no preservative. Discard any unused portion.

17 PATIENT COUNSELING INFORMATION

See FDA-approved patient labeling (Patient Information).

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

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Manufactured By:

Cangene Corporation, a subsidiary of Emergent BioSolutions Inc.

Winnipeg, Manitoba

Canada, R3T 5Y3

U.S. License No. 1201

PATIENT INFORMATION

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

What is botulism?

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

Botulism can cause the following conditions:

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

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

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

What is BAT?

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

Who should use BAT?

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

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

How will you receive BAT?

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

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

The most common side effects of BAT are:

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

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

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

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

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

What other information do you need to know about BAT?

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

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

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