1. NAME OF THE MEDICINAL PRODUCT

IDELVION 250 IU powder and solvent for solution for injection

IDELVION 500 IU powder and solvent for solution for injection

IDELVION 1000 IU powder and solvent for solution for injection

IDELVION 2000 IU powder and solvent for solution for injection

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

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

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

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

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

The potency (International Units [IU]) is determined using an in-vitro activated partial thromboplastin time (aPTT)-based one-stage clotting assay calibrated against the World Health Organization (WHO) International Standard for factor IX concentrate.

Albutrepenonacog alfa is a purified protein produced by recombinant DNA technology, generated by the genetic fusion of recombinant albumin to recombinant coagulation factor IX. The genetic fusion of the cDNA of human albumin to the cDNA of human coagulation factor IX enables the protein to be produced as a single recombinant protein and assures product homogeneity by avoiding chemical conjugation. The recombinant factor IX portion is identical to the Thr148 allelic form of plasma-derived factor IX. The cleavable linker between the recombinant factor IX and albumin molecules is derived from the endogenous “activation peptide” in native factor IX.

Excipient with known effect:
Up to 25.8 mg (1.13 mmol) sodium per dose (bodyweight 70 kg).
For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Powder and solvent for solution for injection.
Pale yellow to white whole or cracked cake and clear, colourless solvent for solution for injection.
After reconstitution- yellow to colorless clear liquid free of visible particles.

pH: 6.6 - 7.2

Osmolality:
IDELVION 250 IU powder and solvent for solution for injection
175 – 215 mOsm/kg.

IDELVION 500 IU powder and solvent for solution for injection
260 – 300 mOsm/kg.

IDELVION 1000 IU powder and solvent for solution for injection
260 – 300 mOsm/kg.

IDELVION 2000 IU powder and solvent for solution for injection
260 – 300 mOsm/kg.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Treatment and prophylaxis of bleeding in patients with haemophilia B (congenital factor IX deficiency).

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.

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

Treatment monitoring
During the course of treatment, appropriate determination of factor IX levels is advised to guide the dose to be administered and the frequency of repeated infusions. Individual patients may vary in their responses to factor IX, demonstrating different half-lives and recoveries. Dose based on bodyweight may require adjustment in underweight or overweight patients. In the case of major surgical interventions in particular, precise monitoring of the substitution therapy by means of coagulation analysis (plasma factor IX activity) is indispensable.

When using an in vitro thromboplastin time (aPTT)-based one stage clotting assay for determining Factor IX activity in patients' blood samples, plasma factor IX activity results can be significantly affected by both the type of aPTT reagent and the reference standard used in the assay. Measurement with a one-stage clotting assay using a kaolin based aPTT reagent or Actin FS aPTT reagent will likely result in an underestimation of activity level. This is of importance particularly when changing the laboratory and/or reagents used in the assay.

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

The number of units of factor IX administered is expressed in International Units (IU), which 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 International Unit (IU) factor IX per kg body weight is expected to increase the circulating level of factor IX by an average of 1.3 IU/dl (1.3 % of normal) in patients ≥ 12 years of age and by 1.0 IU/dl (1.0 % of normal) in patients < 12 years of age. The required dose is determined using the following formulae:

Required dose (IU) = body weight (kg) x desired factor IX rise (% of normal or IU/dl) x {reciprocal of observed recovery (IU/kg per IU/dl)}

Expected factor IX rise (IU/dl or % of normal) = Dose (IU) x Recovery (IU/dl per IU/kg)/body weight (kg)

The amount to be administered and the frequency of administration should always be oriented to the clinical effectiveness in the individual case.

Patients < 12 years of age
For an incremental recovery of 1 IU/dl per 1 IU/kg, the dose is calculated as follows:
Dose (IU) = body weight (kg) x desired factor IX increase (IU/dl) x 1 dl/kg

Example
1. A peak level of 50 % of normal is required in a 20 kg patient with severe haemophilia B. The appropriate dose would be 20 kg x 50 IU/dl x 1 dl/kg = 1000 IUs.

2. A dose of 1000 IUs of IDELVION, administered to a 25 kg patient, should be expected to result in a peak post-injection factor IX increase of 1000 IUs/25 kg x 1.0 (IU/dl per IU/kg) = 40 IU/dl (40 % of normal).

Patients ≥ 12 years of age
For an incremental recovery of 1.3 IU/dl per 1 IU/kg, the dose is calculated as follows:
Dose (IU) = body weight (kg) x desired factor IX increase (IU/dl) x 0.77 dl/kg

Example
3. A peak level of 50 % of normal is required in a 80 kg patient with severe haemophilia B. The appropriate dose would be 80 kg x 50 IU/dl x 0.77 dl/kg = 3080 IUs.

4. A dose of 2000 IUs of IDELVION, administered to a 80 kg patient, should be expected to result in a peak post-injection factor IX increase of 2000 IUs x 1.3 (IU/dl per IU/kg) /80 kg = 32.5 IU/dl (32.5 % of normal).

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

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

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

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

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

Paediatric population
For routine prophylaxis the recommended dose regimen for paediatric subjects is 35 to 50 IU/kg once weekly (see sections 5.1 and 5.2).

Method of administration
Intravenous use.

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

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

4.3 Contraindications

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

Known allergic reaction to hamster protein.

4.4 Special warnings and precautions for use

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

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

There have been reports in the literature showing a correlation between the occurrence of a factor IX inhibitor and allergic reactions. Therefore, patients experiencing allergic reactions should be evaluated for the presence of an inhibitor. It should be noted that patients with factor IX inhibitors may be at an increased risk of anaphylaxis with subsequent challenge with factor IX.

Because of the risk of allergic reactions with factor IX products, the initial administration of factor IX should, according to the treating physician's judgement, be performed under medical observation where proper medical care for allergic reactions could be provided.

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

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

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

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

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

Immune tolerance induction

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

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

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

4.5 Interaction with other medicinal products and other forms of interaction

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

4.6 Fertility, pregnancy and lactation

Animal reproduction studies have not been conducted with factor IX. Based on the rare occurrence of haemophilia B in women, experience regarding the use of factor IX during pregnancy and 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.

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

Patients with haemophilia B may develop neutralising antibodies (inhibitors) to factor IX. If such inhibitors occur, the condition will manifest itself as an insufficient clinical response. In such cases, it is recommended that a specialised haemophilia centre be contacted. Inhibitor development was reported in an ongoing clinical study with previously untreated patients. Inhibitor development has been observed in previously treated patients in the post-marketing experience with IDELVION.
There is a potential risk of thromboembolic episodes following the administration of factor IX products, with a higher risk for low purity preparations. The use of low purity factor IX products has been associated with instances of myocardial infarction, disseminated intravascular coagulation, venous thrombosis and pulmonary embolism. The use of high purity factor IX is rarely associated with such adverse reactions.

Tabulated list of adverse reactions
Four open label clinical studies included 107 subjects with at least one exposure to IDELVION reporting 13 adverse reactions in 7 subjects.
The table presented below is according to the MedDRA system organ classification (SOC and Preferred Term Level).

Frequencies have been evaluated according to the following convention: very common (≥1/10); common (≥1/100 to <1/10); uncommon (≥1/1,000 to <1/100); rare (≥1/10,000 to <1/1,000); very rare (<1/10,000), not known (cannot be estimated from the available data).

Within each frequency grouping, adverse reactions are presented in order of decreasing seriousness.

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

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

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

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Any suspected adverse events should be reported to the Ministry of Health according to the National Regulation by using an online form

/https://sideeffects.health.gov.il

and emailed to the Registration Holder's Patient Safety Unit at: drugsafety@neopharmgroup.com

4.9 Overdose

No symptoms of overdose with IDELVION have been reported.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

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

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

Pharmacodynamic effects
Haemophilia B is a sex linked hereditary disorder of blood coagulation due to decreased levels of factor IX and results in profuse bleeding into joints, muscles or internal organs, either spontaneously or as a result of accidental or surgical trauma. By replacement therapy the plasma levels of factor IX is increased, thereby enabling a temporary correction of the factor deficiency and correction of the bleeding tendencies.

Factor IX is activated by factor VII/tissue factor complex in the extrinsic pathway as well as factor XIa in the intrinsic coagulation pathway. Activated factor IX, in combination with activated factor VIII, activates factor X. This results ultimately in the conversion of prothrombin to thrombin. Thrombin then converts fibrinogen into fibrin and a clot can be formed. Factor IX activity is absent or greatly reduced in patients with haemophilia B and substitution therapy may be required.

Clinical efficacy and safety
A phase 1/2 study evaluated the treatment efficacy and prevention of bleeding episodes of rIX-FP in 17 subjects (ages 13-46 years), 13 subjects in the prophylaxis arm received weekly prophylaxis with IDELVION for approximately 11 months, and 4 subjects in the on-demand arm received IDELVION upon occurrence of bleeding events. All 85 bleeding episodes were successfully treated with 1 or 2 doses of IDELVION.

The efficacy of IDELVION has been evaluated in the open-label, uncontrolled part of a phase 2/3 study, in which a total of 63 male, previously treated patients (PTPs) between 12 and 61 years of age received IDELVION either for prophylaxis once every 7-, 10- and/or 14-day intervals and/or for the treatment of bleeding episodes on an on-demand basis. All subjects had severe (FIX level <1%) or moderately severe (FIX level ≤ 2%) haemophilia B. Forty PTPs received IDELVION for prophylaxis.

Subjects who received prophylactic treatment started with 35-50 IU/kg once weekly. A subgroup of patients 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). 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.

Clinical studies investigating safety and efficacy of longer treatment intervals than once weekly are ongoing.

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

Haemostasis was maintained throughout the study duration.

5.2 Pharmacokinetic properties

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

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

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

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

Paediatric population

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

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

PK Parameters	1 to <6 years (N=12)	6 to <12 years (N=15)	12 to <18 years (N=5)
IR (IU/dl)/(IU/kg)	0.968 (0.660, 1.280)	1.07 (0.70, 1.47)	1.11 (0.84, 1.61)
C_{max} (IU/dl)	48.2 (33.0, 64.0)	50.5 (34.9, 73.6)	55.3 (40.5, 80.3)
$AUC_{0\text{-}inf}$ (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)

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

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

5.3 Preclinical safety data

Non-clinical data reveal no special hazard for humans based on conventional studies of safety pharmacology, single and repeat dose toxicity, genotoxicity, thrombogenicity and local tolerability.

No investigations on carcinogenicity and reproductive toxicology have been conducted.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

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

Solvent:
Water for injections

6.2 Incompatibilities

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

6.3 Shelf life

The expiry date of the product is indicated on the packaging materials

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 (rubber) a disc (plastic) and a cap (aluminium).
2.5 ml of solvent in a vial (type I glass), with a stopper (rubber) a disc (plastic) and a cap (aluminium).

IDELVION 500 IU powder and solvent for solution for injection
Powder (500 IU) in a 6 ml vial (type I glass), with a stopper (rubber) a disc (plastic) and a cap (aluminium).
2.5 ml of solvent in a vial (type I glass), with a stopper (rubber) a disc (plastic) and a cap (aluminium).

IDELVION 1000 IU powder and solvent for solution for injection
Powder (1000 IU) in a 6 ml vial (type I glass), with a stopper (rubber) a disc (plastic) and a cap (aluminium).
2.5 ml of solvent in a vial (type I glass), with a stopper (rubber) a disc (plastic) and a cap (aluminium).

IDELVION 2000 IU powder and solvent for solution for injection
Powder (2000 IU) in a 10 ml vial (type I glass), with a stopper (rubber) a disc (plastic) and a cap (aluminium).
5 ml of solvent in a vial (type I glass), with a stopper (rubber) a disc (plastic) and a cap (aluminium).

Presentations

Each pack contains:

IDELVION 250 IU powder and solvent for solution for injection:
1 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

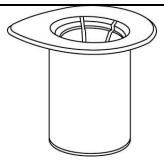
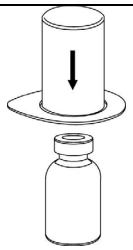
IDELVION 2000 IU powder and solvent for solution for injection
1 vial with powder
1 vial with 5 ml water for injections
1 filter transfer device 20/20
One inner box containing:
1 disposable 10 ml syringe
1 venipuncture set
2 alcohol swabs
1 non-sterile plaster

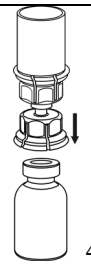
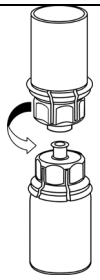
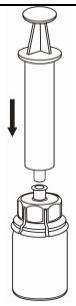
Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

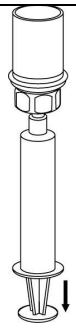
General instructions
- The reconstituted solution should be yellow to colorless clear liquid free of visible particles. After filtering/withdrawal (see below) the reconstituted product should be inspected visually for particulate matter and discoloration prior to administration.
- Do not use solutions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

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

 1	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 **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 product vial stopper. The solvent will automatically flow into the product vial.
 5	5. With one hand grasp the powder-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 product 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 product vial is upright, connect the syringe to the Mix2Vial's Luer Lock fitting by screwing clockwise. Inject air into the product vial.

Withdrawal and application

 8	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, only the provided administration sets should be used because treatment failure can occur as a consequence of factor IX adsorption to the internal surface of some injection equipment.

Care should be taken that no blood enters the syringe filled with product, as there is a risk that the blood could coagulate in the syringe and fibrin clots could therefore be administered to the patient.

The IDELVION solution must not be diluted.

The reconstituted solution should be administered by slow intravenous injection. The rate of administration should be determined by the patient's comfort level, up to a maximum of 5 ml/min.

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

7. MANUFACTURER

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

8. REGISTRATION HOLDER

GenMedix
12 Beit Harishonim Street
12085 Emek – Hefer
Industrial Park 3877701
Israel

9. REGISTRATION NUMBER(S)

Idelvion 250 IU - 159-29-35013
Idelvion 500 IU - 159-30-35014
Idelvion 1000 IU - 159-31-35015
Idelvion 2000 IU - 159-32-35016

The content of this leaflet was approved by the Ministry of Health in October 2017 and updated according to the guidelines of the Ministry of Health in November 2019