Package Leaflet: Information for the user

IDELVION® 250 IU powder and solvent for solution for injection
IDELVION® 500 IU powder and solvent for solution for injection
IDELVION® 1000 IU powder and solvent for solution for injection
IDELVION® 2000 IU powder and solvent for solution for injection
IDELVION® 3500 IU powder and solvent for solution for injection

albutrepenonacog alfa (recombinant coagulation factor IX)

Read all of this leaflet carefully before you start using this medicine because it contains important information for you.
- Keep this leaflet. You may need to read it again.
- If you have further questions, ask your doctor, pharmacist or nurse.
- This medicine has been prescribed for you only. Do not pass it on to others. It may harm them, even if their signs of illness are the same as yours.
- If you get any side effects talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet:

1. What IDELVION is and what it is used for
2. What you need to know before you use IDELVION
3. How to use IDELVION
4. Possible side effects
5. How to store IDELVION
6. Contents of the pack and other information

1. What IDELVION is and what it is used for

What is IDELVION?

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

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

What is IDELVION used for?

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

2. What you need to know before you use IDELVION

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

Warnings and precautions

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

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

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

If you need a central venous access device (CVAD for injection of IDELVION), the risk of complications including local infections, bacteria in the blood (bacteraemia) and the formation of a blood clot in the blood vessel (thrombosis) where the catheter is inserted should be considered by your doctor.

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

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

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

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

3. How to use IDELVION

Your treatment should be started and monitored by a doctor who is experienced in the treatment of blood clotting disorders.

Always take this medicine exactly as your doctor has told you. Check with your doctor if you are not sure.

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

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

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

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

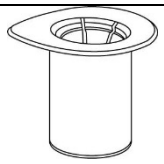
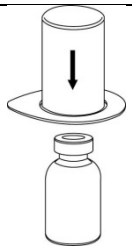
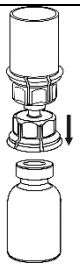
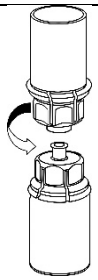
Reconstitution and administration

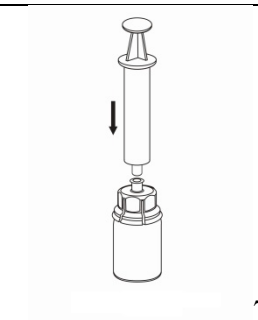
General Instructions
- The powder must be mixed with the solvent (liquid) and withdrawn from the vial while keeping the medicine sterile (germ free). Your doctor will show you how to prepare the solution and how to withdraw the solution from the vial correctly.
- IDELVION must not be mixed with other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

Reconstitution
Without opening the vials, warm the IDELVION powder and the liquid to room or body temperature. This can be done either by leaving the vials at room temperature for about an hour, or by holding them in your hands for a few minutes.

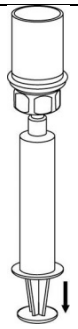
DO NOT expose the vials to direct heat. The vials must not be heated above body temperature (37 °C).

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

 1	1. Open the Mix2Vial by peeling off the lid. Do **not** remove the Mix2Vial from the blister package!
 2	2. Place the **solvent vial** on an even, clean surface and hold the vial tight. Take the Mix2Vial together with the blister package and push the spike of the **blue** adapter end **straight down** through the solvent vial stopper.
 3	3. Carefully remove the blister package from the Mix2Vial set by holding at the rim and pulling **vertically** upwards. Make sure that you only pull away the blister package and not the Mix2Vial set.
 4	4. Place the IDELVION **powder vial** on an even and firm surface. Invert the solvent vial with the Mix2Vial set attached and push the spike of the **transparent** adapter end **straight down** through the IDELVION vial stopper. The solvent will automatically flow into the IDELVION vial.
 5	5. With one hand grasp the IDELVION side of the Mix2Vial set and with the other hand grasp the solvent-side and unscrew the set carefully counter-clockwise into two pieces. Discard the solvent vial with the blue Mix2Vial adapter attached.
 6	6. Gently swirl the IDELVION vial with the transparent adapter attached until the substance is fully dissolved. Do not shake.

 7	7. Draw air into an empty, sterile syringe. While the IDELVION vial is upright, connect the syringe to the Mix2Vial's Luer Lock fitting by screwing clockwise. Inject air into the IDELVION vial.

Withdrawal and administration

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

Use the venipuncture kit supplied with the product, insert the needle into a vein. Let blood flow back to the end of the tube. Attach the syringe to the threaded, locking end of the venipuncture kit.

Inject the reconstituted solution slowly (as comfortable for you, up to a maximum of 5 ml/min) into the vein following the instructions given to you by your doctor. Take care not to get any blood in the syringe containing the product.

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

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

4. Possible side effects

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

Please contact your doctor immediately:
- **if you notice symptoms of allergic reactions (see below)**

- **if you notice that the medicine stops working properly**

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

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

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

- **Side effects in children and adolescents**

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

Reporting of side effects
If you get any side effects, talk to your doctor or healthcare professional. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via the UK Yellow Card Scheme at www.mhra.gov.uk/yellowcard or search for MHRA Yellow Card in the Google Play or Apple App Store.

By reporting side effects, you can help provide more information on the safety of this medicine.

5. How to store IDELVION

- Keep this medicine out of the sight and reach of children.
- Do not use this medicine after the expiry date, which is stated on the label and carton.
- Do not store above 25 °C.
- Do not freeze.
- Keep the vial in the outer carton in order to protect from light.
- The reconstituted product should preferably be used immediately.
- If the reconstituted product is not administered immediately, storage times and conditions prior to use are in the responsibility of the user.

6. Contents of the pack and other information

What IDELVION contains

The active substance is:

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

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

What IDELVION looks like and contents of the pack

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

Presentations

One pack with 250, 500 or 1000 IU containing:
1 vial with powder
1 vial with 2.5 ml water for injections
1 filter transfer device 20/20

One inner box containing:
1 disposable 5 ml syringe
1 venipuncture set
2 alcohol swabs
1 non-sterile plaster

One pack with 2000 or 3500 IU containing:
1 vial with powder
1 vial with 5 ml water for injections
1 filter transfer device 20/20

One inner box containing:
1 disposable 10 ml syringe
1 venipuncture set
2 alcohol swabs
1 non-sterile plaster

Not all pack sizes may be marketed.

Marketing Authorization Holder and Manufacturer

CSL Behring GmbH

Emil-von-Behring-Strasse 76
35041 Marburg
Germany

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

United Kingdom
CSL Behring UK Ltd.
Tel: +44 1444 447405

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The following information is intended for healthcare professionals only:

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

The number of units of factor IX administered is expressed in International Units (IU), which are related to the current WHO standard for factor IX products. Factor IX activity in plasma is expressed either as a percentage (relative to normal human plasma) or in International Units (relative to an International Standard for factor IX in plasma).

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

On demand treatment
The calculation of the required dose of factor IX is based on the empirical finding that 1 IU factor IX per kg body weight raises the plasma factor IX activity by an average of 1.3 IU/dl (1.3 % of normal activity) in patients ≥ 12 years of age and by 1.0 IU/dl (1.0 % of normal activity) in patients < 12 years of age. The required dose is determined using the following formulae:

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

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

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

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

Example:

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

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

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

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

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

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

Degree of haemorrhage / Type of surgical procedure	**Factor IX level required (%) (IU/dl)**	**Frequency of doses (hours) / Duration of therapy (days)**
<u>Haemorrhage</u> 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.
<u>Major haemorrhage</u> 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.
<u>Minor surgery</u> Including uncomplicated tooth extraction	50 – 80 (pre-and post-operative)	Single dose may be sufficient for the majority of minor surgeries. If needed, maintenance dose can be provided after 24 – 72 hours until bleeding stops and healing is achieved.
<u>Major surgery</u>	60 - 100 (pre-and post-operative)	Repeat every 24 – 72 hours for the first week, and then maintenance dose 1 – 2 times per week until

		bleeding stops and healing is achieved.

Prophylaxis
For long-term prophylaxis against bleeding in patients with severe 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. For patients >18 years, further extension of the treatment interval may be considered

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

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

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

Special warnings and precautions for use

Inhibitors
After repeated treatment with human coagulation factor IX products, patients should be monitored for the development of neutralising antibodies (inhibitors) that should be quantified in Bethesda Units (BU) using appropriate biological testing.

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

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

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

This is of importance particularly when changing the laboratory and/or reagents used in the assay.