CSL Behring

Beriplex P／N 250／500

第九凝血因子複合注射劑 250／500

衛署菌疫輸字第 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，請詢問你的醫師或藥師。
- 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，請告知你的醫生或藥師。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（prothrombin complex）。藥品中含有如下表所示之人體血漿凝血因子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100ml溶液含約達343mg（大約15mmol）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

－治療及手術前後期間預防因後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。

－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製劑時之出血。

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，或凝血酵素複合物量的整體試驗（on global tests of the prothrombin 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/或凝血酵素複合物量的整體性試驗)。

-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(配製後藥品每公斤體重毫升數及每公斤體重的第九因子IU數)。

Pre-treatment INR	2.0 – 3.9	4.0 – 6.0	> 6.0
每公斤體重的藥品毫升數的約略劑量（ml/kg）	1	1.4	2
每公斤體重的第九因子 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 100kg。而對於體重大於 100kg 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 2500IU，INR 4.0-6.0 時應不超過 3500IU，INR 大於 6.0 時應不超過 5000IU。

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。

-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/每公斤體重，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/每公斤體重，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/每公斤體重，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/每公斤體重，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/每公斤體重，會增加 0.019IU/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(Older 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 賦型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，可能會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。

當過敏或類過敏性反應發生時，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，尤其是重覆投與，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，應予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、手術前或後的患者，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疾病的血栓栓塞風險。應儘快謹慎考量恢復抗凝血治療。

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在heparin之下(先前100天之內)， 可能會在10個小時之內發生。

腎病症候群已見於單一個案報告中，在帶有第九凝血因子抑制因子(inhibitor)及過敏反應病史的B型血友病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備製成的藥劑時，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特定感染指標檢測、和使用有效的製造程序去活化/去除病毒。即使如此，當投與由人體血液或血漿配製而成的藥品，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。

這些措施被認定為對具套膜的病毒例如 human immunodeficiency virus (HIV)、hepatitis B virus(HBV)、和hepatitis C virus(HCV) 及不具套膜的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紀錄，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、胚胎/胎兒發育、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
未有可使用之生殖數據。

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
過敏及類過敏型反應，包含嚴重的過敏反應，並不常被觀察到 (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，它會造成不足夠的臨床反應。若發生這樣的案例，建議與專業的血友病中心聯繫取得指引。過敏反應曾於具針對 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，有血栓栓塞症風險 (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詞典系統器官分類（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（≥ 1/10）；常見（≥ 1/100 至<1/10）；不常見（≥ 1/1,000 至<1/100）；罕見（≥ 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）。

國際醫學用語詞典 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
	抗體的形成	未知
神經系統失調	頭痛	常見

全身性失調及注射部位症狀	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良反應。

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酵素類factor VIIa的酵素原，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凝血機制後，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，纖維素原轉變成纖維素，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，像是凝血液抑制因子 Protein C 及 Protein S，也是在肝臟被合成。Protein C 的生物活性會被輔因子 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，其特徵為腹膜後或腦部出血，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 50IU/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0.016IU/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.)	
		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)

†信賴區間(Confidence Interval)

*末相半衰期: 二室模型(two-compartment-model)

Beriplex在體內跟內源性第二、第七、第九、第十凝血因子以同樣的方式分佈及代謝。

靜脈投與意指能夠立即供應藥劑。生體可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，老鼠可耐受之單一靜脈注射量達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，進行重覆給予劑量的臨床前研究(慢性毒性、致癌性、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部分(neoepitop)產生。

5. 藥劑學特性

5.1 賦型劑清單

粉末：

Heparin
Human albumin
Human antithrombin III
Sodium chloride
Sodium citrate
HC1 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℃)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℃。

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，及塑膠掀除蓋密封。

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，及塑膠掀除蓋密封。
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，及塑膠掀除蓋密封。
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，及塑膠掀除蓋密封。
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

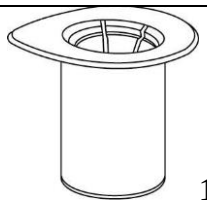
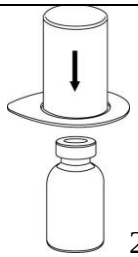
投與方式

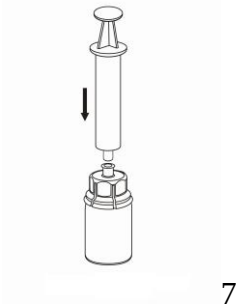
一般通則

- 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。

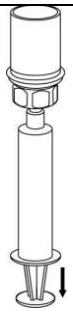
配製

- 將溶劑置於室溫下。
- 確認產品及溶劑小瓶的塑膠掀除蓋已移除，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。

 1	1.剝去上蓋以打開過濾轉注裝置包裝。**不可**將過濾轉注裝置由透明塑料包裝中取出。
 2	2. 放置稀釋劑小瓶於平整，清潔的平面上並緊握小瓶。將過濾轉注裝置連同透明塑料包裝迅速將藍色端直接向下壓入溶液劑的瓶塞中。
 3	3.小心地將透明塑料包裝由過濾轉注裝置**垂直**向上移除。確保你只有移除透明塑料包裝部份而非這個過濾轉注裝置。

 4	4.將含粉末藥瓶放置在平整、扎實的表面上，將溶液劑小瓶連同轉注裝置翻轉過來並迅速將透明轉接頭直接向下壓入藥品小瓶瓶塞中。溶液劑將會自動流入藥品小瓶中。
 5	5. 一手抓緊藥品小瓶這一邊的過濾轉注裝置組，另一手抓緊溶液劑小瓶這一邊的過濾轉注裝置組，小心地逆時針旋開本裝置成兩個部份。連同藍色轉接器接頭及溶液劑小瓶一起丟棄。
 6	6. 連同透明轉接頭一起，以手輕輕旋轉藥品小瓶，使乾粉能完全溶解。不要搖動。
 7	7. 抽取空氣進滅菌空注射針筒中。把藥瓶朝上放置，連接注射針筒與過濾轉注裝置組上的以順時針旋緊旋緊式接頭。將空氣注入藥瓶中。

抽取及應用

 8	8.保持壓緊注射針筒柱塞將整組上下反轉，緩慢地拉回柱塞將溶液抽入針筒。
 9	9. 現在溶液已經轉注到針筒裡了緊緊地抓緊注射針筒（保持注射針筒柱塞朝下）由注射針筒上以逆時針旋開，移去透明的過濾轉注器接頭。

- 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醫材進行單次輸注。

Beripex 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

8. 藥 商

傑特貝林有限公司
臺北市信義區基隆路1段333號16樓(1612室)
電話：(02)2757-6970

CSL Behring

PACKAGE LEAFLET

Read all of this leaflet carefully before you start using this medicine.
- 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. Do not pass it on to others. It may harm them, even if their symptoms are the same as yours.
- If any of the side effects gets serious, or if you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist.

Beriplex® P/N 500

Powder and solvent for solution for injection.
Active ingredient: Human prothrombin complex (PCC)

QUALITATIVE AND QUANTITATIVE COMPOSITION

Beriplex P/N 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 500 content per vial (IU)
Active Ingredients		
Human coagulation factor II	20 – 48	400 – 960
Human coagulation factor VII	10 – 25	200 – 500
Human coagulation factor IX	20 – 31	400 – 620
Human coagulation factor X	22 – 60	440 – 1200
Further active ingredients		
Protein C	15 – 45	300 – 900
Protein S	12 – 38	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.

Other ingredients
Powder:
Heparin
Human albumin
Human antithrombin III
Sodium chloride
Sodium citrate
HCl or NaOH (in small amounts for pH adjustment)
Solvent:
Water for injections

PHARMACEUTICAL FORM AND PRESENTATIONS

Pharmaceutical form
Powder and solvent for solution for injection.

Presentations
Beriplex P/N 500:
1 vacuum vial with dried substance
1 vial with 20 ml water for injections
1 filter transfer device 20/20
Beriplex P/N 250:
1 vacuum vial with dried substance
1 vial with 10 ml water for injections
1 filter transfer device 20/20

Not all pack sizes may be marketed.

PHARMACOTHERAPEUTIC GROUP

Antihaemorrhagics/Blood coagulation factors II, VII, IX and X in combination
ATC code: B02B D01

NAME AND ADDRESS OF THE MANUFACTURER AND MARKETING AUTHORISATION HOLDER

CSL Behring GmbH
Emil-von-Behring-Str. 76
35041 Marburg
Germany

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.

CONTRAINDICATIONS

Known hypersensitivity to any of the components of the product.
Risk of thrombosis, angina pectoris, recent myocardial infarction (exception: life-threatening haemorrhages following overdosage of oral anticoagulants, and before induction of fibrinolytic therapy).
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.

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 P/N 500 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 hypercoaguable 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 P/N 500 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 P/N 500 to patients with a history of coronary heart disease or myocardial infarction, to patients with liver disease, to patients 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 P/N 500 should be weighed against the potential risk of such complications. In patients with DIC and sepsis antithrombin III substitution should be considered prior to treatment with Beriplex P/N 500.
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).
When Beriplex P/N 500 is used to normalize impaired coagulation, prophylactic administration of heparin should be considered.
No data are available regarding the use of Beriplex P/N 500 in case of perinatal bleeding due to vitamin K deficiency in neonates.
Beriplex P/N 500 contains up to 343 mg sodium (approximately 15 mmol) per 100 ml. To be taken into consideration by patients on a controlled sodium diet.

Pregnancy and lactation
The safety of Beriplex P/N 500 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/foetal development, parturition or postnatal development.
Therefore, Beriplex P/N 500 should be used during pregnancy and lactation only if clearly indicated.

Virus safety
When medicines are made from human blood or plasma, certain measures are put in place to prevent infections being passed on to patients. These include:
- careful selection of blood and plasma donors to make sure those at risk of carrying infections are excluded, and
- the testing of each donation and pools of plasma for signs of virus/infections.

Manufacturers of these products also include steps in the processing of the blood or plasma that can inactivate or remove viruses. Despite these measures, when medicines prepared from human blood or plasma are administered, the possibility of passing on infection cannot be totally excluded. This also applies to any unknown or emerging viruses or other types of infections.
The measures taken are considered effective for enveloped viruses such as human immunodeficiency virus (HIV, the AIDS virus), hepatitis B virus, hepatitis C virus (inflammation of the liver), and for the non-enveloped virus hepatitis A (inflammation of the liver).
The measures taken may be of limited value against non-enveloped viruses such as parvovirus B19.
Parvovirus B19 infection may be serious
- for pregnant women (infection of the unborn child) and
- for individuals with a depressed immune system or with an increased production of red blood cells due to certain types of anaemia (e.g. sickle cell anaemia or haemolytic anaemia).

Your doctor may recommend that you consider vaccination against hepatitis A and B if you regularly/repeatedly receive human plasma-derived products.
It is strongly recommended that every time that Beriplex P/N 500 is given, your doctor should record the date of administration, the batch number and the injected volume.

INTERACTIONS WITH OTHER MEDICINAL PRODUCTS AND OTHER FORMS OF INTERACTIONS

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.

Incompatibilities
Beriplex P/N 500 must not be mixed with other medicinal products, diluents or solvents.

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 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. Individual dosage requirements 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).
The posology and method of administration in elderly people (> 65 years) is equivalent to the general recommendations.
There is no experience in children (see section "Special warnings and precautions for use").

– Treatment and perioperative prophylaxis of bleedings during vitamin K antagonist treatment.
The dose will depend on the INR before treatment and the targeted INR. In the following table approximate doses (ml/kg body weight of the reconstituted product and IU FIX/kg b.w.) required for normalisation of INR (e.g. ≤ 1.3) at different initial INR levels are given.

Initial INR	2.0 – 3.9	4.0 – 6.0	> 6.0
Approximate dose ml/kg body weight	1	1.4	2
Approximate dose IU (Factor IX)/kg body weight	25	35	50

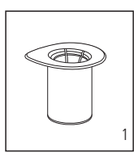
It is recommended that the maximum single dose should not exceed 5000 IU FIX.
The correction of the vitamin K antagonist-induced impairment of haemostasis is reached at the latest 30 minutes after the injection and will persist for approximately 6 – 8 hours. However, the effect of vitamin K, if administered simultaneously, is usually achieved within 4 – 6 hours. Thus, repeated treatment with human prothrombin complex is not usually required when vitamin K has been administered.
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 1.8 % (0.018 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 for each factor. 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 0.018 IU/ml.
The required dosage is determined using the following formula:
Required units = body weight [kg] x desired factor X rise [IU/ml] x 56 where 56 (ml/kg) is the reciprocal of the estimated recovery.
If the individual recovery is known, that value should be used for calculation.

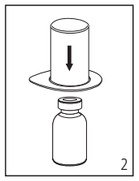
Overdose
To avoid overdosage, regular monitoring of the coagulation status is indicated during the treatment as the use of high doses of prothrombin complex concentrate (overdosage) has been associated with instances of myocardial infarction, disseminated intravascular coagulation, venous thrombosis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

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.

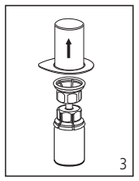
Reconstitution
Bring the solvent to room temperature. Ensure that product and solvent vial flip caps are removed and the stoppers are treated with an aseptic solution and allowed to dry prior to opening the Mix2Vial package.



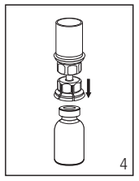
1. Open the Mix2Vial package by peeling away the lid.



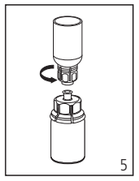
2. Place the solvent vial on an even, clean surface and hold the vial tight. Take the Mix2Vial together with the package and push the blue end straight down through the solvent stopper.



3. Carefully remove the package from the Mix2Vial set. Make sure that you only pull up the package and not the Mix2Vial set.

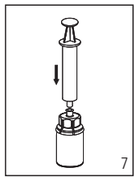


4. Place the product vial on an even and firm surface. Invert the solvent vial with the Mix2Vial set attached and push the transparent adapter straight down through the product vial stopper. The solvent will automatically flow into the product vial.



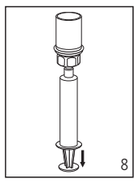
5. With one hand hold the product-side of the Mix2Vial set, hold the solvent-side with the other hand and unscrew the set into two pieces.
Discard the solvent vial with the blue part attached.

6. Gently swirl the product vial until the substance is fully dissolved. Do not shake.

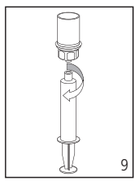


7. Draw air into an empty, sterile syringe. While the product vial is upright, connect the syringe to the Mix2Vial's Luer Lock fitting. Inject air into the product vial.

Withdrawal and application



8. While keeping the syringe plunger pressed, invert the system upside down and draw the concentrate into the syringe by pulling the plunger back slowly.



9. Now that the concentrate has been transferred into the syringe, firmly hold on to the barrel of the syringe (keeping the syringe plunger facing down) and disconnect the Mix2Vial set from the syringe.

The reconstituted solution should be administered intravenously (not more than 3 IU/kg/min, max. 210 IU/min, approximately 8 ml/min).
It has to be taken care that no blood enters the syringe filled with product, as there is a risk that the blood could coagulate in the syringe and fibrin clots would therefore be administered to the patient.
The reconstituted solution should be administered by a separate infusion line.

UNDESIRABLE EFFECTS
If you experience reactions, especially those which are not mentioned in this package leaflet, please inform your doctor or pharmacist.
The following adverse reactions are based on post marketing experience as well as scientific literature. The following standard categories of frequency are used:
Very common: ≥ 1/10
Common: ≥ 1/100 and < 1/10
Uncommon: ≥ 1/1,000 and < 1/100
Rare: ≥ 1/10,000 and < 1/1,000
Very rare: < 1/10,000 (including reported single cases)
Renal and urinary disorders:
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.
Vascular disorders:
There is a risk of thromboembolic episodes following the administration of human prothrombin complex (see section "Special warnings and precautions for use").
General disorders and administration site conditions:
Increase in body temperature is observed in very rare cases.
Immune system disorders:
Hypersensitivity or allergic reactions (which may include angioedema, burning and stinging at the injection site, chills, flushing, generalized urticaria, headache, hives, hypotension, lethargy, nausea, restlessness, tachycardia, angina pectoris, tingling, vomiting or wheezing) have been observed very rarely in patients treated with factor IX containing products. In some cases, these reactions have progressed to severe anaphylaxis, and they have occurred in close temporal association with development of factor IX inhibitors (see section "Special warnings and precautions for use").
If allergic-anaphylactic reactions occur, the administration of Beriplex P/N 500 has to be discontinued immediately (e.g. discontinue injection) and an appropriate treatment has to be initiated (see section "Special warnings and precautions for use").
Development of antibodies to one or several factors of the prothrombin complex may occur in very rare cases. 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.
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).
For safety with regard to transmissible agents, see section "Special warnings and precautions for use".

STORAGE AND STABILITY
Do not store above 25 °C. Do not freeze.
Keep the vial in the outer carton, in order to protect from light.
Beriplex P/N 500 must not be used after the expiry date given on the pack and container.
After reconstitution, from a microbiological point of view and as Beriplex P/N 500 contains no preservative, the reconstituted product should be used immediately. The physico-chemical stability has been demonstrated for 24 hours at room temperature (max. 25 °C). However, if it is not administered immediately, storage shall not exceed 8 hours at room temperature.
Any unused product or waste material should be disposed of in accordance with local requirements.

Keep out of the reach and sight of children.

DATE OF LAST REVISION
July 2011