CSL Behring

愛必凝基因工程第九凝血因子注射劑250國際單位
IDELVION 250 IU 衛部菌疫輸字第001059號

愛必凝基因工程第九凝血因子注射劑500國際單位
IDELVION 500 IU 衛部菌疫輸字第001060號

愛必凝基因工程第九凝血因子注射劑1000國際單位/2000國際單位
IDELVION 1000 IU/ 2000IU 衛部菌疫輸字第001061號

本藥限由醫師使用

1. 藥品名稱

IDELVION 250 IU，粉末及注射用溶液之溶劑
IDELVION 500 IU，粉末及注射用溶液之溶劑
IDELVION 1000 IU，粉末及注射用溶液之溶劑
IDELVION 2000 IU，粉末及注射用溶液之溶劑

2. 定性及定量組成

IDELVION 250 IU，粉末及注射用溶液之溶劑

一個藥瓶依標示含有250 IU的連結第九凝血因子與白蛋白的重組融合蛋白質(rIX-FP) (國際通用名[INN] = albutrepenonacog alfa)。使用2.5 ml注射用水配製之後，溶液含有100 IU/ml的albutrepenonacog alfa。

IDELVION 500 IU，粉末及注射用溶液之溶劑

一個藥瓶依標示含有500 IU的連結第九凝血因子與白蛋白的重組融合蛋白質(rIX-FP) (INN = albutrepenonacog alfa)。使用2.5 ml注射用水配製之後，溶液含有200 IU/ml的albutrepenonacog alfa。

IDELVION 1000 IU，粉末及注射用溶液之溶劑

一個藥瓶依標示含有1000 IU的連結第九凝血因子與白蛋白的重組融合蛋白質(rIX-FP) (INN = albutrepenonacog alfa)。使用2.5 ml注射用水配製之後，溶液含有400 IU/ml的albutrepenonacog alfa。

IDELVION 2000 IU，粉末及注射用溶液之溶劑

一個藥瓶依標示含有2000 IU的連結第九凝血因子與白蛋白的重組融合蛋白質(rIX-FP) (INN = albutrepenonacog alfa)。使用5 ml注射用水配製之後，溶液含有400 IU/ml的albutrepenonacog alfa。

效價(國際單位[IU])使用以體外活化部分凝血活酶時間(aPTT)為基礎的單步驟凝血分析法進行判定，並對照世界衛生組織(WHO)第九凝血因子濃縮液國際標準進行校正。

Albutrepenonacog alfa是一種利用重組去氧核糖核酸(DNA)技術製作的純蛋白質，將重組白蛋白和重組第九凝血因子進行基因融合所產生。人類白蛋白的互補去氧核糖核酸(cDNA)和人類第九凝血因子的互補去氧核糖核酸進行基因融合，能夠以單一重組蛋白質方式產生蛋白質，並透過避免化學接合作用而確保成品的均一性。重組第九凝血因子的部分，與血漿衍生之第九凝血因子的Thr148等位基因型相同。重組第九凝血因子與白蛋白分子之間的可裂解連接子，是衍生自天然第九凝血因子的內生性「活化肽鏈」。

已知作用的賦形劑：

每劑鈉最多25.8毫克(1.13 mmol) (體重70公斤)。

完整賦形劑列表，請參閱第6.1節。

3. 藥物劑型

注射溶液用粉劑及溶劑。

淡黃色至白色粉末及澄清、無色注射用溶液之溶劑。

pH：6.6 - 7.2

滲透壓：

IDELVION 250 IU，粉末及注射用溶液之溶劑
175 – 215 mOsm/kg。
IDELVION 500 IU，粉末及注射用溶液之溶劑
260 – 300 mOsm/kg。
IDELVION 1000 IU，粉末及注射用溶液之溶劑
260 – 300 mOsm/kg。
IDELVION 2000 IU，粉末及注射用溶液之溶劑
260 – 300 mOsm/kg。

4. 臨床使用細節

4.1 適應症

適用於預防及治療B型血友病患者(先天性第九凝血因子缺乏症)之出血，包括接受外科手術時出血的控制與預防。

4.2 劑量及用法

應在有治療B型血友病經驗的醫師監督下進行治療。

先前未曾接受過治療之患者

目前尚未建立先前未曾接受過治療之患者使用IDELVION的安全性與療效。

治療監測

治療過程期間，建議適當測量第九凝血因子濃度以指引給藥劑量及重複輸注的頻率。個別患者對於第九凝血因子的反應可能有所差異，而表現出不同的半衰期和回復率。依照體重給藥時，未達或超過正常體重的患者可能需要調整劑量。特別是在重大手術介入治療的情況下，使用凝血分析方式(血漿第九凝血因子活性)精準監測替代療法是不可或缺的。

當使用以體外凝血活酶時間(aPTT)為基礎的單步驟凝血分析法來判斷患者血液檢體中第九凝血因子活性時，血漿第九凝血因子活性結果會顯著受到aPTT試劑類型及分析所用之參照標準的影響。當使用含高嶺土(Kaolin)之aPTT試劑或Actin FS aPTT試劑的單步驟凝血分析法測量時，將可能造成活性濃度被低估，這在變更實驗室和／或分析所使用之試劑時特別重要。

劑量

替代療法的劑量和持續時間取決於第九凝血因子缺乏的嚴重程度、出血的部位和程度，以及患者的臨床狀況。

給予第九凝血因子的單位數以國際單位(IU)表示，這與現行WHO的第九凝血因子藥品標準有關。血漿中第九凝血因子活性以百分比(相對於正常人體血漿)或國際單位(相對於血漿中第九凝血因子國際標準)表示。

一國際單位(IU)的第九凝血因子活性相當於一毫升正常人體血漿中第九凝血因子的量。

需要時治療

計算第九凝血因子的所需劑量，是基於臨床經驗發現的結果，以每公斤體重1國際單位(IU)第九凝血因子預期可增加第九凝血因子循環濃度，在≥ 12歲患者平均增加1.3 IU/dl (正常值的1.3 %)及< 12歲患者增加1.0 IU/dl (正常值的1.0 %)。使用下列公式判定所需劑量：

所需劑量(IU) = 體重(公斤) x 預計提升的第九凝血因子(正常值的%或IU/dl) x {已觀察到回復率的倒數(IU/kg每IU/dl)}

預計提升的第九凝血因子(IU/dl或正常值%) = 劑量(IU) x 回復率(IU/dl每IU/kg) / 體重(公斤)

投與的劑量及給藥頻率需依個別案例的臨床效果而定。

患者< 12歲

對於1 IU/dl每1 IU/kg的增量回復率，劑量計算方式為：

劑量(IU) = 體重(公斤) x 預計增加的第九凝血因子(IU/dl) x 1 dl/kg

範例

1. 體重20公斤的重度B型血友病患者，需要最高濃度為正常值的50%。適當劑量應為20公斤 x 50 IU/dl x 1 dl/kg = 1000 IU。
2. 給予25公斤患者劑量為1000 IU的IDELVION時，應預期可產生注射後第九凝血因子最高濃度增加為1000 IU/25公斤 x 1.0 (IU/dl每IU/kg) = 40 IU/dl (正常值的40 %)。

患者≥ 12歲

對於1.3 IU/dl每1 IU/kg的增量回復率，劑量計算方式為：

劑量(IU) = 體重(公斤) x 預計增加的第九凝血因子(IU/dl) x 0.77 dl/kg

範例

3. 體重80公斤的重度B型血友病患者，需要最高濃度為正常值的50%。適當劑量應為80公斤 x 50 IU/dl x 0.77 dl/kg = 3080 IU。
4. 給予80公斤患者劑量為2000 IU的IDELVION時，應預期可產生注射後第九凝血因子最高濃度增加為2000 IU x 1.3 (IU/dl每IU/kg) / 80公斤 = 32.5 IU/dl (正常值的32.5 %)。

在下列出血事件情況中，第九凝血因子活性不應下降到低於在相對應時期所設定的血漿活性濃度(正常值%或IU/dl)。下表可作為出血症狀及手術時之控制及預防出血的劑量指導原則：

出血程度／手術類型	第九凝血因子所需濃度(%) (IU/dl)	給藥頻率(小時)／治療持續時間(天)
出血 輕度或中度關節血腫、肌肉出血(不包括髂腰肌)或口腔出血	30 - 60	對於大多數出血單次劑量應可足夠。如果有進一步出血跡象，24–72小時之後給予維持劑量。
重度 可能致命的出血、深層肌肉出血(包括髂腰肌)	60 - 100	第一週可每24–72小時重複給予，接著每週給予維持劑量，直到出血停止且達到癒合。
小型手術 包括簡單拔牙	50 - 80 (初始濃度)	對於大多數小型手術單次劑量應可足夠。若需要，24–72小時之後可給予維持劑量，直到出血停止且達到癒合。
大型手術	60 - 100 (初始濃度)	第一週可每24–72小時重複給予，接著每週給予1–2次維持劑量，直到出血停止且達到癒合。

常規預防

患者≧12歲：常規預防重度B型血友病患者的出血時，建議療程為每週一次35至50 IU/kg。每週一次療程可穩定控制者，部分病人可能可更換療程至每14天一次，每次50-75 IU/kg。

患者< 12歲： 常規預防的建議療程為每週一次35至50 IU/kg。

在有些案例中，特別是較年輕的患者可能有必要使用較短的給藥間隔時間或較高劑量。

常規預防期間出血發作之後，患者應盡可能密切維持他們的預防性治療療程，給予2劑IDELVION之間至少間隔24小時，但適合患者時可間隔較長時間。

用法

靜脈注射使用。

本藥品給藥前的配製指示，請參閱第6.6節。已配製藥劑應以患者感覺舒適的速度，緩慢進行靜脈注射，速度最高5 ml/min。

4.3 禁忌症

對有效成分（連結第九凝血因子與白蛋白的重組融合蛋白質(rIX-FP)）或列於第6.1節的任何賦形劑過敏。

已知對倉鼠蛋白質有過敏反應。

4.4 特殊警語及使用注意事項

過敏

使用IDELVION可能發生過敏類型的過敏反應，本藥品含微量倉鼠蛋白質。如果發生過敏症狀，應建議患者立即停用本藥品並聯絡其醫師。應告知患者過敏反應的早期徵象，包括蕁麻疹、全身性蕁麻疹、胸悶、喘鳴、低血壓及全身型過敏反應(anaphylaxis)。建議應依據主治醫師的判斷，在能夠針對過敏反應提供適當醫療照護的醫療觀察下，執行第九凝血因子的初次給藥。

如果發生休克，應予以施行休克的標準醫藥治療。

抑制因子(Inhibitors)

已有報導在使用IDELVION作為替代療法治療B型血友病患者期間生成對第九凝血因子之抑制因子。使用人類第九凝血因子藥品重複治療之後，應監測患者是否產生中和抗體(抑制因子)，使用適當的生物檢驗以Bethesda Units (BU)加以量化。

目前已有文獻報告顯示第九凝血因子抑制因子的出現與過敏反應之間有相關性。因此，出現過敏反應的患者應評估是否有抑制因子。應該注意的是，有第九凝血因子抑制因子的患者於後續使用第九凝血因子時，可能會增加全身型過敏反應的風險。

因為使用第九凝血因子藥品有發生過敏反應的風險，應依據主治醫師的判斷，在能夠針對過敏反應提供適當醫療照護的醫療觀察下，執行第九凝血因子的初次給藥。

血栓栓塞

因為有血栓併發症的潛在風險，讓患有肝臟疾病患者、手術後患者、新生嬰兒，或是有血栓或瀰漫性血管內凝血(DIC)風險的患者使用本藥品時，應採取適當的生物檢驗，進行血栓及消耗性凝血病變早期徵象的臨床監視。針對在這些情況中的每一項，使用IDELVION治療的效益及這些併發症的風險應進行衡量。

心血管事件

對於有既存心血管風險因子的患者，使用第九凝血因子的替代療法可能增加心血管風險。

導管相關併發症

如果需要放置中心靜脈導管裝置(CVAD)，應考量CVAD相關併發症，包括局部感染、菌血症及導管部位血栓。

兒童族群

所列之警語與注意事項皆適用成年人和兒童。

老年人

IDELVION的臨床試驗並未納入65歲以上的受試者，目前未知他們的反應是否和較年輕的受試者不同。

免疫耐受誘導療法(Immune tolerance induction)

使用IDELVION作為免疫耐受誘導療法的安全性和療效目前尚未確立。

鈉含量

如果使用最高劑量(15毫升 = 6000 IU)，本藥品每劑含鈉最多25.8毫克(1.13 mmol) (體重70公斤)。對於控制鈉飲食的患者應列入考量。

使用記錄

強烈建議每次給予患者使用IDELVION時，應記錄藥品名稱和批號，以便保持患者和藥品批號之間的聯結。

4.5 和其他藥品的交互作用及其他交互作用形式

目前沒有人類第九凝血因子藥品與其他藥品之交互作用的報告。

4.6 生育能力、懷孕與授乳

第九凝血因子目前尚未進行動物生殖研究。基於女性發生B型血友病的情形罕見，目前還沒有關於懷孕與授乳期間使用第九凝血因子的經驗。

因此，只有絕對必要時，才可在懷孕與授乳期間使用第九凝血因子。

目前沒有第九凝血因子對生育能力影響的資訊。

4.7 對駕駛和操作機械能力的影響

IDELVION目前尚未觀察到對於駕駛和機械操作能力之影響。

4.8 不良反應

安全性特性摘要

目前已觀察到罕見的過敏或過敏反應(可能包括血管性水腫、輸注部位燒灼感及刺痛、發冷、潮紅、全身性蕁麻疹、頭痛、蕁麻疹、低血壓、萎靡嗜睡、噁心、煩亂不安、心搏過速、胸悶、針刺感、嘔吐、喘鳴)，而且在部分案例可能惡化為嚴重全身型過敏反應(包括休克)。在部分案例中，這些反應可能惡化成嚴重全身型過敏反應而且和第九凝血因子抑制因子的產生有密切時間關聯性(請參閱第4.4節)。曾有對已產生第九凝血因子抑制因子且具過敏反應病史的B型血友病患者嘗試進行免疫耐受誘導療法後，發生腎病症候群之報告。

使用從中國倉鼠卵巢(CHO)細胞取得之第九凝血因子藥品，已觀察到極罕見對倉鼠蛋白質產生抗體。

B型血友病患者可能對第九凝血因子產生中和抗體(抑制因子)。若形成這類抑制因子，將呈現為臨床反應不足的情況。在此情況下，建議與專業血友病中心聯繫。有報導在一項持續進行之臨床試驗中，未曾接受過治療之患者形成抑制因子。在IDELVION上市後使用經驗發現，曾接受過治療患者形成抑制因子。

給予第九凝血因子藥品之後有血栓栓塞發作的潛在風險，以低純度製劑有較高風險。使用低純度第九凝血因子藥品已發現與下列狀況有相關性：心肌梗塞、瀰漫性血管內凝血、靜脈栓塞及肺栓塞。使用高純度第九凝血因子藥品則罕見和這些不良反應相關。

不良反應列表

四項開放性臨床試驗中，至少投與一次IDELVION之107名受試者，共7名受試者通報13件不良反應。

下表依據《國際醫學用語詞典》(MedDRA)系統器官分類(SOC及Preferred Term Level)。

發生頻率已依據下列慣例進行評估：極常見(≥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)、極罕見(<1/10,000)、未知(無法從現有資料進行估計)。

每項頻率分組中，以嚴重度遞減的方式呈現不良反應。

《國際醫學用語詞典》(MedDRA)標準系統器官分類	不良反應	依據患者的頻率
血液與淋巴異常	第九凝血因子抑制/抑制因子生成	未知
全身性異常和給藥部位狀況	注射部位反應	常見
神經系統異常	頭痛	常見
	頭暈	少見
免疫系統異常	過敏	少見
皮膚和皮下組織異常	皮疹	少見
	濕疹	少見

特定不良反應說明

於進行中的臨床試驗，一名先前未曾接受過治療之患者(PUP)對第九凝血因子產生高效價抑制因子。目前沒有充分資料可提供先前未曾接受過治療之患者的抑制因子發生率資訊。

兒童族群

兒童的不良反應頻率、類型及嚴重度預期與成年人相似。

疑似不良反應之通報

上市後通報藥品疑似之不良反應是重要的，其可持續監測藥品利益／風險間的平衡。醫護專業人員應通報任何疑似的不良反應。

4.9 過量

目前尚無使用IDELVION過量的症狀被報告。

5. 藥理學特性

5.1 藥效學特性

藥理治療分類：抗出血劑：血液第九凝血因子。

ATC code：B02BD04

作用機轉

IDELVION (INN: albutrepenonacog alfa)是一種重組第九凝血因子，通過與重組白蛋白融合可達到延長IDELVION的半衰期並提升全身暴露量。白蛋白為血漿中天然的非活性載體蛋白質，其半衰期約為20天。重組第九凝血因子與白蛋白的基因融合延長了第九凝血因子的半衰期(請參閱第5.2節)。

IDELVION在循環中保持非活性，直到第九凝血因子受到活化，因此需要用於凝血的時候會與白蛋白分離，釋放出已活化的第九凝血因子(FIXa)。

藥效學作用

B型血友病是一種性聯遺傳、由於第九凝血因子濃度減少而造成的凝血障礙，因自發性或是意外或手術創傷而導致關節、肌肉或內部器官大量出血。藉由替代療法可增加血漿第九凝血因子濃度，因而能夠暫時性矯正凝血因子缺乏和出血傾向。

第九凝血因子的活化是透過外在路徑的第七凝血因子／組織因子複合物，以及內在凝血路徑的XIa凝血因子。已活化的第九凝血因子與已活化的第八凝血因子結合可活化第十凝血因子，最後可將凝血酶原轉化成凝血酶。凝血酶接著將纖維蛋白原轉化成纖維蛋白因而形成血塊。B型血友病患者因第九凝血因子活性缺乏或大幅減少，可能需要進行替代療法。

臨床療效及安全性

一項第1/2期試驗針對17名受試者(年齡13-46歲)評估rIX-FP對出血事件的治療療效和預防，其中13名受試者為預防性治療組，每週接受IDELVION預防性治療持續約11個月；4名受試者為需求治療組，於出血事件發生時接受IDELVION治療。於所有85次出血事件中以1劑或2劑IDELVION均可治療成功。

IDELVION的療效經一項第2/3期開放性、未具對照組之試驗進行評估，總計63名男性之曾接受過治療患者(PTPs)，年齡為12至61歲之間，接受IDELVION每隔7天、10天和／或14天一次的預防性治療，和／或依據需求作為出血事件的治療。所有受試者患有重度(FIX濃度<1%)或中度(FIX濃度≤2%) B型血友病，其中有40名PTPs接受IDELVION的預防性治療。

受試者接受預防性治療的起始劑量為每週一次35-50 IU/kg，這當中有一組子群患者改為延長的治療間隔時間(每10天或14天)，使用建議劑量75 IU/kg並依據個別調整。21名PTPs在額外治療期間之98至575 (中位數386)天中，持續接受延長的每14天一次預防性治療。在那些受試者中，有8名(38%)受試者在每14天預防性治療期間中至少發生一次出血，而在每週預防性治療期間中並沒有發生出血事件。使用IDELVION的每七天預防性治療，針對所有出血症狀的年出血率(ABR)中位數為0.0 (範圍0-6)，而每14天預防性治療之ABR為1.08 (範圍0-9.1)。雖然相較於每週一次療程，延長治療間隔時間可能與出血風險增加有關，但目前可知資訊支持部分患者延長治療間隔時間。

值得注意的是，在不同因子濃度之間，以及不同臨床試驗之間的ABR是無法比較的。

未滿12歲PTPs的預防性治療及出血控制

IDELVION的療效已在一項第3期試驗進行評估，總計27名男性之PTPs，年齡1至10歲之間(中位數年齡6.0歲)，其中有12名<6歲的患者，接受IDELVION作為預防性治療及出血事件的控制。全部27名受試者接受IDELVION每週一次預防性治療，平均試驗時間為13.1個月(9，18個月)。

在106次出血事件中，大多數事件(94；88.7%)使用單次注射治療，103次；97.2%的事件使用1-2次注射治療。出血緩解後，96%出血事件之止血效果評估為優異或良好。

目前正在進行評估大於每週一次之治療間隔時間的安全性和療效的臨床試驗。

手術前後期間處置

手術前後期間之安全性和療效，已在兩項第3期樞紐試驗(Study 3001, 3002)，以及目前進行中的第3期安全性延伸試驗(Study 3003)中進行評估。依計劃書之療效分析中包含12名年齡介於8-51歲的患者所進行的15次手術，手術類型包含重大或小型手術、牙科或其他外科侵入性程序。

IDELVION以靜脈大量輸注(bolus injection)方式給藥。

整個試驗期間維持止血。

小兒族群

歐洲藥品管理局已延遲要求提供針對使用IDELVION在之前未曾治療之患者，進行B型血友病出血治療及預防性治療之試驗結果(小兒使用資訊請參閱第 4.2 節)。

5.2 藥物動力學特性

成人族群

IDELVION的藥物動力學(PK)是經由靜脈注射單次劑量25、50和75 IU/kg評估。單次注射50 IU/kg IDELVION之後的藥物動力學參數(請參閱下表)是依據單步驟凝血分析所測量的血漿第九凝血因子活性而定。使用單劑量50 IU/kg IDELVION之後，第7天和第14天的平均第九凝血因子活性分別為13.76%和6.10%。重複藥物動力學評估持續達30週，顯示穩定的藥物動力學特性及經過一段時間的增量回復率保持一致。

接受預防性治療時為達到出血控制，在臨床試驗中以最低濃度5-10%為目標。藥物動力學模擬顯示單次注射50 IU/kg IDELVION之後，成年人血漿FIX活性達到5%的時間為12.5天。

重度血友病受試者於單次注射50 IU/kg IDELVION後的藥物動力學參數（中位數(最小值，最大值)）

藥物動力學參數	IDELVION（50 (IU/kg)）(N=22)
IR (IU/dl) / (IU/kg)	1.18 (0.86, 1.86)
最高血中濃度(C_{max}) (IU/dl)	62.7 (40.5, 87.0)
AUC_{0-inf} (h*IU/dl)	6638 (2810, 9921)
Elimination $t_{1/2}$ (小時[h])	95.3 (51.5, 135.7)
CL (ml/h/kg)	0.875 (0.748, 1.294)

IR = 增量回復率；AUC = 第九凝血因子活性時間曲線下面積；CL = 經體重調整之清除率；Elimination $t_{1/2}$ = 排除半衰期

小兒族群

在青少年(12至<18歲)及兒童(1至<12歲)接受靜脈注射單次劑量50 IU/kg之後，評估IDELVION的藥物動力學參數。藥物動力學參數(如下列)估計值是依據單步驟凝血分析所測量的血漿第九凝血因子活性之時間輪廓。

單次注射50 IU/kg IDELVION之後，比較依據年齡類別的IDELVION藥物動力學參數（中位數(最小值，最大值)）

藥物動力學參數	1至未滿6歲 (N=12)	6至未滿12歲 (N=15)	12至未滿18歲 (N=5)
IR (IU/dl) / (IU/kg)	0.968 (0.660, 1.280)	1.07 (0.70, 1.47)	1.11 (0.84, 1.61)
最高血中濃度(C_{max}) (IU/dl)	48.2 (33.0, 64.0)	50.5 (34.9, 73.6)	55.3 (40.5, 80.3)
AUC_{0-inf} (h*IU/dl)	4301 (2900, 8263)	4718 (3212, 7720)	4804 (2810, 9595)
Elimination $t_{1/2}$ (小時[h])	86.2 (72.6, 105.8)	89.3 (62.1, 123.0)	88.8 (51.5, 130.0)
CL (ml/h/kg)	1.16 (0.61, 1.72)	1.06 (0.65, 1.56)	1.04 (0.52, 1.67)

IR = 增量回復率；AUC = 第九凝血因子活性時間曲線下面積；CL = 經體重校正清除率；Elimination $t_{1/2}$ = 排除半衰期

接受預防性治療時為達到出血控制，在臨床試驗中以最低濃度5-10%為目標。藥物動力學模擬顯示單次注射50 IU/kg IDELVION之後，血漿FIX活性藥達到5%的時間，1-<6歲者為7天、6-<12歲者為9天、12-<18歲者為11天。

5.3 臨床前安全性資料

非臨床數據根據傳統安全藥理學、單次及重複劑量毒性、基因毒性、血栓形成能力及局部耐受性研究結果顯示本藥品對人類無特殊危害。

目前尚未執行關於致癌性及生殖毒性的研究。

6. 產品資訊

6.1 賦形劑清單

粉末：

檸檬酸三鈉(Tri-sodium citrate dihydrate)、聚山梨醇酯80 (Polysorbate 80)、甘露醇(Mannitol)、蔗糖(Sucrose)、鹽酸(用於調整pH值)。

溶劑：

注射用水

6.2 不相容性

由於缺乏相容性研究，因此本藥品不可與除第6.1節中所提及之外的其他藥品、稀釋劑或溶劑混合。

6.3 效期

IDELVION 250 IU，粉末及注射用溶液之溶劑
3年
IDELVION 500 IU，粉末及注射用溶液之溶劑
3年
IDELVION 1000 IU，粉末及注射用溶液之溶劑
3年
IDELVION 2000 IU，粉末及注射用溶液之溶劑
3年

配製溶液後，物理化學的使用安定性已被證實可在2-25°C下維持8小時。以微生物觀點來看，本藥品應立即使用。如果未立即使用，則使用前的存放時間和條件在室溫下(低於25°C)不應超過4小時。

6.4 儲存的特殊注意事項

儲存溫度勿超過25°C。

請勿冷凍。將藥瓶裝於外盒中，避免光線直射。

有關本藥品配製後的儲存條件，請參閱第6.3節。

6.5 容器材質和內容物

IDELVION 250 IU，粉末及注射用溶液之溶劑

粉末(250 IU)裝於6 ml小瓶(Type I glass)，與瓶塞(橡膠)、圓盤(塑膠)和瓶蓋(鋁)。

2.5 ml溶劑裝於小瓶中(Type I glass)，與瓶塞(橡膠)、圓盤(塑膠)和瓶蓋(鋁)。

IDELVION 500 IU，粉末及注射用溶液之溶劑

粉末(500 IU)裝於6 ml小瓶(Type I glass)，與瓶塞(橡膠)、圓盤(塑膠)和瓶蓋(鋁)。

2.5 ml溶劑裝於小瓶中(Type I glass)，與瓶塞(橡膠)、圓盤(塑膠)和瓶蓋(鋁)。

IDELVION 1000 IU，粉末及注射用溶液之溶劑

粉末(1000 IU)裝於6 ml小瓶(Type I glass)，與瓶塞(橡膠)、圓盤(塑膠)和瓶蓋(鋁)。

2.5 ml溶劑裝於小瓶中(Type I glass)，與瓶塞(橡膠)、圓盤(塑膠)和瓶蓋(鋁)。

IDELVION 2000 IU，粉末及注射用溶液之溶劑

粉末(2000 IU)裝於10 ml小瓶(Type I glass)，與瓶塞(橡膠)、圓盤(塑膠)和瓶蓋(鋁)。

5 ml溶劑裝於小瓶中(Type I glass)，與瓶塞(橡膠)、圓盤(塑膠)和瓶蓋(鋁)。

說明

每個包裝內含：

IDELVION 250 IU，粉末及注射用溶液之溶劑
1產品小瓶
1溶劑小瓶(2.5 ml注射用水)
1個過濾轉注裝置20/20
一 個內盒包裝內含：
1個拋棄式5 ml注射針筒
1組靜脈穿刺組
2片酒精棉片
1片非無菌貼布

IDELVION 500 IU，粉末及注射用溶液之溶劑
1產品小瓶
1溶劑小瓶(2.5 ml注射用水)
1個過濾轉注裝置20/20
一個內盒包裝內含：
1個拋棄式5 ml注射針筒
1組靜脈穿刺組
2片酒精棉片
1片非無菌貼布

IDELVION 1000 IU，粉末及注射用溶液之溶劑
1產品小瓶
1溶劑小瓶(2.5 ml注射用水)
1個過濾轉注裝置20/20
一個內盒包裝內含：
1個拋棄式5 ml注射針筒
1組靜脈穿刺組
2片酒精棉片
1片非無菌貼布

IDELVION 2000 IU，粉末及注射用溶液之溶劑
1產品小瓶
1溶劑小瓶(5 ml注射用水)
1個過濾轉注裝置20/20
一個內盒包裝內含：
1個拋棄式10 ml注射針筒
1組靜脈穿刺組
2片酒精棉片
1片非無菌貼布

並非所有包裝規格皆會銷售。

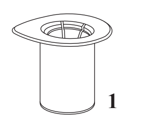
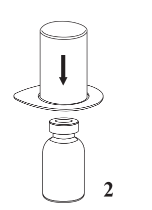
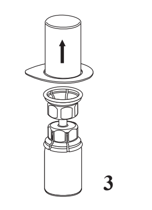
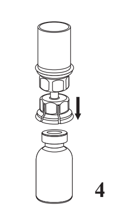
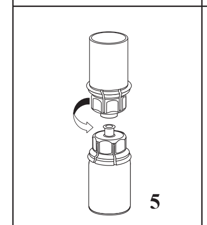
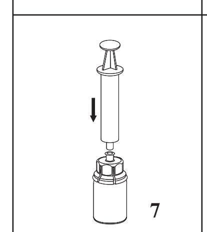
6.6 丟棄與其他處理的特殊注意事項

一般指示說明

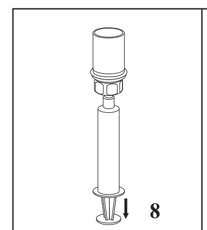
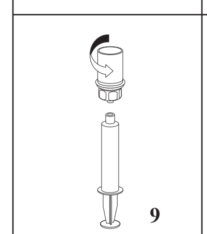
- 配製好的溶液應為清澈或些微乳白色、黃色至無色。過濾／抽取之後(參閱下圖)，給藥之前應以肉眼檢查已配製藥品是否有微粒物質及變色。
- 請勿使用混濁或有沉澱物的溶液。
- 必須在無菌條件下進行配製及抽取。

配製

將溶劑回溫至室溫(25°C之下)。確保產品及溶劑小瓶移去掀蓋，在打開過濾轉注裝置(Mix2Vial)包裝前，以抗菌溶液消毒兩小瓶之瓶塞表面並待乾燥。

 1	1. 剝去上蓋以打開Mix2Vial包裝。**請勿**將Mix2Vial由透明塑料包裝中取出！
 2	2. 請將**溶劑小瓶**放在平整、清潔的表面上，並緊握小瓶。一併拿起Mix2Vial及透明塑料包裝，將**藍色**轉接頭末端**垂直向下**壓入溶劑小瓶的瓶塞中。
 3	3. 小心握住邊緣將透明塑料包裝由Mix2Vial套組**垂直向上**移除。確保您只有移除透明塑料包裝部份，而非Mix2Vial套組。
 4	4. 將**產品小瓶**放在平整而穩固的表面。將溶劑小瓶連同Mix2Vial套組翻轉過來，並將**透明**轉接器末端穿刺針**直接向下**壓入產品小瓶瓶塞中。溶劑將會自動流進產品小瓶中。
 5	5. 一手抓緊Mix2Vial套組的產品小瓶端，另一手抓緊溶劑小瓶端，小心地以逆時針方向將套組轉開成兩部分。 丟棄附有藍色Mix2Vial轉接器接頭的溶劑小瓶。
 6	6. 輕輕轉動附有透明轉接頭的產品小瓶，直到成分完全溶解。請勿搖動。
 7	7. 抽取空氣進滅菌空注射針筒中。將產品小瓶朝上放置，以順時針旋轉將注射器連接Mix2Vial的Luer Lock裝置。將空氣注入產品小瓶中。

抽取及應用

 8	8. 保持壓緊注射針筒柱塞將整組上下反轉，緩慢拉回柱塞將溶液抽入針筒。
 9	9. 現在溶液已經轉注至針筒中，緊緊握住注射針筒(保持注射針筒柱塞朝下)，並以逆時針旋轉將透明的Mix2Vial轉接頭從注射針筒上移除。

注射IDELVION應只使用所提供之給藥套組，因為部分注射裝置的內部表面會吸收第九凝血因子，進而可能造成治療失敗。

應小心注意不讓血液進入裝有產品的注射針筒，因為會有血液可能在注射器針筒內凝結，並因而可能使纖維蛋白血塊注射至病患體內的風險。

IDELVION溶液不可以進行稀釋。

已配製的溶液應以緩慢靜脈內注射方式給予。給藥速度應依患者的舒適程度進行判斷，最高至5 ml/min。

任何未使用的藥品或廢棄物應根據當地規定丟棄。

7. 製造廠：

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

8. 藥商：傑特貝林有限公司

地址：臺北市信義區基隆路1段333號16樓(1612室)
電話：(02)2757-6970

9. 最後更新日期

2019年11月

CSL Behring

IDELVION 250 IU MoHW-Biologics-Import-Reg. No. 001059
IDELVION 500 IU MoHW-Biologics-Import-Reg. No. 001060
IDELVION 1000 IU/ 2000IU MoHW-Biologics-Import-Reg. No. 001061

This medicine is only prescribed by physician.

1. NAME OF THE MEDICINAL PRODUCT

IDELVION 250 IU powder and solvent for solution for injection
IDELVION 500 IU powder and solvent for solution for injection
IDELVION 1000 IU powder and solvent for solution for injection
IDELVION 2000 IU powder and solvent for solution for injection

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

IDELVION 250 IU powder and solvent for solution for injection
One vial contains nominally 250 IU of recombinant fusion protein linking coagulation factor IX with albumin (rIX-FP), (INN = albutrepenonacog alfa). After reconstitution with 2.5 ml water for injections the solution contains 100 IU/ml of albutrepenonacog alfa.

IDELVION 500 IU powder and solvent for solution for injection
One vial contains nominally 500 IU of recombinant fusion protein linking coagulation factor IX with albumin (rIX-FP), (INN = albutrepenonacog alfa). After reconstitution with 2.5 ml water for injections the solution contains 200 IU/ml of albutrepenonacog alfa.

IDELVION 1000 IU powder and solvent for solution for injection
One vial contains nominally 1000 IU of recombinant fusion protein linking coagulation factor IX with albumin (rIX-FP), (INN = albutrepenonacog alfa). After reconstitution with 2.5 ml water for injections the solution contains 400 IU/ml of albutrepenonacog alfa.

IDELVION 2000 IU powder and solvent for solution for injection
One vial contains nominally 2000 IU of recombinant fusion protein linking coagulation factor IX with albumin (rIX-FP), (INN = albutrepenonacog alfa). After reconstitution with 5 ml water for injections the solution contains 400 IU/ml of albutrepenonacog alfa.
The potency (International Units [IU]) is determined using an in-vitro activated partial thromboplastin time (aPTT)-based one-stage clotting assay calibrated against the World Health Organization (WHO) International Standard for factor IX concentrate.
Albutrepenonacog alfa is a purified protein produced by recombinant DNA technology, generated by the genetic fusion of recombinant albumin to recombinant coagulation factor IX. The genetic fusion of the cDNA of human albumin to the cDNA of human coagulation factor IX enables the protein to be produced as a single recombinant protein and assures product homogeneity by avoiding chemical conjugation. The recombinant factor IX portion is identical to the Thr148 allelic form of plasma derived factor IX. The cleavable linker between the recombinant factor IX and albumin molecules is derived from the endogenous "activation peptide" in native factor IX.
Excipient with known effect:
Up to 25.8 mg (1.13 mmol) sodium per dose (bodyweight 70 kg).
For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Powder and solvent for solution for injection.
Pale yellow to white powder and clear, colourless solvent for solution for injection.

pH: 6.6 - 7.2
Osmolality:
IDELVION 250 IU powder and solvent for solution for injection
175 – 215 mOsm/kg.
IDELVION 500 IU powder and solvent for solution for injection
260 – 300 mOsm/kg
IDELVION 1000 IU powder and solvent for solution for injection
260 – 300 mOsm/kg.
IDELVION 2000 IU powder and solvent for solution for injection
260 – 300 mOsm/kg.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Treatment and prophylaxis of bleeding in patients with haemophilia B (congenital factor IX deficiency) including control and prevention of bleeding in surgical settings.

4.2 Posology and method of administration

Treatment should be under the supervision of a physician experienced in the treatment of haemophilia B.

Previously untreated patients
The safety and efficacy of IDELVION in previously untreated patients have not yet been established.

Treatment monitoring
During the course of treatment, appropriate determination of factor IX levels is advised to guide the dose to be administered and the frequency of repeated infusions. Individual patients may vary in their responses to factor IX, demonstrating different half-lives and recoveries. Dose based on bodyweight may require adjustment in underweight or overweight patients. In the case of major surgical interventions in particular, precise monitoring of the substitution therapy by means of coagulation analysis (plasma factor IX activity) is indispensable.
When using an in vitro thromboplastin time (aPTT)-based one stage clotting assay for determining Factor IX activity in patients' blood samples, plasma factor IX activity results can be significantly affected by both the type of aPTT reagent and the reference standard used in the assay. Measurement with a one-stage clotting assay using a kaolin based aPTT reagent or Actin FS aPTT reagent will likely result in an underestimation of activity level. This is of importance particularly when changing the laboratory and/or reagents used in the assay.

Posology
Dose and duration of the substitution therapy depend on the severity of the factor IX deficiency, on the location and extent of the bleeding and on the patient's clinical condition.
The number of units of factor IX administered is expressed in International Units (IU), which arerelated to the current WHO standard for factor IX products. Factor IX activity in plasma is expressed either as a percentage (relative to normal human plasma) or in International Units (relative to an International Standard for factor IX in plasma).
One International Unit (IU) of factor IX activity is equivalent to that quantity of factor IX in one ml of normal human plasma.
On demand treatment
The calculation of the required dose of factor IX is based on the empirical finding that 1 International Unit (IU) factor IX per kg body weight is expected to increase the circulating level of factor IX by an average of 1.3 IU/dl (1.3 % of normal) in patients ≥ 12 years of age and by 1.0 IU/dl (1.0 % of normal) in patients < 12 years of age. The required dose is determined using the following formulae:
Required dose (IU) = body weight (kg) x desired factor IX rise (% of normal or IU/dl) x [reciprocal of observed recovery (IU/kg per IU/dl)]
Expected factor IX rise (IU/dl or % of normal) = Dose (IU) x Recovery (IU/dl per IU/kg)/body weight (kg)
The amount to be administered and the frequency of administration should always be oriented to the clinical effectiveness in the individual case.
Patients < 12 years of age
For an incremental recovery of 1 IU/dl per 1 IU/kg, the dose is calculated as follows:
Dose (IU) = body weight (kg) x desired factor IX increase (IU/dl) x 1 dl/kg
Example
1. A peak level of 50 % of normal is required in a 20 kg patient with severe haemophilia B. The appropriate dose would be 20 kg x 50 IU/dl x 1 dl/kg = 1000 IUs.
2. A dose of 1000 IUs of IDELVION, administered to a 25 kg patient, should be expected to result in a peak post-injection factor IX increase of 1000 IUs/25 kg x 1.0 (IU/dl per IU/kg) = 40 IU/dl (40 % of normal).

Patients ≥ 12 years of age
For an incremental recovery of 1.3 IU/dl per 1 IU/kg, the dose is calculated as follows:
Dose (IU) = body weight (kg) x desired factor IX increase (IU/dl) x 0.77 dl/kg
Example
3. A peak level of 50 % of normal is required in a 80 kg patient with severe haemophilia B. The appropriate dose would be 80 kg x 50 IU/dl x 0.77 dl/kg = 3080 IUs.
4. A dose of 2000 IUs of IDELVION, administered to a 80 kg patient, should be expected to result in a peak post-injection factor IX increase of 2000 IUs x 1.3 (IU/dl per IU/kg) /80 kg = 32.5 IU/dl (32.5 % of normal).

In the case of the following haemorrhagic events, the factor IX activity should not fall below the given plasma activity level (in % of normal or in IU/dl) in the corresponding period.
The following table can be used to guide dosing for control and prevention of in bleeding episodes and surgery:

Degree of Haemorrhage / Type of surgical procedure	Factor IX level required (%) (IU/dl)	Frequency of doses (hours) / Duration of therapy (days)
Haemorrhage Minor or moderate Haemarthrosis, muscle bleeding (except iliopsoas) or oral bleeding	30 - 60	Single dose should be sufficient for majority of bleeds. Maintenance dose after 24 – 72 hours if there is further evidence of bleeding.
Major haemorrhage Life threatening haemorrhages, deep muscle bleeding including iliopsoas	60 - 100	Repeat every 24 – 72 hours for the first week, and then maintenance dose weekly until bleeding stops and healing is achieved.
Minor surgery Including uncomplicated tooth extraction	50 - 80 (initial level)	Single dose may be sufficient for a majority of minor surgeries. If needed, maintenance dose can be provided after 24 – 72 hours until bleeding stops and healing is achieved.
Major surgery	60 - 100 (initial level)	Repeat every 24 – 72 hours for the first week, and then maintenance dose 1 – 2 times per week until bleeding stops and healing is achieved.

Routine Prophylaxis
For patients ≥12 years of age: For routine prophylaxis against bleeding in patients with severe hemophilia B, the usual doses are 35 to 50 IU/kg once weekly.Some Patients who are well-controlled on this regimen may be switched to a 14- day interval at 50-75 IU/kg.
For patients <12 years of age: the usual doses of prophylaxis are 35 to 50 IU/kg once weekly.
In some cases, especially in younger patients, shorter dosage intervals or higher doses may be necessary.
After a bleeding episode during prophylaxis, patients should maintain their prophylaxis regimen unless it is not possible, with 2 doses of IDELVION being administered at least 24 hours apart but longer as deemed suitable for the patient.

Method of administration
Intravenous use.
For instructions on reconstitution of the medicinal product before administration, see section 6.6. The reconstituted preparation should be injected slowly intravenously at a rate comfortable for the patient up to a maximum of 5 ml/min.

4.3 Contraindications

Hypersensitivity to the active substance (recombinant fusion protein linking coagulation factor IX with albumin (rIX-FP)) or to any of the excipients listed in section 6.1.
Known allergic reaction to hamster protein.

4.4 Special warnings and precautions for use

Hypersensitivity
Allergic type hypersensitivity reactions are possible with IDELVION. The product contains traces of hamster proteins. If symptoms of hypersensitivity occur, patients should be advised to discontinue use of the medicinal product immediately and contact their physician. Patients should be informed of the early signs of hypersensitivity reactions including hives, generalised urticaria, tightness of the chest, wheezing, hypotension and anaphylaxis. It is suggested that the initial administrations of factor IX should, according to the treating physician's judgment, be performed under medical observation where proper medical care for allergic reactions could be provided.
In case of shock, standard medical treatment for shock should be implemented.

Inhibitors
Formation of inhibitor to factor IX has been reported during factor replacement therapy with IDELVION in the treatment of haemophilia B. After repeated treatment with human coagulation factor IX products, patients should be monitored for the development of neutralising antibodies (inhibitors) that should be quantified in Bethesda Units (BU) using appropriate biological testing.
There have been reports in the literature showing a correlation between the occurrence of a factor IX inhibitor and allergic reactions. Therefore, patients experiencing allergic reactions should be evaluated for the presence of an inhibitor. It should be noted that patients with factor IX inhibitors may be at an increased risk of anaphylaxis with subsequent challenge with factor IX.
Because of the risk of allergic reactions with factor IX products, the initial administration of factor IX should, according to the treating physician's judgement, be performed under medical observation where proper medical care for allergic reactions could be provided.

Thromboembolism
Because of the potential risk of thrombotic complications, clinical surveillance for early signs of thrombotic and consumptive coagulopathy should be initiated with appropriate biological testing when administering this product to patients with liver disease, to patients post-operatively, to new-born infants, or to patients at risk of thrombotic phenomena or DIC. In each of these situations, the benefit of treatment with IDELVION should be weighed against the risk of these complications.

Cardiovascular events
In patients with existing cardiovascular risk factors, substitution therapy with FIX may increase the cardiovascular risk.

Catheter-related complications
If a central venous access device (CVAD) is required, risk of CVAD-related complications including local infections, bacteraemia and catheter site thrombosis should be considered.

Paediatric population
The listed warnings and precautions apply both to adults and children.

Elderly
Clinical studies of IDELVION did not include subjects aged 65 and over. It is not known whether they respond differently from younger subjects.

Immune tolerance induction
The safety and efficacy of using IDELVION for immune tolerance induction has not been established.

Sodium content
This medicinal product contains up to 25.8 mg (1.13 mmol) sodium per dose (bodyweight 70 kg) if the maximal dose (15 ml = 6000 IU) is applied. To be taken into consideration by patients on a controlled sodium diet.

Record of use
It is strongly recommended that every time that IDELVION 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 medicinal product.

4.5 Interaction with other medicinal products and other forms of interaction

No interactions of human coagulation factor IX products with other medicinal products have been reported.

4.6 Fertility, pregnancy and lactation

Animal reproduction studies have not been conducted with factor IX. Based on the rare occurrence of haemophilia B in women, experience regarding the use of factor IX during pregnancy and lactation is not available.
Therefore, factor IX should be used during pregnancy and lactation only if clearly indicated.
There is no information on the effects of factor IX on fertility.

4.7 Effects on ability to drive and use machines

IDELVION has no influence on the ability to drive and use machines.

4.8 Undesirable effects

Summary of the safety profile
Hypersensitivity or allergic reactions (which may include angioedema, burning and stinging at the infusion site, chills, flushing, generalised urticaria, headache, hives, hypotension, lethargy, nausea, restlessness, tachycardia, tightness of the chest, tingling, vomiting, wheezing) have been observed rarely and may in some cases progress to severe anaphylaxis (including shock). 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 also section 4.4). Nephrotic syndrome has been reported following attempted immune tolerance induction in haemophilia B patients with factor IX inhibitors and a history of allergic reaction.
With the use of factor IX products obtained from CHO cells very rarely development of antibodies to hamster protein has been observed.
Patients with haemophilia B may develop neutralising antibodies (inhibitors) to factor IX. If such inhibitors occur, the condition will manifest itself as an insufficient clinical response. In such cases, it is recommended that a specialised haemophilia centre be contacted. Inhibitor development was reported in an ongoing clinical study with previously untreated patients. Inhibitor development has been observed in previously treated patients in the post-marketing experience with IDELVION.
There is a potential risk of thromboembolic episodes following the administration of factor IX products, with a higher risk for low purity preparations. The use of low purity factor IX products has been associated with instances of myocardial infarction, disseminated intravascular coagulation, venous thrombosis and pulmonary embolism. The use of high purity factor IX is rarely associated with such adverse reactions.

Tabulated list of adverse reactions
Four open label clinical studies included 107 subjects with at least one exposure to IDELVION reporting 13 adverse reactions in 7 subjects.
The table presented below is according to the MedDRA system organ classification (SOC and Preferred Term Level).
Frequencies have been evaluated according to the following convention: very common (≥1/10); common (≥1/100 to <1/10); uncommon (≥1/1,000 to <1/100); rare (≥1/10,000 to <1/1,000); very rare (<1/10,000), not known (cannot be estimated from the available data).
Within each frequency grouping, adverse reactions are presented in order of decreasing seriousness.

MedDRA Standard System Organ Class	Adverse reactions	Frequency per patient
Blood and lymphatic disorders	FIX inhibition/ Inhibitor development	Not known
General disorders and administration site conditions	Injection site reactions	Common
Nervous system disorders	Headache	Common
	Dizziness	Uncommon
Immune system disorders	Hypersensitivity	Uncommon
Skin and subcutaneous tissue disorders	Rash	Uncommon
	Eczema	Uncommon

Description of selected adverse reactions
One previously untreated patient (PUP) from the ongoing clinical trial developed high titre inhibitor against factor IX. There are insufficient data to provide information on inhibitor incidence in PUPs.

Paediatric Population
Frequency, type and severity of adverse reactions in children are expected to be similar as in adults.

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.

4.9 Overdose

No symptoms of overdose with IDELVION have been reported.

5. PHARMACOLOGICAL PROPERTIES

5.1. Pharmacodynamic properties

Pharmacotherapeutic group: Antihaemorrhagics: Blood coagulation factor IX.
ATC code: B02BD04

Mechanism of action
IDELVION (INN: albutrepenonacog alfa) is a recombinant coagulation factor IX. Prolongation of the half-life of IDELVION and the enhanced systemic exposure are achieved by fusion with recombinant albumin. Albumin is a natural, inert carrier protein in plasma with a half-life of approximately 20 days. Genetic fusion of recombinant coagulation factor IX with albumin extends the half-life of factor IX (see section 5.2).
IDELVION remains intact in the circulation until factor IX is activated, whereupon albumin is cleaved, releasing activated factor IX (FIXa) when it is needed for coagulation.

Pharmacodynamic effects
Haemophilia B is a sex linked hereditary disorder of blood coagulation due to decreased levels of factor IX and results in profuse bleeding into joints, muscles or internal organs, either spontaneously or as a result of accidental or surgical trauma. By replacement therapy the plasma levels of factor IX is increased, thereby enabling a temporary correction of the factor deficiency and correction of the bleeding tendencies.
Factor IX is activated by factor VII/tissue factor complex in the extrinsic pathway as well as factor XIa in the intrinsic coagulation pathway. Activated factor IX, in combination with activated factor VIII, activates factor X. This results ultimately in the conversion of prothrombin to thrombin.
Thrombin then converts fibrinogen into fibrin and a clot can be formed. Factor IX activity is absent or greatly reduced in patients with haemophilia B and substitution therapy may be required.

Clinical efficacy and safety
A phase 1/2 study evaluated the treatment efficacy and prevention of bleeding episodes of rIX-FP in 17 subjects (ages 13-46 years), 13 subjects in the prophylaxis arm received weekly prophylaxis with IDELVION for approximately 11 months, and 4 subjects in the on-demand arm received IDELVION upon occurrence of bleeding events. All 85 bleeding episodes were successfully treated with 1 or 2 doses of IDELVION.
The efficacy of IDELVION has been evaluated in the open-label, uncontrolled part of a phase 2/3 study, in which a total of 63 male, previously treated patients (PTPs) between 12 and 61 years of age received IDELVION either for prophylaxis once every 7-, 10- and/or 14-day intervals and/or for the treatment of bleeding episodes on an on-demand basis. All subjects had severe (FIX level <1%) or moderately severe (FIX level ≤ 2%) haemophilia B. Forty PTPs received IDELVION for prophylaxis.
Subjects who received prophylactic treatment started with 35-50 IU/kg once weekly. A subgroup of patients was switched to extended treatment intervals (every 10 or 14 days) with a recommended dose of 75 IU/kg and individual adjustments. 21 PTPs remained on the extended 14 day prophylaxis interval for additional treatment duration of 98 to 575 (median 386) days. From those subjects, 19 (98%) experienced at least one bleeding during the 14 day-prophylaxis, while they had no bleeding events during once weekly prophylaxis. Median Annualised Bleeding Rate (ABR) on 7 day prophylaxis with IDELVION for all bleeds was 0.0 (range 0-6) and on 14 day-prophylaxis it was 1.08 (range 0-9.1). Currently available information support extension of treatment intervals for some patients though potentially associated with an increased risk for bleeding compared to a once weekly regimen.
Of note, ABR is not comparable between different factor concentrates and between different clinical studies.

Prophylaxis and control of bleeding in PTPs below 12 years
The efficacy of IDELVION has been evaluated in a phase 3 study, in which a total of 27 male PTPs between 1 and 10 years (median age 6.0 years) with 12 patients < 6 years, received IDELVION for prophylaxis and control of bleeding episodes. All 27 subjects received once weekly prophylaxis treatment with IDELVION for a mean time on study of 13.1 months (9, 18 months).
Of the 106 bleeding episodes, the majority (94; 88.7%) was treated with single injection, 103; 97.2% were treated with 1-2 injections. Haemostatic efficacy at resolution of a bleed was rated excellent or good in 96% of all treated bleeding episodes.
Clinical studies investigating safety and efficacy of longer treatment intervals than once weekly are ongoing.

Perioperative management
The safety and efficacy in the perioperative setting was evaluated in two pivotal Phase 3 studies (Study 3001 and 3002) and the on-going Phase 3 safety extension study (Study 3003). The perprotocol efficacy analysis includes 15 surgeries performed in 12 patients between 8 and 51 years of age undergoing major or minor surgical, dental or other surgical invasive procedures.
IDELVION was administered by bolus injection.
Haemostasis was maintained throughout the study duration.

Paediatric population
The European Medicines Agency has deferred the obligation to submit the results of studies with IDELVION in previously untreated patients in the treatment and prophylaxis of bleeding in haemophilia B (see section 4.2 for information on paediatric use).

5.2 Pharmacokinetic properties

Adult population
The pharmacokinetics (PK) of IDELVION were evaluated following an intravenous injection of a single dose of 25, 50 and 75 IU/kg. The PK parameters following a single injection of 50 IU/kg IDELVION (see table below) were based on plasma factor IX activity measured by the one-stage clotting assay. The mean factor IX activity at day 7 and day 14 was 13.76% and 6.10%, respectively, after a single dose of 50 IU/kg IDELVION. Repeat PK assessment for up to 30 weeks demonstrated a stable pharmacokinetic profile and incremental recovery was consistent over time.
Trough levels of 5-10% have been targeted in clinical trials for achieving bleeding control while on prophylaxis. PK simulations suggest the time to reach 5% plasma FIX activity following a single injection of 50 IU/kg IDELVION to be 12.5 days for adults.

Pharmacokinetic Parameters for subjects with severe haemophilia (Median (min, max)) following a single injection of 50 IU/kg IDELVION

PK Parameters	IDELVION (50 (IU/kg)) (N=22)
IR (IU/dl)/(IU/kg)	1.18 (0.86, 1.86)
C_{max} (IU/dl)	62.7 (40.5, 87.0)
AUC_{0-inf} (h*IU/dl)	6638 (2810, 9921)
Elimination $t_{1/2}$ (h)	95.3 (51.5, 135.7)
CL (ml/h/kg)	0.875 (0.748, 1.294)

IR = incremental recovery; AUC = area under the factor IX activity time curve; CL = body weight adjusted clearance; Elimination $t_{1/2}$ = Elimination half-life

Paediatric population
Pharmacokinetic (PK) parameters of IDELVION were evaluated in adolescents (12 to <18 years of age) and children (1 to <12 years of age) following an intravenous injection of a single dose of 50 IU/kg. PK parameters (presented below) were estimated based on the plasma factor IX activity over time profile measured by the one-stage clotting assay.

Comparison of Pharmacokinetic Parameters of IDELVION by Age Category (Median (min, max)) Following a Single Injection of 50 IU/kg IDELVION

PK Parameters	1 to <6 years (N=12)	6 to <12 years (N=15)	12 to <18 years (N=5)
IR (IU/dl)/(IU/kg)	0.968 (0.660, 1.280)	1.07 (0.70, 1.47)	1.11 (0.84, 1.61)
C_{max} (IU/dl)	48.2 (33.0, 64.0)	50.5 (34.9, 73.6)	55.3 (40.5, 80.3)
AUC_{0-inf} (h*IU/dl)	4301 (2900, 8263)	4718 (3212, 7720)	4804 (2810, 9595)
Elimination $t_{1/2}$ (h)	86.2 (72.6, 105.8)	89.3 (62.1, 123.0)	88.8 (51.5, 130.0)
CL (ml/h/kg)	1.16 (0.61, 1.72)	1.06 (0.65, 1.56)	1.04 (0.52, 1.67)

IR = incremental recovery; AUC = area under the factor IX activity time curve; CL = body weight adjusted clearance; Elimination $t_{1/2}$ = Elimination half-life

Trough levels of 5-10% have been targeted in clinical trials for achieving bleeding control while on prophylaxis. PK simulations suggest the time to reach 5% plasma FIX activity following a single injection of 50 IU/kg IDELVION to be 7 days for 1-<6years, 9 days for 6-<12 years and 11 days for 12-<18 years of age).

5.3 Preclinical safety data

Non-clinical data reveal no special hazard for humans based on conventional studies of safety pharmacology, single and repeat dose toxicity, genotoxicity, thrombogenicity and local tolerability.
No investigations on carcinogenicity and reproductive toxicology have been conducted.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Powder:
Tri-sodium citrate dihydrate, Polysorbate 80, Mannitol, Sucrose, HCl (for pH adjustment).
Solvent:
Water for injections

6.2 Incompatibilities

In the absence of compatibility studies, this medicinal product must not be mixed with other medicinal products, diluents or solvents except those mentioned in section 6.1.

6.3 Shelf life

IDELVION 250 IU powder and solvent for solution for injection
3 years
IDELVION 500 IU powder and solvent for solution for injection
3 years
IDELVION 1000 IU powder and solvent for solution for injection
3 years
IDELVION 2000 IU powder and solvent for solution for injection
3 years
After reconstitution the chemical and physical in-use stability has been demonstrated for 8 hours at 2-25 °C). From a microbiological point of view, the product should be used immediately. If not used immediately, in-use storage times and conditions prior to use should not be longer than 4 hours at room temperature (below 25 °C).

6.4 Special precautions for storage

Do not store above 25 °C.
Do not freeze. Keep vials in the outer carton in order to protect from light.
For storage conditions after reconstitution of the medicinal product, see section 6.3.

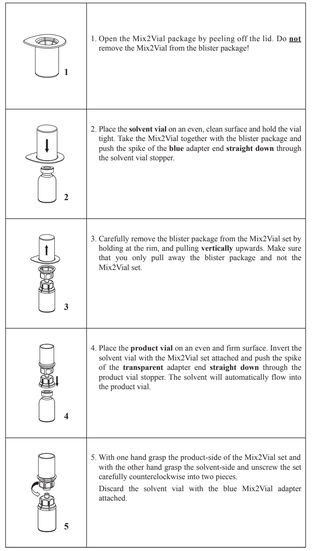
6.5 Nature and contents of container

IDELVION 250 IU powder and solvent for solution for injection
Powder (250 IU) in a 6 ml vial (type I glass), with a stopper (rubber) a disc (plastic) and a cap (aluminium).
2.5 ml of solvent in a vial (type I glass), with a stopper (rubber) a disc (plastic) and a cap (aluminium).
IDELVION 500 IU powder and solvent for solution for injection
Powder (500 IU) in a 6 ml vial (type I glass), with a stopper (rubber) a disc (plastic) and a cap (aluminium).
2.5 ml of solvent in a vial (type I glass), with a stopper (rubber) a disc (plastic) and a cap (aluminium).
IDELVION 1000 IU powder and solvent for solution for injection
Powder (1000 IU) in a 6 ml vial (type I glass), with a stopper (rubber) a disc (plastic) and a cap(aluminium).
2.5 ml of solvent in a vial (type I glass), with a stopper (rubber) a disc (plastic) and a cap (aluminium).
IDELVION 2000 IU powder and solvent for solution for injection
Powder (2000 IU) in a 10 ml vial (type I glass), with a stopper (rubber) a disc (plastic) and a cap (aluminium).
5 ml of solvent in a vial (type I glass), with a stopper (rubber) a disc (plastic) and a cap (aluminium).
Presentations
Each pack contains:
IDELVION 250 IU powder and solvent for solution for injection
1 product vial
1 solvent vial (2.5 ml water for injections)
1 filter transfer device 20/20
One inner box containing:
1 disposable 5 ml syringe
1 venipuncture set
2 alcohol swabs
1 non-sterile plaster
Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

General instructions
- The reconstituted solution should be clear or slightly opalescent, yellow to colourless. After filtering/withdrawal (see below) the 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 (below 25 °C). 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 .



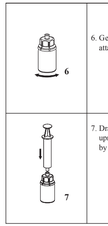
1. Open the Mix2Vial package by peeling off the lid. Do **not** remove the Mix2Vial from the blister package!
2. Place the **solvent vial** on an even, clean surface and hold the vial tight. Take the Mix2Vial together with the blister package and push the spike of the **blue** adapter end **straight 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.
4. Place the **product vial** on an even and firm surface. Invert the solvent vial with the Mix2Vial set attached and push the spike of the **transparent** adapter end **straight down** through the product vial stopper. The solvent will automatically flow into the product vial.
5. With one hand grasp the product-side of the Mix2Vial set and with the other hand grasp the solvent-side and unscrew the set carefully counterclockwise into two pieces.
   Discard the solvent vial with the blue Mix2Vial adapter attached.

One inner box containing:
1 disposable 5 ml syringe
1 venipuncture set
2 alcohol swabs
1 non-sterile plaster
IDELVION 1000 IU powder and solvent for solution for injection
1 product vial
1 solvent vial (2.5 ml water for injections)
1 filter transfer device 20/20
One inner box containing:
1 disposable 5 ml syringe
1 venipuncture set
2 alcohol swabs
1 non-sterile plaster
IDELVION 2000 IU powder and solvent for solution for injection
1 product vial
1 solvent vial (5 ml water for injections)
1 filter transfer device 20/20
One inner box containing:
1 disposable 10 ml syringe
1 venipuncture set
2 alcohol swabs
1 non-sterile plaster
Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

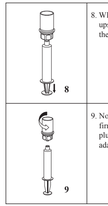
General instructions
- The reconstituted solution should be clear or slightly opalescent, yellow to colourless. After filtering/withdrawal (see below) the reconstituted product should be inspected visually for particulate matter and discoloration prior to administration.
- Do not use solutions that are cloudy or have deposits.
- Reconstitution and withdrawal must be carried out under aseptic conditions.

Reconstitution
Bring the solvent to room temperature (below 25 °C). 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 .



6. Gently swirl the product vial with the transparent adapter attached 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 by screwing clockwise. Inject air into the product vial.

Withdrawal and application



8. While keeping the syringe plunger pressed, turn the system upside down and draw the solution into the syringe by pulling the plunger back slowly.
9. Now that the solution has been transferred into the syringe, firmly hold on to the barrel of the syringe (keeping the syringe plunger facing down) and disconnect the transparent Mix2Vial adapter from the syringe by unscrewing counterclockwise.

For injection of IDELVION, only the provided administration sets should be used because treatment failure can occur as a consequence of factor IX adsorption to the internal surface of some injection equipment.
Care should be taken 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 could therefore be administered to the patient.
The IDELVION solution must not be diluted.
The reconstituted solution should be administered by slow intravenous injection. The rate of administration should be determined by the patient's comfort level, up to a maximum of 5 ml/min.
Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7. MANUFACTURER:

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9. DATE OF REVISION OF THE TEXT

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