

Beriplex P/N 250/500
第九凝血因子複合注射劑 250/500

衛署登陸字號 000520 號

- 使用藥品前，請先仔細閱讀此說明書的所有資訊，因其可能包含給您的重要資訊。
- 請妥善保管說明書，以便日後若有需要時參考。
 - 若有任何其他的疑慮，請詢問您的醫師或藥師。
 - 此藥品處方只開立給您，請勿轉讓給他人，可能會對他人造成傷害，即便他們的症狀與您的相同。
 - 若您有任何副作用發生，請告知您的醫生或藥師。包含任何說明書上沒有載明的可能副作用。請參見章節“不良反應”。

Beriplex P/N 250 粉末及注射用溶液之溶劑
Beriplex P/N 500 粉末及注射用溶液之溶劑

1. 定性與定量的組成

Beriplex為粉末及注射用溶液之溶劑，含有人體凝血酶原複合物(thromboplastin complex)。藥品中含如下表所示之人體凝血酶原複合物IU量。

成分名稱	配製後的成分 (IU/ml)	每瓶 Beriplex P/N 250 含量(IU)	每瓶 Beriplex P/N 500 含量(IU)
主成分			
Human coagulation factor II	20 – 48	200 – 480	400 – 960
Human coagulation factor VII	10 – 25	100 – 250	200 – 500
Human coagulation factor IX	20 – 31	200 – 310	400 – 620
Human coagulation factor X	22 – 60	220 – 600	440 – 1200
其他主成分			
Protein C	15 – 45	150 – 450	300 – 900
Protein S	12 – 38	120 – 380	240 – 760

配製後溶液的總蛋白質含量為6 – 14 mg/ml。

第九凝血因子的比活性(specific activity)為每毫克總蛋白質2.5 IU。

所有的凝血因子、Protein C及Protein S (抗原)的活性，都是根據目前有效的國際 WHO 標準品，進行測試。

已知作用的賦形劑：

每100 ml溶液含約達343 mg (大約15 mmol)的鈉。

其他完整的成分清單，請見5.1 賦形劑清單章節。

2. 劑型

粉末及注射用溶液之溶劑。

白色或略帶顏色之粉末或易碎固體。

3. 臨床特性

3.1 適應症

一治療及手術前後期間預防因先天性缺乏凝血酶原複合凝血因子，如因接受維生素K拮抗劑治療造成之缺乏或維生素K拮抗劑過量，且須快速校正缺乏量時之出血。

一治療及手術前後期間預防因先天性缺乏任一種維生素K依賴型凝血因子的情況下，且無法供應純化之特定凝血因子濃縮劑時之出血。

3.2 使用劑量及投與方式

使用劑量

以下只提供一般劑量的指導原則。必須在有治療凝血失調經驗的醫師的監督下，進行治療。替代治療的劑量與使用期間，必須視治療適應症、疾病的嚴重性、出血的部位及程度，與患者的臨床狀況而定。

投與的量與頻率必須以個別患者為基礎來計算。劑量的間隔時間必須適合在凝血酶原複合物中，各個凝血因子的不同的循環半衰期(參考4.2藥物動力學特性)。個別的劑量需求，只能以常規的方式，依照個別血漿中的特定凝血因子為基礎，或凝血酶素複合物量的整體試驗(global tests of the thromboplastin complex levels(INR, Quick's test)來決定，並持續監測患者的臨床情況。

在重大外科手術時，藉由凝血試驗，精確地監測替代治療是必要的(特定的凝血因子試驗及/或凝血酶素複合物量的整體性試驗)。

一在**使用維生素K拮抗劑治療期間，治療出血及預防手術前後期間出血。**

劑量必須視治療前的INR及目標INR而定。治療前(Pre-treatment)之INR應儘可能於接近投與時間時做測量，以計算Beriplex的適當投與劑量。

下表為在不同的起始INR下，達到正常INR (e.g. ≤ 1.3)所需的大約劑量(配製後藥品每公升體重毫升數及每公升體重的第九因子IU數)。

Pre-treatment INR	2.0 – 3.9	4.0 – 6.0	> 6.0
每公升體重的藥品毫升數的約略劑量(ml/kg)	1	1.4	2
每公升體重的第九因子IU數的約略劑量(IU/kg)	25	35	50

劑量根據體重決定，但體重不超過100 kg。而對於體重大於100 kg之患者，最大單一劑量(第九因子IU數)於INR 2.0-3.9時應不超過2500 IU，INR 4.0-6.0時應不超過3500 IU，INR 大於6.0時應不超過5000 IU。

改善由維生素K拮抗劑所誘發的凝血障礙，通常約在注射後的30分鐘會達到效果。對於為了緊急逆轉維生素K拮抗劑作用而接受Beriplex的患者，應考慮同時投與維生素K。因維生素K通常在4-6個小時內見效。臨床數據未支持重複投與Beriplex給需要緊急逆轉維生素K拮抗劑作用的患者，因此不予建議。

這些建議的根據，是來自於有限的實驗對象，所進行的臨床研究資料。效果的恢復及持續期，可能會因人而異，因此監控治療期間的INR是必要的。

一在**先天缺乏任一種維生素K依賴型凝血因子中的情況下，當無法供應特定凝血因子產品時的出血治療及預防手術前後期間出血。**

根據臨床研究資料，計算凝血酶原複合物濃縮物的所需劑量：

- 1 IU第九因子/每公升體重，預計會提高血漿第九因子活性為正常量的1.3% (0.013 IU/ml)。
- 1 IU第七因子/每公升體重，會提高血漿第七因子活性為正常量的1.7% (0.017 IU/ml)。
- 1 IU第二因子/每公升體重，會提高血漿第二因子活性為正常量的1.9% (0.019 IU/ml)。
- 1 IU第十因子/每公升體重，會提高血漿第十因子活性為正常量的1.9% (0.019 IU/ml)。

特定因子的投與劑量是以International Units (IU)表示，這與各個因子現行的WHO標準值有關。特定凝血因子在血漿中的活性是以百分比(對應於正常血漿或International Units (對應於特定凝血因子的國際標準品))表示。

1 International Unit (IU)的凝血因子活性，相當於1 ml的正常人體血漿的量。

例如計算第十因子的所需劑量，是根據1 International Unit (IU)第十因子/每公升體重，會增加0.019 IU/ml血漿第十因子活性。

依照以下公式，計算所需的劑量：

所需劑量=體重 (kg) × 希望增加的第十因子 (IU/ml) × 53

53 ml/kg為預估回復率的倒數。

此計算依據接受維生素K拮抗劑患者之數據。若以健康受試者之數據估算，將提供較低之預估所需劑量。

若個體回復率為已知，則需將此數值用於計算。

產品特性之資訊可由健康自願者(N=15)，針對需逆轉維生素K拮抗劑作用治療急性大量出血或是預防手術前後期間出血(N=98，N=43)之臨床研究獲得(請見章節4.2藥物動力學特性)。

小兒族群(Paediatric Population)

目前尚未有Beriplex對於兒童及青少年(<18歲)的安全性及功效的對照臨床研究(請參見章節3.4 特別警告及使用前的注意事項)。

高齡族群(Elder Population)

高齡者(> 65歲)的使用劑量與投與方式與一般建議相同。

投與方式

投與本藥品前的配製指示，請參見5.6廢棄物及其他處理方式之特別注意事項章節。配製後的溶液必須以靜脈注射方式投與(不可超過3 IU/kg/minute，最大值210 IU/minute，約8 ml/minute。)

3.3 禁忌症

對主成分或列於章節5.1賦形劑清單中的任一賦形劑過敏。

若是瀰漫性血管內凝固症候群，凝血酶原複合物製劑，僅可在凝血因子消耗階段(consumptive state)結束後使用。

已知有heparin引發的血小板過低病史。

3.4 特別警告及使用前的注意事項

應尋求有處理凝血失調經驗的專科醫師協助。

後天性缺乏維生素K依賴型凝血因子的患者(例：因使用維生素K拮抗劑治療而誘發)，Beriplex只應用在必須迅速修正凝血酶原複合物血中濃度的時候，例如大量出血或緊急手術時。在其他案例，減少維生素K拮抗劑的劑量及/或投與維生素K通常就已足夠。

接受維生素K拮抗劑的患者，可能有潛在的血液凝固性過高狀態，而輸注人體凝血酶原複合物可能會使情況更加惡化。

在先天性缺乏任一種維生素K依賴型凝血因子的情況下，若能取得特定的凝血因子產品，則必須給予。

當過敏或類過敏反應發生時，必須立即停止投與Beriplex (例如：停止注射)，並採取適當的治療。治療措施必須視不良反應的種類及嚴重性而定。必須遵守現有的休克處理醫療標準。

不論是先天性或後天性缺乏的患者，投與人體凝血酶原複合物，尤其是重複投與，都有血栓或瀰漫性血管內凝固症的危險。在治療只有缺乏第七凝血因子的患者時，風險會提高，這是因為其他維生素K依賴型凝血因子的半衰期較長，可能會累積到高於正常量。患者投與人體凝血酶原複合物時，應密切觀察是否有瀰漫性血管內凝固症或血栓的徵兆或症狀。

因為有發生血栓栓塞併發症的潛在危險，所以當注射Beriplex於有冠狀動脈心臟疾病或心肌梗塞病史、肝臟疾病、手術前後的患者，新生兒及可能發生血栓栓塞現象或瀰漫性血管內凝固症的患者，或同時缺乏抑制因子的患者時，應嚴密監控。在這些情況下，應衡量注射Beriplex的潛在利益與其發生上述併發症的潛在風險。

罹患瀰漫性血管內凝固症的患者，在某些情形下可能需要替代凝血酶原複合物中的凝血因子。然而，此替代治療只能在消耗狀態結束後施行(例如：治療根本的病因，或持續維持antithrombin III量在正常濃度。)

逆轉維生素K拮抗劑作用將使患者暴露於潛在的血栓栓塞風險。應儘快謹慎考量恢復抗凝治療。

不良反應可能包括形成heparin誘發的第II型血小板低下症(HIT, type II)。HIT的特徵為在heparin治療期間，血小板數量下降超過50%及/或發生新的或無法解釋的血栓栓塞併發症。症狀發作一般會在開始heparin治療後的4-14天後，但若患者最近曾暴露於heparin之下(先前100天之內)，可能會在10個小時之內發生。

腎病徵候群已見於單一案例報告中，在帶有第九凝血因子抑制因子(inhibitor)及過敏反應病史的B型血及病患患者企圖進行免疫耐受治療之後發生。

並無Beriplex使用於治療新生兒因缺乏維生素K，所造成的出生前後的出血相關資料。Beriplex每100 ml中，含約達343 mg (約15 mmol)的鈉。使用在限鈉飲食患者時應予考慮。

病毒安全性

使用由人體血液或血漿製成製劑時，為了避免傳染症，採取的標準措施包括：挑選捐贈者、針對個別捐贈及混合血漿做傳染性指標檢測、和使用有效的製過程序去活化/去除病毒。即使如此，當投與由人體血液或血漿製成製劑的藥品，其傳輸感染媒介的可能性是無法被完全排除的。這也適用於未知或新興的病毒或其他病原體。這些措施被認為是對具套膜的病毒例如human immunodeficiency virus (HIV)、hepatitis B virus (HBV)、hepatitis C virus (HCV)及具套膜的hepatitis A virus及parvovirus B19有效。

適當的疫苗接種(A型肝炎及B型肝炎)，應用於規律重複接受人體血液製劑凝血酶原複合物(prothrombin complex)產品的患者。

強烈建議每次投與Beriplex給患者時，產品名稱及批號必須要記錄，以維持患者及產品批次之間的聯繫。

3.5 與其他藥物的交互作用及其他形式的交互作用

人體凝血酶原複合物產品會中和維生素K拮抗劑治療的功效，但尚無已知與其他藥品的交互作用。

對注射高劑量的人體凝血酶原複合物的患者，進行heparin敏感的凝固試驗(Clotting tests)時，必須考量到投與的產品成分中含有 heparin。

3.6 生殖、懷孕及哺乳

懷孕與哺乳

目前尚未建立人體凝血酶原複合物於人體懷孕及哺乳期間的安全性資料。動物實驗並不適合用於評估懷孕、分娩或產後發育的安全性。因此，人體凝血酶原複合物只有在明確的指示下，才能使用於懷孕及哺乳期間。

生殖

未有可使用的生殖數據。

3.7 對駕駛及操作機械能力上的影響

尚無使用本藥對駕駛或操作機械的能力影響的相關實驗。

3.8 不良反應

安全性檔案摘要

過敏及類過敏反應，包含嚴重的過敏反應，並不被觀察到(參見3.4特別警告及使用前的注意事項章節)。

替代療法可能會導致循環性抗體的生成，抑制一個或更多的人體凝血酶原複合因子。若產生這些抑制因子，它會造成足夠的臨床反應。若發生這樣的案例，建議與專業的血液病中心聯繫取得指引。過敏反應曾於針對Beriplex所含因子之抗體的患者被觀察到。

體溫上升是常見的。

在投與人體凝血酶原複合物之後，有血栓栓塞風險(請參見3.4特別警告及使用前的注意事項章節)。

Beriplex藥物不良反應之列表

以下不良反應皆依據臨床實驗數據、上市後經驗及科學文獻。

以下表格是依國際醫學用語系統器官分類(SOC and Preferred Term Level)。頻率根據臨床實驗數據，依以下常規訂定：很常見($\geq 1/10$)；常見($\geq 1/100$ 至 $<1/10$)；不常見($\geq 1/1,000$ 至 $<1/100$)；罕見($\geq 1/10,000$ 至 $<1/1,000$)；非常罕見($< 1/10,000$)，未知(從可得資料無法估計)。

國際醫學用語系統器官分類	患者藥物不良反應	頻率
血管失調及其他系統器官分類	血栓栓塞形成*	常見
血液及淋巴系統失調	瀰漫性血管內凝固症	未知
免疫系統失調	過敏症或過敏反應	不常見
	類過敏性反應包含類過敏性休克	未知
神經系統失調	抗體的形成	未知
全身性失調及注射部位症狀	頭痛	常見
	體溫升高	常見

* 含致命案例

關於傳染性物質的安全性，請參見3.4特別警告及使用前的注意事項章節。

小兒族群

尚無Beriplex使用於小兒族群之相關數據。

疑似不良反應之報告

於藥品上市後報告疑似的不良反應是重要的。其可持續的監控藥品的利益/風險。健康照護專業人士被要求需報告任何疑似的不利反應。

3.9 用藥過量

為避免用藥過量，在治療期間定期監控凝血狀況是必要的，因為使用高劑量的複合濃縮劑(用藥過量)可能和發生心肌梗塞、瀰漫性血管內凝固症、靜脈栓塞及肺栓塞相關。在用藥過量的情形下，這些具有併發症危險的患者發生血栓併發症或瀰漫性血管內凝固症的危險性會增高。

4. 藥理學特性

4.1 藥效動力學特性

藥理治療分類：抗出血劑，血液凝集第二、第七、第九、第十因子組合物。

ATC code: B02B D01

第二、第七、第九、第十凝血因子，會在肝臟藉由維生素K的幫助進行合成，通常稱為凝血酶原複合物。除了凝血因子外，Beriplex，也含有維生素K依賴型凝血抑制因子Protein C及Protein S。

第七因子是活性絲氨酸蛋白酶類factor VIIa的酶原，藉由它才能啟動血液凝結的外部路徑。Tissue thromboplastin factor-factor VIIa complex能活化factor IX及factor X，因而形成factor IXa及factor Xa。藉由更進一步的活化機制後，凝血酶原(factor II)被活化，並轉變為凝血酶(thrombin)。藉由凝血酶的作用，纖維素原轉變為纖維素，並形成血液凝塊。正常生成凝血酶，對於作為初步止血的一部分，血小板的功能，是相當重要的。

只有第七因子的嚴重缺乏，因為損及纖維素的形成及初步止血，會導致凝血酶的形成減少及出血傾向。只有第九因子的缺乏是一種典型的血友病(B型血友病)。只有第二及第十因子的缺乏非常罕見，但在嚴重的情況下，會造成類似典型血友病的出血傾向。

至於其他成分，像是凝血抑制因子Protein C及Protein S，也是在肝臟被合成。Protein C的生物活性會被轉因子Protein S增強。活化的Protein C會藉由使凝血因子Va及VIIIa去活化，抑制凝血。Protein S為Protein C的輔因子，幫助凝血作用去活化。Protein C的缺乏與血栓的危險性增加有關。

後天性維生素K依賴型凝血因子的缺乏，會發生在進行維生素K拮抗劑治療期間。若缺乏的情況加劇，會導致嚴重的出血傾向，其特徵為腹股溝或關節出血，而不是肌肉及關節的出血。嚴重的肝功能不全也會導致維生素K依賴型凝血因子血中濃度明顯減少及臨床相關的出血傾向。然而，這常常是複雜的情形，因為同時會有低程度的血管內凝血、低血小板量、凝血抑制因子的缺乏，及受到干擾的纖維蛋白溶解，一起進行。

投與人體凝血酶原複合物，會增加維生素K依賴型凝血因子的量，及暫時矯正缺乏一個或數個上述凝血因子的患者之凝血缺陷。

4.2 藥物動力學特性

藥物動力學和體內恢復率數據由健康自願者研究產生(N=15)，並有兩個研究針對需逆轉維生素K拮抗劑作用治療急性嚴重出血或是預防手術前後期間出血(N=98，N=43)。

健康自願者研究：

15名健康自願者投與Beriplex 50 IU/kg。IVR是指血漿中可測量因子濃度(IU/ml)之增加，其可能藉由輸注因子(IU/kg)推測，如投與Beriplex之劑量。已評估第二、七、九、十因子及Protein C和S所增加的IVRs。所有組成將於三個小時之時間間隔內達到最高濃度。IVRs平均增加的範圍介於第九因子0.016 IU/ml及0.028 Protein C間。血漿半衰期的中位數及增加的IVR須依以下指示：

Parameter	Median Plasma half-lived (range) hours	Incremental IVR (IU/ml per IU/kg b.w.)
Factor II	60 (25-135)	0.022 (0.020-0.023)
Factor VII	4 (2-9)	0.024 (0.023-0.026)
Factor IX	17 (10-127)*	0.016 (0.014-0.018)
Factor X	31 (17-44)	0.021 (0.020-0.023)
Protein C	47 (9-122)*	0.028 (0.027-0.030)
Protein S	49 (33-83)*	0.020 (0.018-0.021)

* 信賴區間(Confidence Interval)

* 未相半衰期：二室模型(two-compartment-model)

Beriplex在體內與內源性第二、第七、第九、第十凝血因子以同樣的方式分佈及代謝。靜脈投與應能迅速即供應藥物。生體利用率與投與劑量成正比。

針對需逆轉維生素K拮抗劑作用治療急性嚴重出血的研究：

平均體內恢復率(IVR)由98位使用Beriplex治療於維生素K拮抗劑治療期間出血之受試者計算而得。增量的IVR反應分佈於 ≥ 0.016 IU/ml 第七因子及 0.019 IU/ml Protein C之間。

針對需逆轉維生素K拮抗劑作用治療急性嚴重出血或預防手術前後期間出血的研究：

平均體內恢復率(IVR)由43位使用Beriplex於維生素K拮抗劑治療期間治療出血或預防手術前後期間出血之受試者計算而得。靜脈注射Beriplex 1 IU/kg將使維生素K依賴型凝血因子血中濃度由 0.013 增加至 0.023 IU/ml。

4.3 臨床前安全性資料

Beriplex含有活性成分凝血酶原複合物(第二、第七、第九和第十因子)。他們取自於人體血漿，且作用與內源性血漿成分相同。

使用先以巴斯德加熱殺菌法，而非使用奈米過濾產品進行的單一劑量毒性研究顯示，老鼠在投與最高測試劑量 200 IU/kg後，呈現中等程度的毒性。巴斯德滅菌且經奈米過濾後產品，老鼠可耐受之一靜脈注射量達100 IU/kg。由於注射異質的人體蛋白後，會產生抗體，因此不能應用傳統的動物模式，進行重複給予劑量的臨床前研究(慢性毒性、致毒性、及生殖毒性)。

兔子實驗顯示Beriplex靜脈投與後產生局部耐受性。以兔子進行的新抗原性研究中，已經顯示沒有導因於巴斯德加熱殺菌法的過程的新抗原原蛋白(neoepitop)產生。

5. 藥劑學特性

5.1 賦形劑清單

粉末：

Heparin
Human albumin
Human antithrombin III
Sodium chloride
Sodium citrate
HCl或NaOH (少量用於pH修正)

溶劑：

注射用水

5.2 不能相容性

本品不可與除章節5.6廢棄物及其他處理方式之特別注意事項所提及以外之其他藥品混合使用。

5.3 效期

3年

使用時的物理化學安定性已被證實可在室溫下(最高 25°C)維持 24 小時。無論如何，以微生物學的觀點看來，本品應立即使用。

5.4 貯存之特別注意事項

不可超過 25°C。

不可冷凍。

將小瓶置於外盒中，避免光線照射。

本藥品配製後的貯存方式，請參見5.3效期章節。

5.5 容器材質與內容

Beriplex P/N 250:

粉末：無色玻璃注射小瓶(Type II)，不含乳膠之輸注瓶塞(bromobutyl rubber)，密封鋁皮，及塑膠瓶蓋蓋密封。

溶劑：10 ml注射用水，無色玻璃注射小瓶(Type I)，以不含乳膠之輸注瓶塞(chlorobutyl rubber)，密封鋁皮，及塑膠瓶蓋蓋密封。

注射裝置：一個過濾轉注裝置20/20

Beriplex P/N 500:

粉末：無色注射玻璃小瓶(Type II)，以不含乳膠之輸注瓶塞(bromobutyl rubber)，密封鋁皮，及塑膠瓶蓋蓋密封。

溶劑：20 ml注射用水，無色注射玻璃小瓶(Type I)，以不含乳膠之輸注瓶塞(chlorobutyl rubber)，密封鋁皮，及塑膠瓶蓋蓋密封。

注射裝置：一個過濾轉注裝置 20/20

並非所有包裝規格皆有銷售。

5.6 廢棄物及其他處理方式之特別注意事項

投與方式

一般通則

- 溶液應為清澈或些許半透明。過濾或抽取配製後(參見下面內容)，在投與前，配製後的產品必須以肉眼觀察是否有微粒狀物質或變色。

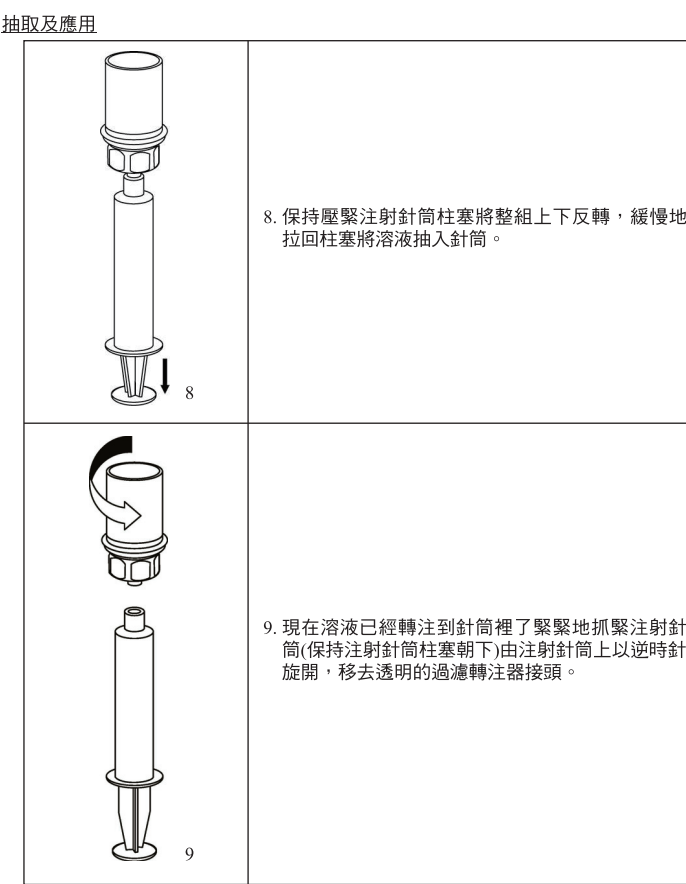
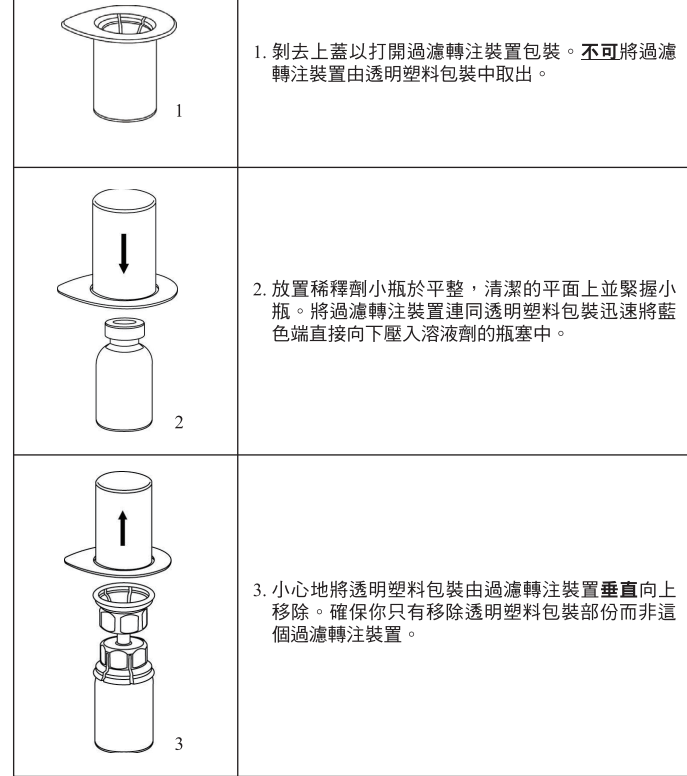
- 若溶液混濁或含沉澱物，需棄置不用。

- 須在無菌狀態下配製與抽取溶液。

配製

- 將溶劑置於室溫下。

- 確認產品及溶劑小瓶的塑膠瓶蓋已移除，瓶塞以無菌溶液處理，並在打開過濾轉注裝置(Mix2Vial)的包裝前，靜置待乾。



- 注意不可有血液流入填滿藥品的注射器，因為會有血液凝結在注射器中的危險，使纖維素凝塊因而被投與患者。

若需要使用一瓶以上Beriplex，可將數瓶Beriplex集合於可購得之輸注器材進行單次輸注。

Beriplex溶液絕不可稀釋使用。

- 配製好的溶液應以個別的注射/輸注線投與，緩慢靜脈輸注，速率不可超過 3 IU/kg/minute，最大值210 IU/kg/minute，約8 ml/minute。

- 任何未使用的藥品或廢棄物，必須按照當地衛生法規丟棄。

6. 最後更新日期

2016年 12月

7. 製造廠：CSL Behring GmbH

地 址：Emil-von-Behring-Str. 76
35041 Marburg
Germany

BERIPLEX P/N 250/500

Taiwan DOH Reg. No. 000520

Read all of this leaflet carefully before you start using this medicine because it contains important information for you.

- Keep this leaflet. You may need to read it again.
- If you have further questions, ask your doctor or pharmacist.
- This medicine has been prescribed for you only. Do not pass it on to others. It may harm them, even if their signs of illness are the same as yours.
- If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet. See section "undesirable effects".

Beriplex P/N 250, powder and solvent for solution for injection.
Beriplex P/N 500, powder and solvent for solution for injection.

1. QUALITATIVE AND QUANTITATIVE COMPOSITION

Beriplex is presented as powder and solvent for solution for injection containing human prothrombin complex. The product nominally contains the following IU of the human coagulation factors tabled below:

Name of the ingredients	Content after reconstitution (IU/ml)	Beriplex P/N 250 content per vial (IU)	Beriplex P/N 500 content per vial (IU)
Active Ingredients			
Human coagulation factor II	20 – 48	200 – 480	400 – 960
Human coagulation factor VII	10 – 25	100 – 250	200 – 500
Human coagulation factor IX	20 – 31	200 – 310	400 – 620
Human coagulation factor X	22 – 60	220 – 600	440 – 1200
Further active ingredients			
Protein C	15 – 45	150 – 450	300 – 900
Protein S	12 – 38	120 – 380	240 – 760

The total protein content is 6 – 14 mg/ml of reconstituted solution.
The specific activity of factor IX is 2.5 IU per mg total protein.
The activities of all coagulation factors as well as Protein C and S (antigen) have been tested according to the current valid international WHO-Standards.
Excipients with known effect:
Sodium up to 343 mg (approximately 15 mmol) per 100 ml solution.
For the full list of excipients, see section 5.1 List of excipients.

2. PHARMACEUTICAL FORM

Powder and solvent for solution for injection.
White or slightly coloured powder or friable solid.

3. CLINICAL PARTICULARS

3.1 Therapeutic indications

- Treatment and perioperative prophylaxis of bleedings in acquired deficiency of the prothrombin complex coagulation factors, such as deficiency caused by treatment with vitamin K antagonists, or in case of overdose of vitamin K antagonists, when rapid correction of the deficiency is required.
- Treatment and perioperative prophylaxis of bleedings in congenital deficiency of any of the vitamin K dependent coagulation factors when purified specific coagulation factor products are not available.

3.2 Posology and method of administration

Posology
Only general dosage guidelines are given below. Treatment should be initiated under the supervision of a physician experienced in the treatment of coagulation disorders. The dosage and duration of the substitution therapy depend on the indication for treatment, severity of the disorder, on the location and extent of bleeding and on the patient's clinical condition.

The amount and the frequency of administration should be calculated on an individual patient basis. Dosage intervals must be adapted to the different circulating half-lives of the respective coagulation factors in the prothrombin complex (see section 4.2 Pharmacokinetic properties). Individual dosage intervals can only be identified on the basis of regular determinations of the individual plasma levels of the coagulation factors of interest, or on global tests of the prothrombin complex levels (INR, Quick's test), and a continuous monitoring of the clinical condition of the patient.

In case of major surgical interventions, precise monitoring of the substitution therapy by means of coagulation assays is essential (specific coagulation factor assays and/or global tests for prothrombin complex levels).

- Bleeding and perioperative prophylaxis of bleedings during vitamin K antagonist treatment.

The dose will depend on the INR before treatment and the targeted INR.

The pre-treatment INR should be measured as close as possible to the time of dosing in order to calculate the appropriate dose of Beriplex. In the following table approximate doses (ml/kg body weight of the reconstituted product and IU Factor IX/kg b.w.) required for normalisation of INR (e.g. ≤ 1.3) at different initial INR levels are given.

Pre-treatment INR	2.0 – 3.9	4.0 – 6.0	> 6.0
Approximate dose of the product ml/kg body weight	1	1.4	2
Approximate dose IU Factor IX/kg body weight	25	35	50

Dose is based on body weight up to but not exceeding 100 kg body weight. For patients weighing more than 100 kg the maximum single dose (IU of Factor IX) should therefore not exceed 2500 IU for an INR of 2.0 - 3.9, 3500 IU for an INR of 4.0 - 6.0 and 5000 IU for an INR of > 6.0.

The correction of the vitamin K antagonist-induced impairment of haemostasis is commonly

reached approximately 30 minutes after the injection. The simultaneous administration of vitamin K should be considered in patients receiving Beriplex for urgent reversal of vitamin K antagonist since vitamin K usually takes effect within 4 - 6 hours. Repeated dosing with Beriplex for patients requiring urgent reversal of vitamin K antagonist treatment is not supported by clinical data and therefore not recommended.

These recommendations are based on data from clinical studies with a limited number of subjects. Recovery and the duration of effect may vary, therefore monitoring of INR during treatment is mandatory.

- Bleedings and perioperative prophylaxis in congenital deficiency of any of the vitamin K dependent coagulation factors when specific coagulation factor products are not available.

The calculation of the required dosage of prothrombin complex concentrate is based on data from clinical studies:

- 1 IU of factor IX per kg body weight can be expected to raise the plasma factor IX activity by 1.3 % (0.013 IU/ml) of normal
- 1 IU of factor VII per kg body weight raises the plasma factor VII activity by 1.7 % (0.017 IU/ml) of normal
- 1 IU of factor II per kg body weight raises the plasma factor II activity by 1.9 % (0.019 IU/ml) of normal
- 1 IU of factor X per kg body weight raises the plasma factor X activity by 1.9 % (0.019 IU/ml) of normal.

The dose of a specific factor administered is expressed in International Units (IU), which are related to the current WHO standard. The activity in the plasma of a specific coagulation factor is expressed either as a percentage (relative to normal plasma) or in International Units (relative to the international standard for the specific coagulation factor).

One International Unit (IU) of a coagulation factor activity is equivalent to the quantity in one ml of the normal human plasma.

For example, the calculation of the required dosage of factor X is based on the finding that 1 International Unit (IU) of factor X per kg body weight raises the plasma factor X activity by 0.019 IU/ml.

The required dosage is determined using the following formula:
Required units = body weight [kg] x desired factor X rise [IU/ml] x 53
where 53 (ml/kg) is the reciprocal of the estimated recovery.

Note that the calculation is based upon data from patients receiving vitamin K antagonists. A calculation based upon data from healthy subjects would provide a lower estimate of the required dose.

If the individual recovery is known, that value should be used for calculation.

Product specific information is available from clinical studies in healthy volunteers (N = 15), in reversal of vitamin K antagonist treatment for acute major bleeding or perioperative prophylaxis of bleeding (N = 98, N = 43) (see section 4.2 Pharmacokinetic properties).

Paediatric population

The safety and efficacy of Beriplex in children and adolescents (< 18 years) has not yet been established in controlled clinical studies (see sections 3.4 Special warnings and precautions for use).

Older population

The posology and method of administration in older people (> 65 years) is equivalent to the general recommendations.

Method of administration

For instructions on reconstitution of the medicinal product before administration, see section 5.6 Special precautions for disposal and other handling. The reconstituted solution should be administered intravenously (not more than 3 IU/kg/minute, max. 210 IU/minute, approximately 8 ml/minute).

3.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section 5.1 List of excipients.

In the case of disseminated intravascular coagulation, prothrombin complex- preparations may only be applied after termination of the consumptive state.

Known history of heparin-induced thrombocytopenia.

3.4 Special warnings and precautions for use

The advice of a specialist experienced in the management of coagulation disorders should be sought.

In patients with acquired deficiency of the vitamin K-dependent coagulation factors (e.g. as induced by treatment of vitamin K antagonists), Beriplex should only be used when rapid correction of the prothrombin complex levels is necessary, such as major bleedings or emergency surgery. In other cases, reduction of the dose of the vitamin K antagonist and/or administration of vitamin K is usually sufficient.

Patients receiving a vitamin K antagonist may have an underlying hypercoagulable state and infusion of human prothrombin complex may exacerbate this.

In congenital deficiency of any of the vitamin K-dependent factors, specific coagulation factor products should be used when available.

If allergic or anaphylactic-type reactions occur, the administration of Beriplex has to be stopped immediately (e.g. discontinue injection) and an appropriate treatment has to be initiated. Therapeutic measures depend on the kind and severity of the undesirable effect. The current medical standards for shock treatment are to be observed.

There is a risk of thrombosis or disseminated intravascular coagulation when patients, with either congenital or acquired deficiency, are treated with human prothrombin complex particularly with repeated dosing. The risk may be higher in treatment of isolated factor VII deficiency, since the other vitamin K-dependent coagulation factors, with longer half-lives, may accumulate to levels considerably higher than normal. Patients given human prothrombin complex should be observed closely for signs or symptoms of disseminated intravascular coagulation or thrombosis.

Because of the risk of thromboembolic complications, close monitoring should be exercised when administering Beriplex to patients with a history of coronary heart disease or myocardial infarction, to patients with liver disease, to patients per- or postoperatively, to neonates or to patients at risk of thromboembolic phenomena or disseminated intravascular coagulation or simultaneous inhibitor deficiency. In each of these situations, the potential benefit of treatment with Beriplex should be weighed against the potential risk of such complications.

In patients with disseminated intravascular coagulation, it may, under certain circumstances, be necessary to substitute the coagulation factors of the prothrombin complex. This substitution may, however, only be carried out after termination of the consumptive state (e.g. by treatment of the underlying cause, persistent normalization of the antithrombin III level).

Reversing vitamin K antagonists exposes patients to the thromboembolic risk of the

underlying disease. Resumption of anticoagulation should be carefully considered as soon as possible.

Undesirable reactions may include the development of heparin-induced thrombocytopenia, type II (HIT, type II). Characteristic signs of HIT are a platelet count drop > 50 per cent and/or the occurrence of new or unexplained thromboembolic complications during heparin therapy. Onset is typically from 4 to 14 days after initiation of heparin therapy but may occur within 10 hours in patients recently exposed to heparin (within the previous 100 days).

Nephrotic syndrome has been reported in single cases following attempted immune tolerance induction in haemophilia B patients with factor IX inhibitors and a history of allergic reaction. No data are available regarding the use of Beriplex in case of perinatal bleeding due to vitamin K deficiency in neonates.

Beriplex contains up to 343 mg sodium (approximately 15 mmol) per 100 ml. To be taken into consideration by patients on a controlled sodium diet.

Virus safety

Standard measures to prevent infections resulting from the use of medicinal products prepared from human blood or plasma include:

- selection of donors, screening of individual donations and plasma pools for specific markers of infection and the inclusion of effective manufacturing steps for the inactivation/removal of viruses. Despite this, when medicinal products prepared from human blood or plasma are administered, the possibility of transmitting infective agents cannot be totally excluded. This also applies to unknown or emerging viruses and other pathogens.

The measures taken are considered effective for enveloped viruses such as human immunodeficiency virus (HIV), hepatitis B virus (HBV) and hepatitis C virus (HCV) and for the non-enveloped hepatitis A virus and parvovirus B19.

Appropriate vaccination (hepatitis A and hepatitis B) should be considered for patients in regular/repeated receipt of human plasma-derived prothrombin complex products.

It is strongly recommended that every time that Beriplex is administered to a patient, the name and batch number of the product are recorded in order to maintain a link between the patient and the batch of the product.

3.5 Interaction with other medicinal products and other forms of interaction

Human prothrombin complex products neutralise the effect of vitamin K antagonist treatment, but no interactions with other medicinal products are known.

When performing clotting tests which are sensitive to heparin in patients receiving high doses of human prothrombin complex, the heparin as a constituent of the administered product must be taken into account.

3.6 Fertility, pregnancy and lactation

Pregnancy and Breastfeeding

The safety of human prothrombin complex for use in human pregnancy and during lactation has not been established. Animal studies are not suitable to assess the safety with respect to pregnancy, embryonal/fetal development, parturition or postnatal development.

Therefore, human prothrombin complex should be used during pregnancy and lactation only if clearly indicated.

Fertility

No fertility data are available.

3.7 Effects on ability to drive and use machines

No studies on the effects on the ability to drive and use machines have been performed.

3.8 Undesirable effects

Summary of the Safety Profile

Allergic or anaphylactic-type reactions have been uncommonly observed, including severe anaphylactic reactions (see section 3.4 Special warnings and precautions for use).

Replacement therapy may lead to the formation of circulating antibodies inhibiting one or more of the human prothrombin complex factors. If such inhibitors occur, the condition will manifest itself as a poor clinical response. In such cases, it is recommended to contact a specialised haemophilia center for guidance. Anaphylactic reactions have been observed in patients with antibodies to factors contained in Beriplex.

Increase in body temperature has been commonly observed.

There is a risk of thromboembolic episodes following the administration of human prothrombin complex (see section 3.4 Special warnings and precautions for use).

Tabulated list of adverse drug reactions of Beriplex

The following adverse reactions are based on clinical trial data, post marketing experience as well as scientific literature.

The table presented below is according to the MedDRA system organ classification (SOC and Preferred Term Level). Frequencies have been based on clinical trial data, according to the following convention: very common ($\geq 1/10$); common ($\geq 1/100$ to $< 1/10$); uncommon ($\geq 1/1,000$ to $< 1/100$); rare ($\geq 1/10,000$ to $< 1/1,000$); very rare ($< 1/10,000$) or not known (cannot be estimated from the available data).

MedDRA Standard System Organ Class	Adverse Drug Reaction by PT	Frequency
Vascular disorders and other SOCs	Thromboembolic events*	common
Blood and lymphatic system disorders	Disseminated intravascular coagulation	not known
Immune system disorders	Hypersensitivity or allergic reactions	uncommon
	Anaphylactic reactions including anaphylactic shock	not known
	Development of antibodies	not known
Nervous system disorders	Headache	common
General disorders and administration site conditions	Body temperature increased	common

* including cases with fatal outcome

For safety with respect to transmissible agents, see section 3.4 Special warnings and precautions for use.

Paediatric population

No data are available regarding the use of Beriplex in paediatric population.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is

important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions.

3.9 Overdose

To avoid overdose, regular monitoring of the coagulation status is indicated during the treatment as the use of high doses of prothrombin complex concentrate (overdose) has been associated with instances of myocardial infarction, disseminated intravascular coagulation, venous thrombosis and pulmonary embolism. In case of overdose the risk of thromboembolic complications or disseminated intravascular coagulation is enhanced in patients at risk of these complications.

4. PHARMACOLOGICAL PROPERTIES

4.1 Pharmacodynamic properties

Pharmacotheapeutic group: antihemorrhagics, blood coagulation factors II, VII, IX and X in combination

ATC code: B02B D01

The coagulation factors II, VII, IX and X, which are synthesised in the liver with the help of vitamin K, are commonly called the prothrombin complex. In addition to the coagulation factors Beriplex contains the vitamin K dependent coagulation inhibitors Protein C and Protein S.

Factor VII is the zymogen of the active serine protease factor VIIa by which the extrinsic pathway of blood coagulation is initiated. The tissue thromboplastin factor-factor VIIa complex activates coagulation factors IX and X, whereby factor IXa and Xa are formed. With further activation of the coagulation cascade, prothrombin (factor II) is activated and transformed to thrombin. By the action of thrombin, fibrinogen is converted to fibrin, which results in clot formation. The normal generation of thrombin is also of vital importance for platelet function as a part of the primary haemostasis.

Isolated severe deficiency of factor VII leads to reduced thrombin formation and a bleeding tendency due to impaired fibrin formation and impaired primary haemostasis. Isolated deficiency of factor IX is one of the classical haemophilias (haemophilia B). Isolated deficiency of factor II or factor X is very rare but in severe form they cause a bleeding tendency similar to that seen in classical haemophilia.

The further ingredients, the coagulation inhibitors Protein C and Protein S, are also synthesised in the liver. The biological activity of Protein C is enforced by the cofactor Protein S.

Activated Protein C inhibits the coagulation by inactivating the coagulation factors Va and VIIa. Protein S as cofactor of Protein C supports the inactivation of the coagulation. Protein C deficiency is associated with an increased risk of thrombosis.

Acquired deficiency of the vitamin K-dependent coagulation factors occurs during treatment with vitamin K antagonists. If the deficiency becomes severe, a severe bleeding tendency results, characterised by retroperitoneal or cerebral bleeds rather than muscle and joint haemorrhage. Severe hepatic insufficiency also results in markedly reduced levels of the vitamin K-dependent coagulation factors and a clinical relevant bleeding tendency. However this is often complex due to a simultaneously ongoing low-grade intravascular coagulation, low platelet levels, deficiency of coagulation inhibitors and disturbed fibrinolysis.

The administration of human prothrombin complex provides an increase in plasma levels of the vitamin K-dependent coagulation factors, and can temporarily correct the coagulation defect of patients with deficiency of one or several of these factors.

4.2 Pharmacokinetic properties

Pharmacokinetic and *in-vivo* recovery data were generated in a healthy volunteer study (N = 15) and in two studies in reversal of vitamin K antagonist treatment for acute major bleeding or perioperative prophylaxis of bleedings (N = 98, N = 43).

Healthy Volunteer Study

15 healthy volunteers were administered 50 IU/kg of Beriplex. The IVR is the increase in measurable factor levels in plasma (IU/ml) that may be expected following an infusion of factors (IU/kg) administered as a dose of Beriplex. Incremental IVRs for Factors II, VII, IX, X, and Proteins C and S were assessed. All maximum component levels occurred within the 3-hour time interval. Mean incremental IVRs ranged between 0.016 IU/ml for Factor IX and 0.028 for Protein C. Median plasma half-lives and incremental IVR are indicated as follows:

Parameter	Median Plasma half-lived (range) hours	Incremental IVR (IU/ml per IU/kg b.w.)
		Geometric Mean 90%CI†
Factor II	60 (25-135)	0.022 (0.020-0.023)
Factor VII	4 (2-9)	0.024 (0.023-0.026)
Factor IX	17 (10-127)*	0.016 (0.014-0.018)
Factor X	31 (17-44)	0.021 (0.020-0.023)
Protein C	47 (9-122)*	0.028 (0.027-0.030)
Protein S	49 (33-83)*	0.020 (0.018-0.021)

† Confidence Interval

* terminal half-life : two-compartment-model

Beriplex is distributed and metabolized in the organism in the same way as the endogenous coagulation factors II, VII, IX and X.

Intravenous administration means that the preparation is available immediately, bioavailability is proportional to the dose administered.

Study in reversal of vitamin K antagonist treatment for acute major bleeding:

The mean *in-vivo* recovery (IVR) was calculated in 98 subjects who received Beriplex for treatment of bleeding during vitamin K antagonist treatment. The incremental IVR responses ranged between 0.016 IU/ml for Factor VII and 0.019 IU/ml for Protein C.

Study in reversal of vitamin K antagonist treatment for acute major bleeding or perioperative prophylaxis of bleeding:

The mean *in-vivo* recovery (IVR) was calculated in 43 subjects who received Beriplex for treatment of bleeding or perioperative prophylaxis of bleedings during vitamin K antagonist treatment. The intravenous administration of 1 IU/kg Beriplex increased plasma levels of the vitamin K dependent coagulation factors ranging from 0.013 to 0.023 IU/ml.

4.3 Preclinical safety data

Beriplex contains as active ingredients the factors of the prothrombin complex (factors II, VII, IX and X). They are derived from human plasma and act like endogenous constituents of plasma.

Single dose toxicity studies with the predecesing pasteurized but not nanofiltered product showed moderate toxicity in mice after the administration of 200 IU/kg, the highest dose tested. A single i.v. dose of the pasteurized and nanofiltered product of up to 100 IU/kg was tolerated in rats. Preclinical studies with repeated dose applications (chronic toxicity, carcinogenicity and reproductive toxicity) cannot be reasonably performed in conventional animal models due to the development of antibodies following the application of heterologous human proteins.

The local tolerance after intravenous administration of Beriplex was shown in rabbits. A neoantigenicity study with rabbits has shown no indication of generation of a neoepitop due to the pasteurization process.

5. PHARMACEUTICAL PARTICULARS

5.1 List of excipients

Powder:

Heparin
Human albumin
Human antithrombin III
Sodium chloride
Sodium citrate
HCl or NaOH (in small amounts for pH adjustment)

Solvent:

Water for injections

5.2 Incompatibilities

This medicinal product must not be mixed with other medicinal products except those mentioned in section 5.6 Special precautions for disposal and other handling.

5.3 Shelf life

3 years

Chemical and physical in-use stability has been demonstrated for 24 hours at room temperature (max. 25 °C). However, from a microbiological point of view, the product should be used immediately.

5.4 Special precautions for storage

Do not store above 25 °C.

Do not freeze.

Keep the vial in the outer carton, in order to protect from light.

For storage conditions after reconstitution of the medicinal product, see section 5.3 Shelf life.

5.5 Nature and contents of container

Beriplex P/N 250:

Powder: Injection vial of colourless glass (Type II), sealed with latex-free infusion stopper (bromobutyl rubber), aluminium seal and plastic flip-off cap.

Solvent: 10 ml Water for injections in an injection vial of colourless glass (Type I), sealed with latex-free infusion stopper (chlorobutyl rubber), aluminium seal and plastic flip-off cap.

Injection device: 1 filter transfer device 20/20

Beriplex P/N 500:

Powder: Injection vial of colourless glass (Type II), sealed with latex-free infusion stopper (bromobutyl rubber), aluminium seal and plastic flip-off cap.

Solvent: 20 ml Water for injections in an injection vial of colourless glass (Type I), sealed with latex-free infusion stopper (chlorobutyl rubber), aluminium seal and plastic flip-off cap.

Injection device: 1 filter transfer device 20/20

Not all pack sizes may be marketed.

5.6 Special precautions for disposal and other handling

Method of administration

General instructions

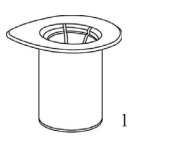
- The solution should be clear or slightly opalescent. After filtering/withdrawal (see below) reconstituted product should be inspected visually for particulate matter and discoloration prior to administration.

- Do not use solutions that are cloudy or have deposits.

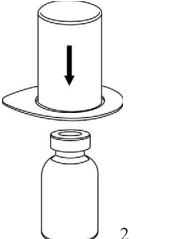
- Reconstitution and withdrawal must be carried out under aseptic conditions.

Reconstitution

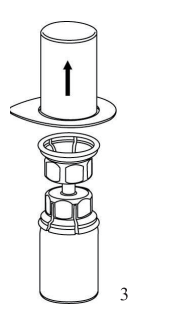
Bring the solvent to room temperature. Ensure product and solvent vial flip caps are removed and the stoppers are treated with an antiseptic solution and allowed to dry prior to opening the Mix2Vial package.



1. Open the Mix2Vial package by peeling off the lid. Do **not** remove the Mix2Vial from the blister package!



2. Place the **solvent vial** on an even, clean surface and hold the vial tight. Take the Mix2Vial together with the blister package and push the spike of the **blue** adapter **straight down** through the solvent vial stopper.



3. Carefully remove the blister package from the Mix2Vial set by holding at the rim, and pulling **vertically** upwards. Make sure that you only pull away the blister package and not the Mix2Vial set.