เอกสารกำกับยาสำหรับบุคลากรทางการแพทย์

CSL Behring CCDS
Recombinant fusion protein linking coagulation factor IX with albumin (rIX-FP)
Version 9.0 Revision date: 04-Sep-2017

1. NAME OF THE MEDICINAL PRODUCT

IDELVION, 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 all patient with haemophilia B (congenital factor IX deficiency) for:

- Treatment and prophylaxis of bleeding
- Control and prevention of bleeding in surgical settings.

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.

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 bleeding	30 - 60	Single dose should be sufficient for majority of bleeds. Maintenance dose after 48 – 72 hours if there is further evidence of bleeding.
Major Life threatening haemorrhages, deep muscle bleeding including	60 - 100	Repeat every 48 – 72 hours for the first week, and then maintenance dose weekly

iliopsoas		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
For routine prophylaxis to prevent bleeding in patients with haemophilia B, the recommended regimens are either 25 to 40 IU/kg once weekly or 50 - 75 IU/kg every 14 days. Adjust dosing regimen based on individual patient's clinical condition and response.

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

Paediatric population
Currently available data are described in section 5.2.

For routine prophylaxis the recommended dose regimen for paediatrics is the same as for adults (see section 5.2). Dosing regimen should be adjusted based on individual patient's clinical condition and response.

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 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.

Inhibitors
Formation of inhibitor to factor IX has been reported during factor replacement therapy 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 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.

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.

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 rarely. In rare cases, these reactions have progressed to anaphylaxis, and they have occurred in close temporal association with development of factor IX inhibitors. No anaphylactic reactions have been observed in clinical trials with 107 patients for IDELVION.

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. No inhibitors have been observed in clinical trials with 107 previously treated patients for IDELVION. Inhibitor development was reported on one previously untreated patient in an ongoing clinical study.

With the use of factor IX products obtained from CHO cells very rarely development of antibodies to hamster protein has been observed. No such antibodies have been detected in clinical trials with 107 patients for IDELVION.

No thrombotic events were reported during clinical studies with 107 patients for IDELVION.

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

During completed uncontrolled, open label clinical trials with IDELVION conducted in 107 previously treated patients, 579 adverse events were reported in 94/107 (87.9 %) subjects who received a total of 6480 injections. Of these 579 events, 15 were reported as related in 8/107 (7.5 %) subjects.

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) and very rare (<1/10,000).

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
Nervous system disorders	Headache	Common	Rare
	Dizziness	Uncommon	Rare
Immune system disorders	Hypersensitivity	Uncommon	Rare
Skin and subcutaneous tissue disorders	Rash	Uncommon	Rare
	Eczema	Uncommon	Rare

One previously untreated patient from the ongoing clinical trial developed 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 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.

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 (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 336 hours (14 days) after dosing. The PK data demonstrate that IDELVION has an improved PK profile, including prolonged circulating half-life.

Pharmacokinetic Parameters (Arithmetic Mean, CV %) following a single injection of 50 IU/kg IDELVION

PK Parameters	IDELVION (50 (IU/kg)) (N=47)

IR (IU/dl)/(IU/kg)	1.30 (23.8)
C_{max} (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)[a]	23.0
Time to 3 % factor IX activity (d)[a]	16.0

[a] = 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. 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 PK after a single dose of 75 IU/kg IDELVION was derived from 8 evaluable subjects. The mean factor IX activity at day 14 was 6.65 %.The estimated time to 1 % of factor IX activity is approximately 28 days after a single dose of 75 IU/kg IDELVION, based on population PK modelling simulations.

The PK after a single dose of 25 IU/kg IDELVION was derived from 7 evaluable subjects. The mean factor IX activity at day 14 was 2.97 %. The estimated time to 1 % factor IX activity is approximately 16.5 days after a single dose of 25 IU/kg IDELVION, based on population PK modelling simulations.

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 (IU/dl)/(IU/kg)	0.951 (21.5)	1.06 (22.6)	1.11 (27.7)
C_{max} (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)

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 dihydrate, 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

250 IU and 500 IU **36 months**
1000 IU and 2000 IU **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

Store at 2 – 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
Filter transfer device 20/20 (Mix2Vial)
Administration set (inner box):
- 1 venipuncture set

- 2 alcohol swabs
- 1 non-sterile plaster
- 1 disposable 5 ml syringe

Box with 2000 IU
containing:
1 vial with powder
1 vial with 5 ml water for injections
Filter transfer device 20/20 (Mix2Vial)
Administration set (inner box):
- 1 venipuncture set
- 2 alcohol swabs
- 1 non-sterile plaster
- 1 disposable 10 ml syringe

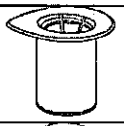
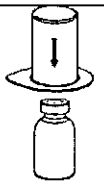
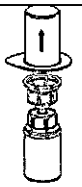
6.6 Special precautions for disposal and other handling

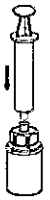
General instructions

- 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.

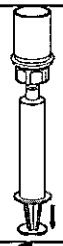
Reconstitution

Bring the solvent to room temperature. Ensure 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 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 **product vial** on an even and firm surface. Invert the solvent vial with the Mix2Vial set attached and push the spike of the **transparent** adapter end **straight down** through the product vial stopper. The solvent will automatically flow into the product vial.
 5	5. With one hand grasp the product-side of the Mix2Vial set and with the other hand grasp the solvent-side and unscrew the set carefully counterclockwise into two pieces. Discard the solvent vial with the blue Mix2Vial adapter attached.
 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, 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. Marketing Authorisation Holder

ZUELLIG PHARMA LTD
Bangkok, Thailand

8. Marketing Authorisation Number(s)

IDELVION (powder and solvent for solution for injection 250 IU) Reg.no. XXXXX
IDELVION (powder and solvent for solution for injection 500 IU) Reg.no. XXXXX
IDELVION (powder and solvent for solution for injection 1000 IU) Reg.no. XXXXX
IDELVION (powder and solvent for solution for injection 2000 IU) Reg.no. XXXXX

9. Date of Revision of The Text

May 2018