1. NAME OF THE MEDICINAL PRODUCT

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

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

One vial IDELVION contains nominally 250/500/1000/2000 IU of the active substance, recombinant fusion protein linking coagulation factor IX with albumin (rIX-FP), (INN = albutrepenonacog alfa).

After reconstitution with 2.5 ml water for injections (250/500/1000 IU) the solution contains 100/200/400 IU/ml of albutrepenonacog alfa. When reconstituted with 5 ml water for injections (2000 IU) 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:
Sodium approximately 75 mmol/l (1.7243 g/l).
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.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

IDELVION is indicated in children and adults with Hemophilia B (congenital Factor IX deficiency) for:

- On-demand treatment and control of bleeding episodes
- Perioperative management of bleeding
- Routine prophylaxis to reduce the frequency of bleeding episodes.

4.2 Posology and method of administration

Initiate treatment of IDELVION under the supervision of a physician experienced in the treatment of haemophilia B.

The decision for an individual patient on the use of home treatment of bleeding and prophylaxis of bleeding in patients with haemophilia B should be made by the treating physician who should ensure that appropriate training is provided and the use is reviewed at intervals.

Previously untreated patients
The safety and efficacy of IDELVION in previously untreated patients is consistent with the known safety and efficacy profile of rIX-FP in adult and pediatric PTPs with hemophilia B.

Monitoring Laboratory Tests
To confirm adequate factor IX levels have been achieved and maintained, monitor plasma factor IX activity by performing the one-stage clotting assay. Factor IX results can be affected by the type of aPTT reagent used. 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.

Posology
The dose and duration of the substitution therapy depend on the severity of the factor IX deficiency, the location and extent of the bleeding and the patient's clinical condition and response.

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

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.
For determination of adequate maintenance dose take into consideration the extended half-life of the product.

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).

The following table can be used to guide dosing for control and prevention of 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	30 - 60	Single dose should be sufficient for majority of bleeds. Maintenance dose after 48 – 72 hours if there

bleeding		is further evidence of bleeding.
Major Life threatening haemorrhages, deep muscle bleeding including iliopsoas	60 - 100	Repeat every 48 – 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 48 – 72 hours until bleeding stops and healing is achieved.
Major surgery	60 - 100 (initial level)	Repeat every 48 – 72 hours for the first week, and then maintenance dose 1 – 2 times per week until bleeding stops and healing is achieved.

Prophylaxis

Adults and adolescents (≥12 years of age)
For routine prophylaxis to prevent bleeding in patients ≥12 years of age with haemophilia B, the recommended dose regimen is: · 25–40 IU/kg once weekly (every 7 days).
Adult and adolescent patients who are well controlled on this once weekly dosing regimen may be switched to: · 50–75 IU/kg every 14 days.
Patients ≥18 years who are well-controlled on a 14 day regimen may be switched to 100IU/kg every 21 days.
Adjust dosing regimen based on individual patient's clinical condition and response.

Paediatrics (<12 years of age)
For routine prophylaxis to prevent bleeding in paediatric patients with haemophilia B, the recommended dose regimen is:
35–50 IU/kg once weekly (every 7 days).
Based on the individual patient's clinical condition and response, it may be appropriate for the specialist treating physician to extend dose interval and increase dose during routine clinical management.

Older people
The posology and method of administration in older people (> 65 years) has not been determined in clinical studies.

Monitoring for inhibitors
Patients should be monitored for the development of factor IX inhibitors. See also section 4.4.

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.

The patient should be observed for any immediate reaction. If any reaction takes place that might be related to the administration of IDELVION, the rate of injection should be decreased or the application should be stopped, as required by the clinical condition of the patient (see also section 4.4).

4.3 Contraindications

IDELVION is contraindicated in patients who have a known hypersensitivity to IDELVION, any of its components, excipients or hamster protein (see section 6.1).

4.4 Special warnings and precautions for use

Hypersensitivity
Allergic type hypersensitivity reactions are possible. The product contains traces of hamster proteins. If symptoms of hypersensitivity occur, discontinue use of the medicinal product immediately and initiate appropriate treatment. Patients should be informed of the early signs of hypersensitivity reactions including hives, generalised urticaria, tightness of the chest, wheezing, hypotension and anaphylaxis. Advise patients to discontinue use of IDELVION and contact their physician. All factor IX products have potential of allergic reactions. It is recommended that the initial administration of factor IX should be performed under medical observation where proper medical care for allergic reactions could be provided.

Inhibitors
Formation of inhibitor to factor IX has been reported during factor replacement therapy with IDELVION in the treatment of haemophilia B. Patients should be monitored for the development of neutralising antibodies (inhibitors) that should be quantified in Bethesda Units (BU) using appropriate biological testing.

Perform an assay that measures factor IX inhibitor concentration if expected plasma factor IX activity levels are not attained, or if the bleeding is not controlled with the appropriate dose. A specialized haemophilia treatment centre is recommended to be contacted in case the bleeding cannot be controlled or inhibitor development is suspected.

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.

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 disseminated intravascular coagulation (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.

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

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

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 IDELVION with other medicinal products have been reported.

4.6 Fertility, pregnancy and lactation

Animal reproduction studies have not been conducted with IDELVION. Based on the rare occurrence of haemophilia B in women, experience regarding the use of IDELVION during pregnancy and breast-feeding is not available.

Therefore, IDELVION should be used during pregnancy and lactation only if clearly indicated.

4.7 Effects on ability to drive and use machines

No effects on ability to drive and use machines have been observed.

4.8 Undesirable effects

Summary of the safety profile

With the use of factor IX products hypersensitivity or allergic reactions (which may include angioedema, burning and stinging at the injection site, chills, flushing, generalised urticaria, headache, hives, hypotension, lethargy, nausea, restlessness, tachycardia, tightness of the chest, tingling, vomiting, wheezing) have been observed. In rare cases, these reactions have progressed to anaphylaxis, and they have occurred in close temporal association with development of factor IX inhibitors.

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 the post-marketing experience with IDELVION.

With the use of factor IX products obtained from CHO cells very rarely development of antibodies to hamster protein has been observed.

During open label clinical trials with IDELVION conducted in 114 previously treated patients, 1078 treatment-emergent adverse events were reported in 103/114 (90.4 %) subjects who received a total of 16567 injections. Of these 1078 events, 18 were reported as related in 11/114 (9.6 %) subjects. In the completed study with previously untreated patients, 11 of 12 PUPs had a total of 137 treatment-emergent adverse events, of which most were mild or moderate. 2 PUPs had 5 events considered related to IDELVION.

Tabulated list of adverse reactions

The table presented below is according to the MedDRA system organ classification (SOC and Preferred Term Level).

The frequency of adverse reactions is based on percentage of related events in rIX-FP clinical studies. It is estimated on a per-patient and per-injection basis and categorised as 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) and not known (cannot be estimated from the available data).

Adverse events in the Table below were from clinical trials and considered related by the investigator:

MedDRA Standard System Organ Class	**MedDRA Preferred Term**	**Frequency per patient**	**Frequency per injection**
General disorders and administration site conditions	Injection site reactions	Common	Rare

Blood and Lymphatic System	FIX inhibition / Inhibitor development*	Not known	Not known
Nervous system disorders	Headache	Common	Rare
	Dizziness	Common	Rare
Immune system disorders	Hypersensitivity	Common	Rare
Skin and subcutaneous tissue disorders	Rash	Common	Rare
	Eczema	Uncommon	Very rare

*Data is from clinical trial and post marketing experience.

Paediatric population
Frequency, type and severity of adverse reactions in children are 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 fusion protein linking recombinant coagulation factor IX with recombinant albumin that effectively replaces the missing coagulation factor IX needed for haemostasis and provides for longer dose regimens. The prolongation of the half-life of IDELVION and the enhanced systemic exposure are achieved by fusion with recombinant albumin, which has a long intrinsic half-life. Albumin is a natural, inert carrier protein in plasma with a long half-life of approximately 20 days that is not involved in immune defense or immune response. 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.

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.

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 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) 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 intravenous injections of single doses of 25, 50, 75 and 100 IU/kg. The PK parameters (see table below) were based on plasma factor IX activity measured by the one-stage clotting assay. Blood samples for PK analysis were collected prior to dosing and up to 504 hours (21 days) after dosing.

Pharmacokinetic Parameters (Arithmetic Mean, CV %) following a single injection of IDELVION in Adults

PK Parameters	**50 IU/kg (N=47)**
IR[a] (IU/dl)/(IU/kg)	1.30 (23.8)
C_{max} [a] (IU/dl)	66.6 (26.7)
$AUC_{0\text{-}inf}$ (h*IU/dl)	7482 (28.4)
$t_{1/2}$ (h)	104.2 (25.4)
MRT (h)	142.8 (22.7)
CL (ml/h/kg)	0.731 (26.8)
Vss (dl/kg)	1.020 (27.9)
Time to 1 % factor IX activity (d)[b]	25.5
Time to 3 % factor IX activity (d)[b]	16.5

[a] = Corrected for baseline levels
[b] = estimated time to median factor IX activity above the pre-specified %
IR = incremental recovery; AUC = area under the factor IX activity time curve; CL = body weight adjusted clearance; Vss = body weight adjusted volume of distribution at steady-state; $t_{1/2}$ = half-life; MRT = mean residence time; time to 1 % factor IX activity = estimated time in days after dose when factor IX activity has declined to approximately 1 IU/dl above baseline

The PK data demonstrate that IDELVION has a prolonged circulating half-life, increased area under the factor IX activity time curve, lower clearance and an increased incremental recovery compared with short-acting FIX replacement products. In the pivotal trial, the mean (CV%) incremental recovery of IDELVION was
1.30 (23.8 %) which is higher than that achieved 1.00 (25.7 %) with the previous factor IX product (pdFIX or rFIX). Therefore, one IU/kg IDELVION provides a mean increase of 1.30 IU/dl in the circulating level of factor IX.

Repeat PK assessment for up to 30 weeks demonstrated a stable pharmacokinetic profile

and incremental recovery was consistent over time.

The mean factor IX activity at day 21 following a single dose of 100 IU/kg IDELVION was 6.4%. The mean factor IX activity at day 14 following a single dose of 75 IU/kg IDELVION was 6.65%. The mean factor IX activity at days 7, 10, and 14 following a single dose of 50 IU/kg IDELVION was 13.76%, 9.59%, and 6.1%, respectively. The mean factor IX activity at days 7, 10, and 14 following a single dose of 25 IU/kg IDELVION was 8.62%, 5.02%, and 2.96%, respectively.

Paediatric population

Pharmacokinetic (PK) parameters of IDELVION were evaluated in 5 adolescents (12 to <18 years of age) and 27 children (1 to <12 years of age) in open-label, multi-centre studies following an intravenous injection of a single dose of 50 IU/kg. The PK samples were collected prior to dosing and at multiple time points up to 336 hours (14 days) after dosing. PK parameters (presented below) were estimated based on the plasma factor IX activity over time profile.

The following table summarizes the PK parameters calculated from the paediatric data of 32 subjects 1 to <18 years of age. Compared to adults, incremental recovery appeared to be slightly lower and body weight-adjusted clearance appeared to be higher in children.

Comparison of Pharmacokinetic Parameters of IDELVION by Age Category (Arithmetic Mean, CV %) 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)	0.951 (21.5)	1.06 (22.6)	1.11 (27.7)
C_{max}[a] (IU/dl)	48.3 (19.0)	52.9 (23.2)	55.3 (28.1)
$AUC_{0\text{-}inf}$ (h*IU/dl)	4583 (33.2)	5123 (31.4)	5347 (48.2)
$t_{1/2}$ (h)	89.6 (12.5)	92.8 (20.5)	87.3 (35.7)
MRT (h)	123 (14.2)	129.2 (19.0)	119 (31.2)
CL (ml/h/kg)	1.18 (27.8)	1.06 (28.5)	1.08 (39.3)
Vss (dl/kg)	1.43 (24.1)	1.32 (19.7)	1.16 (14.0)

a= corrected for basline levels

IR = incremental recovery; AUC = area under the factor IX activity time curve; CL = body weight adjusted clearance; Vss = body weight adjusted volume of distribution at steady-state; $t_{1/2}$ = half-life; MRT = mean residence time

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, Polysorbate 80, Mannitol, Sucrose
HCl (in small amounts 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

36 months.

After reconstitution the chemical and physical in-use stability has been demonstrated for 8 hours at room temperature (below 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

Immediate containers
Powder (250/500/1000 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).

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).Presentation
Box 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
Administration set (inner box):
1 disposable 5 ml syringe
1 venipuncture set
2 alcohol swabs
1 non-sterile plaster

Box with 2000 IU containing:
1 vial with powder
1 vial with 5 ml water for injections
1 filter transfer device 20/20
Administration set (inner box):
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

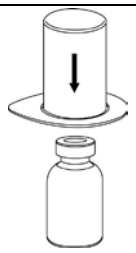
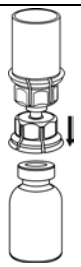
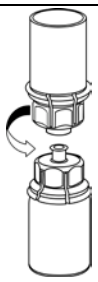
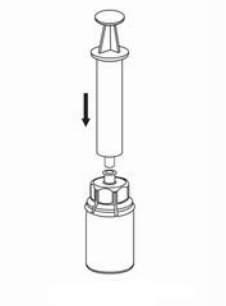
General instructions

- The 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.

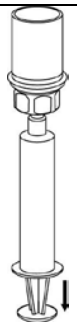
Reconstitution

Bring the solvent to room temperature. 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 package 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 counterclockwise 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 counterclockwise.

For injection of IDELVION, the provided administration sets are recommended to 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.

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7. Manufacturer

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35041 Marburg
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8. Date of Revision of The Text

February 2023