ANNEX I

SUMMARY OF PRODUCT CHARACTERISTICS

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

IDELVION 3500 IU powder and solvent for solution for injection

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

IDELVION 250 IU powder and solvent for solution for injection
Each vial contains nominally 250 IU of recombinant fusion protein linking coagulation factor IX with albumin (rIX-FP), (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
Each vial contains nominally 500 IU of recombinant fusion protein linking coagulation factor IX with albumin (rIX-FP), (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
Each vial contains nominally 1000 IU of recombinant fusion protein linking coagulation factor IX with albumin (rIX-FP), (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
Each vial contains nominally 2000 IU of recombinant fusion protein linking coagulation factor IX with albumin (rIX-FP), (albutrepenonacog alfa). After reconstitution with 5 ml water for injections the solution contains 400 IU/ml of albutrepenonacog alfa.

IDELVION 3500 IU powder and solvent for solution for injection
Each vial contains nominally 3500 IU of recombinant fusion protein linking coagulation factor IX with albumin (rIX-FP), (albutrepenonacog alfa). After reconstitution with 5 ml water for injections the solution contains 700 IU/ml of albutrepenonacog alfa.

The potency (IU) is determined using the European Pharmacopeia one stage clotting test. The specific activity of IDELVION is approximately 54 – 85 IU/mg protein.

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
Each reconstituted 250 IU, 500 IU or 1000 IU vial contains 4.3 mg of sodium.
Each reconstituted 2000 IU or 3500 IU vial contains 8.6 mg of sodium (see section 4.4).
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.

IDELVION 3500 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).

IDELVION can be used for all age groups.

4.2 Posology and method of administration

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

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 are related 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 IU factor IX per kg body weight raises the plasma factor IX activity by an average of 1.3 IU/dl (1.3 % of normal activity) in patients ≥ 12 years of age and by 1.0 IU/dl (1.0 % of normal activity) 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:
Required dose (IU) = body weight (kg) x desired factor IX rise (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:
Required dose (IU) = body weight (kg) x desired factor IX rise (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 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 (pre- and postoperative)	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 (pre- and postoperative)	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.

Prophylaxis
For long term prophylaxis against bleeding in patients with severe haemophilia B, the usual doses are 35 to 50 IU/kg once weekly.
Some patients who are well-controlled on a once-weekly regimen might be treated with up to 75 IU/kg on an interval of 10 or 14 days. For patients >18 years, further extension of the treatment interval may be considered (see section 5.1).

In some cases, especially in younger patients, shorter dose intervals or higher doses may be necessary.

After a bleeding episode during prophylaxis, patients should maintain their prophylaxis regimen as closely as possible, with 2 doses of IDELVION being administered at least 24 hours apart, but longer if deemed suitable for the patient.

Paediatric population
For long term prophylaxis, the recommended dose regimen is 35 to 50 IU/kg once weekly (see sections 5.1 and 5.2). For adolescents of 12 years of age and above, the dose recommendations are the same as for adults (see above).

Method of administration
Intravenous use.

The reconstituted preparation should be injected slowly intravenously at a rate comfortable for the patient up to a maximum of 5 ml/min.

For instructions on reconstitution of the medicinal product before administration, see section 6.6.

4.3 Contraindications

Hypersensitivity to the active substance 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

Traceability
In order to improve the traceability of biological medicinal products, the name and the batch number of the administered product should be clearly recorded.

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.
In case of shock, standard medical treatment for shock should be implemented.

Inhibitors
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. Formation of inhibitor to factor IX has been reported during factor replacement therapy with IDELVION in the treatment of haemophilia B.

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.

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 8.6 mg sodium per vial, equivalent to 0.4% of the WHO recommended maximum daily intake of 2 g sodium for an adult.

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

4.5 Interaction with other medicinal products and other forms of interaction

No interactions of human coagulation factor IX (rDNA) 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 breast-feeding 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.

Very rarely development of antibodies to hamster protein with related hypersensitivity reactions 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. One case with high-titre inhibitor was reported in the clinical study which evaluated 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
The table presented below is according to the MedDRA system organ classification (SOC and Preferred Term Level). The table lists adverse reactions that were reported in clinical trials and/or were identified in post-marketing use.

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
Immune system disorders	Hypersensitivity	Common
Nervous system disorders	Headache	Common
	Dizziness	Common
Skin and subcutaneous tissue disorders	Rash	Common
	Eczema	Uncommon
General disorders and administration site conditions	Injection site reactions	Common

Description of selected adverse reactions
One case with high-titre inhibitor was reported in the clinical study with previously untreated patients (refer to Section 5.1). Due to the narrow data-base no inhibitor-incidence is provided.

Paediatric population
Frequency, type and severity of adverse reactions in children are expected to be the same 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 via the national reporting system listed in Appendix V.

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
Factor IX is a single chain glycoprotein with a molecular mass of about 68,000 Dalton. It is a vitamin-K dependent coagulation factor and it is synthesised in the liver. Factor IX is activated by factor XIa in the intrinsic coagulation pathway and by the factor VII/tissue factor complex in the extrinsic pathway. Activated factor IX, in combination with activated factor VIII, activates factor X. Activated factor X converts prothrombin into thrombin. Thrombin then converts fibrinogen into fibrin and a clot is

formed. 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.

Of note, ABR (annualized bleeding rate) is not comparable between different factor concentrates and between different clinical studies.

Albutrepenonacog alfa is a recombinant coagulation factor IX. Prolongation of the half-life of albutrepenonacog alfa and the enhanced systemic exposure (see section 5.2) are achieved by fusion with recombinant albumin. Albumin is a natural, inert carrier protein in plasma with a half-life of approximately 20 days.
Albutrepenonacog alfa 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.

General information on 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 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, 8 (38%) 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).

The long-term efficacy and safety of routine prophylaxis treatment was confirmed in an open-label extension study for up to 5 years. In this study, a total of 59 PTPs ≥12 years (54 adults and 5 adolescents) received IDELVION either for prophylaxis and/or for the treatment of bleeding episodes on an on-demand basis. Patients who received prophylactic treatment continued or started with 35-50 IU/kg once weekly. A subgroup of patients switched to extended treatment intervals (every 10, 14 or 21 days) with a recommended dose of 75 IU/kg (10 or 14 days) or 100 IU/kg (21 days). At the end of the study 14 PTPs (24%) were on the 7-day prophylaxis interval, and a total of 11 (19%), 25 (42%) and 9 (15%) PTPs remained on the extended prophylaxis interval of 10, 14 and 21 days, respectively. During the study, 2 PTPs (18%) in the 21-day regimen switched back to a more frequent dosing due to increased bleeding complications. The estimated median Annualised Bleeding Rates (ABRs) on 7-, 14-, and 21-day prophylaxis with IDELVION for all bleeds were 1.3 (range 0-8), 0.9 (range 0-13), and 0.3 (range 0-5), respectively.

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.

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 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.

The long-term efficacy and safety of routine prophylaxis treatment was confirmed in an open-label extension study for up to 5 years. In the study, a total of 24 PTPs < 12 years received IDELVION either for prophylaxis and/or for the treatment of bleeding episodes on an on-demand basis. Patients who received prophylactic treatment continued with 35-50 IU/kg once weekly. A subgroup of patients switched to extended treatment intervals (every 10 or 14 days) with a recommended dose of 75 IU/kg. At the end of the study 17 PTPs (71%) were on the 7 day prophylaxis interval, and a total of 3 (12%), and 4 (17%) PTPs remained on the extended prophylaxis interval of 10 and 14 days, respectively. During the study, 4 PTPs (50%) in the 14-day regimen switched back to a more frequent dosing due to increased bleeding complications. The estimated median Annualised Bleeding Rates (ABRs) for 7-, and 14-day prophylaxis with IDELVION for all bleeds were 2.0 (range 0-14), and 5.6 (range 0-8), respectively.

Perioperative management:
The safety and efficacy in the perioperative setting was evaluated in two pivotal Phase 3 studies and a long-term extension study. The per protocol efficacy analysis includes 30 surgeries performed in 21 patients between 5 and 58 years undergoing major or minor surgical, dental or other surgical invasive procedures. Dosing was individualized based on the subject's PK and clinical response to treatment. A single preoperative bolus ranging from 14 to 163 IU/kg was used in 96.7% (n=29) of surgeries. Haemostatic efficacy was rated as excellent or good in all of the assessed procedures. During the 14-day postoperative period, patients received between 0 and 11 infusions and total doses ranging from 0 to 444 IU/kg.

Previously untreated patients (PUP)
Safety and efficacy of IDELVION were evaluated in a multicenter open-label clinical study with 12 previously untreated paediatric patients (PUPs) with hemophilia B (≤2% endogenous FIX activity), of whom 11 were in the age-range of 0 to 1 years. The median number of exposure days (EDs) was 50 (range 22 to 146 EDs), and 8 PUPs achieved ≥50 EDs during on-demand, prophylaxis, surgical and PK periods.
All 12 PUPs received routine prophylaxis with 11 receiving the 7-day regimen. The overall median time on prophylaxis was 11.5 months (range: 3.1 to 32.3 months). In the 9 PUPs on the 7-day prophylaxis regimen who reached > 6 months of treatment, median annualized bleeding rate (ABR) was 1.16 (range 0 to 3.1). Five of the 9 PUPs had an ABR of 0. The median monthly dose was 195.9 IU/kg (range 171.8 to 215.6 IU/kg) for the 7-day prophylaxis regimen (N = 9).
Five subjects received on-demand treatment over varying periods prior to prophylaxis, with the number of EDs ranging from 1 to 4.
Of the 37 bleeding events observed in 10 PUPs across all study periods, 94% were successfully controlled with 1 or 2 infusions.

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 studies 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 IDELVION in adults

PK parameters	**50 IU/kg (N=22)**
IR [a] (IU/dl)/(IU/kg)	1.18 (0.86, 1.86)
C_{max} [a] (IU/dl)	62.7 (40.5, 87.0)
$AUC_{0\text{-}inf}$ (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)

a = corrected for baseline levels

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 parameters of IDELVION were evaluated in adolescents (12 to <18 years of age) and infants 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 in children (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[a] (IU/dl)/(IU/kg)	0.968 (0.660, 1.280)	1.07 (0.70, 1.47)	1.11 (0.84, 1.61)
C_{max} [a] (IU/dl)	48.2 (33.0, 64.0)	50.5 (34.9, 73.6)	55.3 (40.5, 80.3)
$AUC_{0\text{-}inf}$ (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)

a = corrected for baseline levels

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 studies 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:
Sodium citrate
Polysorbate 80
Mannitol
Sucrose
Hydrochloric acid (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.

Only the provided injection sets should be used because treatment failure can occur as a consequence of human coagulation factor IX adsorption to the internal surfaces of some injection equipment.

6.3 Shelf life

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 are in the responsibility of the user.

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 (bromobutyl rubber) a disc (plastic) and a cap (aluminium).
2.5 ml of solvent in a vial (type I glass), with a stopper (bromo- or chlorobutyl 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 (bromobutyl rubber) a disc (plastic) and a cap (aluminium).
2.5 ml of solvent in a vial (type I glass), with a stopper (bromo- or chlorobutyl 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 (bromobutyl rubber) a disc (plastic) and a cap (aluminium).
2.5 ml of solvent in a vial (type I glass), with a stopper (bromo- or chlorobutyl 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 (bromobutyl rubber) a disc (plastic) and a cap (aluminium).
5 ml of solvent in a vial (type I glass), with a stopper (bromo- or chlorobutyl rubber) a disc (plastic) and a cap (aluminium).

IDELVION 3500 IU powder and solvent for solution for injection
Powder (3500 IU) in a 10 ml vial (type I glass), with a stopper (bromobutyl rubber) a disc (plastic) and a cap (aluminium).
5 ml of solvent in a vial (type I glass), with a stopper (bromo- or chlorobutyl rubber) a disc (plastic) and a cap (aluminium).

Presentations

Each pack contains:

IDELVION 250 IU powder and solvent for solution for injection:
1 vial with powder
1 vial with 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 500 IU powder and solvent for solution for injection
1 vial with powder
1 vial with 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 1000 IU powder and solvent for solution for injection
1 vial with powder
1 vial with 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 vial with powder
1 vial with 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

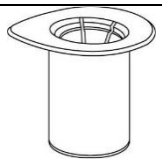
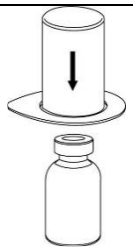
IDELVION 3500 IU powder and solvent for solution for injection
1 vial with powder
1 vial with 5 ml water for injections
1 filter transfer device 20/20
One inner box containing:
1 disposable 10 ml syringe
1 venipuncture set
2 alcohol swabs
1 non-sterile plaster

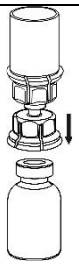
Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

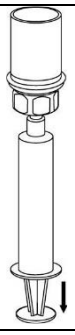
General instructions
- The reconstituted solution should be clear or slightly opalescent, yellow to colourless. After filtering/withdrawal (see below) the reconstituted product should be inspected visually for particulate matter and discoloration prior to administration.
- Do not use solutions that are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

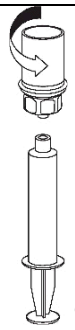
Reconstitution
Bring the solvent to room temperature (below 25 °C). Ensure IDELVION and solvent vial flip caps are removed and the stoppers are treated with an antiseptic solution and allowed to dry prior to opening the Mix2Vial package.

 1	1. Open the Mix2Vial by peeling off the lid. Do **not** remove the Mix2Vial from the blister package!
 2	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	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	4. Place the **IDELVION 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 IDELVION vial stopper. The solvent will automatically flow into the IDELVION vial.
 5	5. With one hand grasp the IDELVION side of the Mix2Vial set and with the other hand grasp the solvent-side and unscrew the set carefully counter-clockwise into two pieces. Discard the solvent vial with the blue Mix2Vial adapter attached.
 6	6. Gently swirl the IDELVION vial with the transparent adapter attached until the substance is fully dissolved. Do not shake.
 7	7. Draw air into an empty, sterile syringe. While the IDELVION vial is upright, connect the syringe to the Mix2Vial's Luer Lock fitting by screwing clockwise. Inject air into the IDELVION vial.

Withdrawal and application

 8	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	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 counter-clockwise.

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 reconstituted 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. MARKETING AUTHORISATION HOLDER

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

8. MARKETING AUTHORIZATION NUMBER(S)

EU/1/16/1095/001
EU/1/16/1095/002
EU/1/16/1095/003
EU/1/16/1095/004
EU/1/16/1095/009

9. DATE OF FIRST AUTHORIZATION/RENEWAL OF THE AUTHORIZATION

Date of first authorisation: 11 May 2016
Date of latest renewal: 04 February 2021

10. DATE OF REVISION OF THE TEXT

Detailed information on this medicinal product is available on the website of the European Medicines Agency http://www.ema.europa.eu

ANNEX II

A. MANUFACTURER OF THE BIOLOGICAL ACTIVE SUBSTANCE AND MANUFACTURER RESPONSIBLE FOR BATCH RELEASE

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

A. MANUFACTURER OF THE BIOLOGICAL ACTIVE SUBSTANCE AND MANUFACTURER RESPONSIBLE FOR BATCH RELEASE

Name and address of the manufacturer of the biological active substance

CSL Behring GmbH
Emil-von-Behring Strasse 76
35041 Marburg
Germany

Name and address of the manufacturer responsible for batch release

CSL Behring GmbH
Emil-von-Behring Strasse 76
35041 Marburg
Germany

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

Medicinal product subject to restricted medical prescription (see Annex I: Summary of Product Characteristics, section 4.2).

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

- **Periodic safety update reports (PSURs)**

The requirements for submission of PSURs for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

- **Risk management plan (RMP)**

The marketing authorization holder (MAH) shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the marketing authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:
- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

ANNEX III

LABELLING AND PACKAGE LEAFLET

A. LABELLING

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

CARTON 250 IU

1. NAME OF THE MEDICINAL PRODUCT

IDELVION 250 IU powder and solvent for solution for injection
albutrepenonacog alfa (recombinant coagulation factor IX)

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Albutrepenonacog alfa 250 IU (100 IU/ml after reconstitution)

3. LIST OF EXCIPIENTS

Other ingredients: Sodium citrate, Polysorbate 80, Mannitol, Sucrose, HCl
Solvent: Water for injections

4. PHARMACEUTICAL FORM AND CONTENTS

powder and solvent for solution for injection
1 vial with powder: 250 IU albutrepenonacog alfa
1 vial with 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

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.
For intravenous use

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Do not store above 25 °C. Do not freeze.
Keep the vials in the outer carton in order to protect from light.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

CSL Behring GmbH, 35041 Marburg, Germany

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/16/1095/001

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

IDELVION 250 IU

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC
SN
NN

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

POWDER VIAL 250 IU

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION

IDELVION 250 IU powder for solution for injection
albutrepenonacog alfa
For intravenous use

2. METHOD OF ADMINISTRATION

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

6. OTHER

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

SOLVENT VIAL LABEL 2.5 ML

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION

Water for injections

2. METHOD OF ADMINISTRATION

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

2.5 ml

6. OTHER

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

CARTON 500 IU

1. NAME OF THE MEDICINAL PRODUCT

IDELVION 500 IU powder and solvent for solution for injection
albutrepenonacog alfa (recombinant coagulation factor IX)

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Albutrepenonacog alfa 500 IU (200 IU/ml after reconstitution)

3. LIST OF EXCIPIENTS

Other ingredients: Sodium citrate, Polysorbate 80, Mannitol, Sucrose, HCl
Solvent: Water for injections

4. PHARMACEUTICAL FORM AND CONTENTS

powder and solvent for solution for injection
1 vial with powder: 500 IU albutrepenonacog alfa
1 vial with 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

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.
For intravenous use

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Do not store above 25 °C. Do not freeze.
Keep the vials in the outer carton in order to protect from light.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

CSL Behring GmbH, 35041 Marburg, Germany

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/16/1095/002

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

IDELVION 500 IU

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC
SN
NN

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

POWDER VIAL 500 IU

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION

IDELVION 500 IU powder for solution for injection
albutrepenonacog alfa
For intravenous use

2. METHOD OF ADMINISTRATION

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

6. OTHER

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

SOLVENT VIAL LABEL 2.5 ML

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION

Water for injections

2. METHOD OF ADMINISTRATION

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

2.5 ml

6. OTHER

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

CARTON 1000 IU

1. NAME OF THE MEDICINAL PRODUCT

IDELVION 1000 IU powder and solvent for solution for injection
albutrepenonacog alfa (recombinant coagulation factor IX)

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Albutrepenonacog alfa 1000 IU (400 IU/ml after reconstitution)

3. LIST OF EXCIPIENTS

Other ingredients: Sodium citrate, Polysorbate 80, Mannitol, Sucrose, HCl
Solvent: Water for injections

4. PHARMACEUTICAL FORM AND CONTENTS

powder and solvent for solution for injection
1 vial with powder: 1000 IU albutrepenonacog alfa
1 vial with 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

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.
For intravenous use

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Do not store above 25 °C. Do not freeze.
Keep the vials in the outer carton in order to protect from light.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

CSL Behring GmbH, 35041 Marburg, Germany

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/16/1095/003

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

IDELVION 1000 IU

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC
SN
NN

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

POWDER VIAL 1000 IU

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION

IDELVION 1000 IU powder for solution for injection
albutrepenonacog alfa
For intravenous use

2. METHOD OF ADMINISTRATION

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

6. OTHER

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

SOLVENT VIAL LABEL 2.5 ML

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION

Water for injections

2. METHOD OF ADMINISTRATION

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

2.5 ml

6. OTHER

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

CARTON 2000 IU

1. NAME OF THE MEDICINAL PRODUCT

IDELVION 2000 IU powder and solvent for solution for injection
albutrepenonacog alfa (recombinant coagulation factor IX)

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Albutrepenonacog alfa 2000 IU (400 IU/ml after reconstitution)

3. LIST OF EXCIPIENTS

Other ingredients: Sodium citrate, Polysorbate 80, Mannitol, Sucrose, HCl
Solvent: Water for injections

4. PHARMACEUTICAL FORM AND CONTENTS

powder and solvent for solution for injection
1 vial with powder: 2000 IU albutrepenonacog alfa
1 vial with 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

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.
For intravenous use

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Do not store above 25 °C. Do not freeze.
Keep the vials in the outer carton in order to protect from light.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

CSL Behring GmbH, 35041 Marburg, Germany

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/16/1095/004

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

IDELVION 2000 IU

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC
SN
NN

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

POWDER VIAL 2000 IU

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION

IDELVION 2000 IU powder for solution for injection
albutrepenonacog alfa
For intravenous use

2. METHOD OF ADMINISTRATION

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

6. OTHER

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

SOLVENT VIAL LABEL 5 ML

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION

Water for injections

2. METHOD OF ADMINISTRATION

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

5 ml

6. OTHER

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

CARTON 3500 IU

1. NAME OF THE MEDICINAL PRODUCT

IDELVION 3500 IU powder and solvent for solution for injection
albutrepenonacog alfa (recombinant coagulation factor IX)

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Albutrepenonacog alfa 3500 IU (700 IU/ml after reconstitution)

3. LIST OF EXCIPIENTS

Other ingredients: Sodium citrate, Polysorbate 80, Mannitol, Sucrose, HCl
Solvent: Water for injections

4. PHARMACEUTICAL FORM AND CONTENTS

powder and solvent for solution for injection
1 vial with powder: 3500 IU albutrepenonacog alfa
1 vial with 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

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.
For intravenous use

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Do not store above 25 °C. Do not freeze.
Keep the vials in the outer carton in order to protect from light.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

CSL Behring GmbH, 35041 Marburg, Germany

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/16/1095/009

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

IDELVION 3500 IU

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC
SN
NN

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

POWDER VIAL 3500 IU

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION

IDELVION 3500 IU powder for solution for injection
albutrepenonacog alfa
For intravenous use

2. METHOD OF ADMINISTRATION

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

6. OTHER

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

SOLVENT VIAL LABEL 5 ML

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION

Water for injections

2. METHOD OF ADMINISTRATION

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

5 ml

6. OTHER

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

CARTON ADMINISTRATION SET (INNER BOX)

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION

Administration set

2. METHOD OF ADMINISTRATION

3. EXPIRY DATE

Exp. date

4. BATCH NUMBER

Lot. No.

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

6. OTHER

CSL Behring

B. PACKAGE LEAFLET

Package Leaflet: Information for the user

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
IDELVION 3500 IU powder and solvent for solution for injection

albutrepenonacog alfa (recombinant coagulation factor IX)

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, pharmacist or nurse.
- 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, pharmacist or nurse. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet:

1. What IDELVION is and what it is used for

What is IDELVION?

IDELVION is a haemophilia medicine that replaces a natural blood clotting (coagulation) factor IX. The active substance in IDELVION is albutrepenonacog alfa (recombinant fusion protein linking coagulation factor IX with albumin (rIX-FP)).

Factor IX is involved in blood clotting. Patients with haemophilia B have a lack of this factor which means that their blood does not clot as quickly as it should so there is an increased tendency to bleed. IDELVION works by replacing factor IX in haemophilia B patients to enable their blood to clot.

What is IDELVION used for?

IDELVION is used to prevent or to halt bleeding caused by the lack of factor IX in patients of all age groups with haemophilia B (also called congenital factor IX deficiency or Christmas disease).

2. What you need to know before you use IDELVION

Do not use IDELVION
- If you are allergic to the active substance (albutrepenonacog alfa) or any of the other ingredients (listed in section 6).
- If you are allergic to hamster proteins.

Warnings and precautions

It is strongly recommended that every time you use IDELVION, you record the name and batch number of the product to keep track of the products and product batches you have used. .

Talk to your doctor, pharmacist or nurse before using IDELVION.

- Allergic (hypersensitivity) reactions are possible. The product contains traces of hamster proteins (see also "Do not use IDELVION"). **If symptoms of allergic reactions occur, you should stop using the medicine immediately and contact your doctor or the treatment centre where you are followed. Your doctor should inform you of the early signs of hypersensitivity reactions.** These include hives, generalised skin rash, tightness of the chest, wheezing, low blood pressure (hypotension), and anaphylaxis (a serious allergic reaction that causes severe difficulty in breathing, or dizziness).
- Because of the risk of allergic reactions with factor IX, your initial administration of IDELVION should be performed under medical observation where proper medical care for allergic reactions can be provided.
- The formation of **inhibitors** (neutralising antibodies) is a known complication that has been reported during treatment with IDELVION. The inhibitors stop the treatment from working properly. If your bleeding is not being controlled with IDELVION, tell your doctor immediately. You should be monitored regularly for the development of inhibitors.
- If you suffer from liver or cardiac disease or if you have recently had major surgery, please inform your doctor, as there is an increased risk for blood clotting (coagulation) complications.
- If you need a central venous access device (CVAD for injection of IDELVION), the risk of complications including local infections, bacteria in the blood (bacteraemia) and the formation of a blood clot in the blood vessel (thrombosis) where the catheter is inserted should be considered by your doctor.

Other medicines and IDELVION
- Tell your doctor or pharmacist if you are taking, have recently taken or might take any other medicines.

Pregnancy and breast-feeding
- If you are pregnant or breast-feeding, think you may be pregnant or are planning to have a baby, ask your doctor or pharmacist for advice before taking this medicine.
- During pregnancy and breast-feeding, IDELVION should be given only if it is clearly needed.

Driving and using machines
IDELVION does not effect your ability to drive and use machines.

IDELVION contains sodium
This medicine contains up to 8.6 mg sodium (main component of cooking/table salt) in each vial. This is equivalent to 0.4% of the recommended maximum daily dietary intake of sodium for an adult.

3. How to use IDELVION

Your treatment should be started and monitored by a doctor who is experienced in the treatment of blood clotting disorders. Always take this medicine exactly as your doctor has told you. Check with your doctor if you are not sure.

Your doctor will calculate the dose of IDELVION you need. The amount of IDELVION you need to take and the duration of treatment depend on:
- the severity of your disease
- the site and intensity of the bleeding
- your clinical condition and response
- your body weight

IDELVION is administered as an injection into a vein (intravenous, IV) after reconstitution of the powder with the provided solvent by your doctor or nurse. You or somebody else might also administer IDELVION as an IV injection but only after receiving adequate training.

If you use more IDELVION than you should
Please contact your doctor immediately if you inject more IDELVION than your doctor recommends.

If you stop using IDELVION
Do not stop using IDELVION without consulting your doctor.

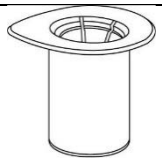
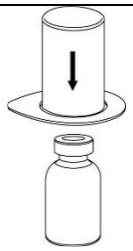
Reconstitution and administration

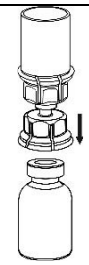
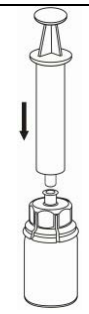
General Instructions

- The powder must be mixed with the solvent (liquid) and withdrawn from the vial while keeping the medicine sterile (germ free). Your doctor will show you how to prepare the solution and how to withdraw the solution from the vial correctly.
- IDELVION must not be mixed with other medicines or solvents except those mentioned in section 6.
- The solution should be clear or slightly opalescent, yellow to colourless, i.e. it might be sparkling when held up to the light but must not contain any obvious particles. After filtering or withdrawal (see below) the solution should be visually checked, before it is used. Do not use the solution if it is cloudy or if it contains flakes or particles.
- Any unused product or waste material should be disposed of in accordance with local requirements and as instructed by your doctor.

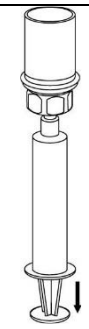
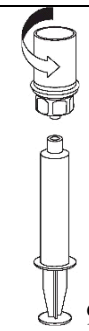
Reconstitution
Without opening the vials, warm the IDELVION powder and the liquid to room or body temperature. This can be done either by leaving the vials at room temperature for about an hour, or by holding them in your hands for a few minutes.
DO NOT expose the vials to direct heat. The vials must not be heated above body temperature (37 °C).

Carefully remove the protective caps from the vials, and clean the exposed rubber stoppers with an alcohol swab. Allow the vials to dry before opening the Mix2Vial package (which contains the filter transfer device), then follow the instructions given below.

 1	1. Open the Mix2Vial by peeling off the lid. Do **not** remove the Mix2Vial from the blister package!
 2	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	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	4. Place the IDELVION **powder 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 IDELVION vial stopper. The solvent will automatically flow into the IDELVION vial.
 5	5. With one hand grasp the IDELVION side of the Mix2Vial set and with the other hand grasp the solvent-side and unscrew the set carefully counter-clockwise into two pieces. Discard the solvent vial with the blue Mix2Vial adapter attached.
 6	6. Gently swirl the IDELVION vial with the transparent adapter attached until the substance is fully dissolved. Do not shake.
 7	7. Draw air into an empty, sterile syringe. While the IDELVION vial is upright, connect the syringe to the Mix2Vial's Luer Lock fitting by screwing clockwise. Inject air into the IDELVION vial.

Withdrawal and administration

 8	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	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 counter-clockwise.

Use the venipuncture kit supplied with the product, insert the needle into a vein. Let blood flow back to the end of the tube. Attach the syringe to the threaded, locking end of the venipuncture kit. **Inject the reconstituted solution slowly (as comfortable for you, up to a maximum of 5 ml/min) into the**

vein following the instructions given to you by your doctor. Take care not to get any blood in the syringe containing the product.

Check yourself for any side effects that might happen straight away. If you have any side effects that might be related to the administration of IDELVION, the injection should be stopped (see also sections 2 and 4).

If you have any further questions on the use of this medicine, ask your doctor, pharmacist or nurse.

4. Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them.

Please contact your doctor immediately:
- **if you notice symptoms of allergic reactions (see below)**
- **if you notice that the medicine stops working properly**

The following side effects have been observed with factor IX medicines:
- Allergic-type hypersensitivity reactions are possible (commonly) and may include the following symptoms: hives, skin rashes (generalised urticaria), tightness of the chest, wheezing, low blood pressure (hypotension) and anaphylaxis (a serious reaction that causes severe difficulty in breathing or dizziness). If this happens, you should stop using the medicine immediately and contact your doctor.
- Inhibitors: the medicine stops working properly (continuous bleeding). You may develop an inhibitor (neutralising antibody) to factor IX (frequency not known), in which case factor IX will not work properly anymore. If this happens, you should stop using the medicine immediately and contact your doctor.

The following side effects have **commonly** been observed with IDELVION (may affect up to 1 in 10 people):
- Headache
- Injection site reactions
- Dizziness
- Rash

The following side effects occurred **uncommonly** (may affect up to 1 in 100 people):
- Eczema

- **Side effects in children and adolescents**

Side effects in children are expected to be the same as in adults.

Reporting of side effects
If you get any side effects, talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via the national reporting system listed in Appendix V. By reporting side effects you can help provide more information on the safety of this medicine.

5. How to store IDELVION

- Keep this medicine out of the sight and reach of children.
- Do not use this medicine after the expiry date, which is stated on the label and carton.
- Do not store above 25 °C.
- Do not freeze.
- Keep the vial in the outer carton in order to protect from light.

- The reconstituted product should preferably be used immediately.
- If the reconstituted product is not administered immediately, storage times and conditions prior to use are in the responsibility of the user.

6. Contents of the pack and other information

What IDELVION contains

The active substance is:
250 IU per vial; after reconstitution with 2.5 ml of water for injections the solution contains 100 IU/ml of albutrepenonacog alfa.
500 IU per vial; after reconstitution with 2.5 ml of water for injections the solution contains 200 IU/ml of albutrepenonacog alfa.
1000 IU per vial; after reconstitution with 2.5 ml of water for injections the solution contains 400 IU/ml of albutrepenonacog alfa.
2000 IU per vial; after reconstitution with 5 ml of water for injections the solution contains 400 IU/ml of albutrepenonacog alfa.
3500 IU per vial; after reconstitution with 5 ml of water for injections the solution contains 700 IU/ml of albutrepenonacog alfa.

The other ingredients are:
Sodium citrate, polysorbate 80, mannitol, sucrose, and hydrochloric acid (for pH adjustment)
See last paragraph of section 2.
Solvent: Water for injections

What IDELVION looks like and contents of the pack

IDELVION is presented as a pale yellow to white powder and is supplied with water for injections as solvent.
The reconstituted solution should be clear to slightly opalescent, yellow to colourless i.e. it might sparkle when held up to the light but must not contain any obvious particles.

Presentations

One pack with 250, 500 or 1000 IU containing:
1 vial with powder
1 vial with 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

One pack with 2000 or 3500 IU containing:
1 vial with powder
1 vial with 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.

Marketing Authorization Holder and Manufacturer

CSL Behring GmbH
Emil-von-Behring-Straße 76
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Germany

For any information about this medicine, please contact the local representative of the Marketing Authorisation Holder:

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This leaflet was last revised in {MM/YYYY}.

Detailed information on this medicine is available on the European Medicines Agency web site: http://www.ema.europa.eu.

The following information is intended for healthcare professionals only:

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 are related 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 IU factor IX per kg body weight raises the plasma factor IX activity by an average of 1.3 IU/dl (1.3 % of normal activity) in patients ≥ 12 years of age and by 1.0 IU/dl (1.0 % of normal activity) 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:
Required dose (IU) = body weight (kg) x desired factor IX rise (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:
Required dose (IU) = body weight (kg) x desired factor IX rise (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 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 (pre-and post-operative)	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 (pre-and post- operative)	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.

Prophylaxis
For long term prophylaxis against bleeding in patients with severe haemophilia B, the usual doses are 35 to 50 IU/kg once weekly.

Some patients who are well-controlled on a once-weekly regimen might be treated with up to 75 IU/kg on an interval of 10 or 14 days. For patients >18 years, further extension of the treatment interval may be considered.

In some cases, especially in younger patients, shorter dose intervals or higher doses may be necessary.

After a bleeding episode during prophylaxis, patients should maintain their prophylaxis regimen as closely as possible, with 2 doses of IDELVION being administered at least 24 hours apart but longer if deemed suitable for the patient.

Paediatric population
For long term prophylaxis, the recommended dose regimen is 35 to 50 IU/kg once weekly. For adolescents of 12 years of age and above, the dose recommendations are the same as for adults (see above).

Special warnings and precautions for use

Inhibitors
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.

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.