

## Product Information

# IDELVION<sup>®</sup>

## Australia

### NAME OF THE MEDICINE

IDELVION<sup>®</sup> (recombinant fusion protein linking coagulation factor IX with albumin (rIX-FP); Albutrepenonacog alfa), powder and solvent for solution for injection.

### DESCRIPTION

Albutrepenonacog alfa is a purified protein produced by recombinant DNA technology, generated by the genetic fusion of recombinant albumin to recombinant coagulation factor IX (FIX). The genetic fusion of the cDNA of human albumin to the cDNA of human coagulation FIX enables the protein to be produced as a single recombinant protein and assures product homogeneity by avoiding chemical conjugation. The recombinant FIX portion is identical to the Thr148 allelic form of plasma-derived FIX. The cleavable linker between the recombinant FIX and albumin molecules is derived from the endogenous activation peptide in native FIX. IDELVION<sup>®</sup> remains intact in the circulation until FIX is activated, whereupon albumin is cleaved, releasing activated FIX (FIXa) when it is needed for coagulation.

No human or animal derived proteins are added during any stage of manufacturing or formulation of IDELVION<sup>®</sup>.

Full-length rIX-FP is expressed in recombinant Chinese hamster ovary (CHO) cells as a single chain glycopeptide of 1018 amino acids with a molecular weight of ~125 kD.

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

IDELVION<sup>®</sup> is a preservative free, sterile, non-pyrogenic, lyophilised powder to be reconstituted with Water for Injections (WFI) for intravenous injection.

IDELVION<sup>®</sup> is a pale yellow to white powder. The solvent (WFI) is a clear colourless solution for reconstitution. One vial of IDELVION<sup>®</sup> contains nominally 250/500/1000/2000 IU of the active substance, 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.

**Table 1: IDELVION<sup>®</sup> composition after reconstitution<sup>a</sup>**

	250 IU vial	500 IU vial	1000 IU vial	2000 IU vial
<b>Active ingredients (IU/mL)</b>				
Factor IX	100	200	400	400
<b>Excipients</b>				
Tri-sodium citrate	25 mM	25 mM	25 mM	25 mM
Polysorbate 80	0.006% w/v	0.012% w/v	0.024% w/v	0.024% w/v
Mannitol	18 mg/mL	29 mg/mL	29 mg/mL	29 mg/mL
Sucrose	7 mg/mL	12 mg/mL	12 mg/mL	12 mg/mL
<b>Reconstitution volume (mL)</b>	<b>2.5</b>	<b>2.5</b>	<b>2.5</b>	<b>5</b>

<sup>a</sup> Nominal values.

The sodium content is approximately 75 mmol/L (1.7243 g/L).

## PHARMACOLOGY

### Pharmacodynamics

Haemophilia B is a sex linked hereditary disorder of blood coagulation due to decreased levels of FIX 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 FIX are increased, thereby enabling a temporary correction of the factor deficiency and correction of the bleeding tendencies.

IDELVION<sup>®</sup> (albutrepenonacog alfa) is a recombinant fusion protein linking recombinant coagulation FIX with recombinant albumin that effectively replaces the missing coagulation FIX needed for haemostasis and provides for longer dose regimens. The prolongation of the half-life of FIX and the enhanced systemic exposure are achieved by fusion with recombinant albumin. Albumin is a natural, inert carrier protein in plasma with a long half-life of approximately 20 days that is not involved in immune defence or immune response. Genetic fusion of recombinant coagulation FIX with albumin extends the half-life of FIX (see **Pharmacokinetics**).

IDELVION<sup>®</sup> remains intact in the circulation until FIX is activated, whereupon albumin is cleaved, releasing activated FIX (FIXa) when it is needed for coagulation.

FIX is activated by factor VII/tissue factor complex in the extrinsic pathway as well as factor XIa in the intrinsic coagulation pathway. Activated FIX, 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. FIX activity is absent or greatly reduced in patients with haemophilia B and substitution therapy may be required.

## Pharmacokinetics

### *Adult population (≥18 years to <65 years)*

The pharmacokinetics (PK) of IDELVION<sup>®</sup> were evaluated following an intravenous injection of a single dose of 25, 50 and 75 IU/kg. The PK parameters (see **Table 2**) were based on plasma FIX 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.

**Table 2: Pharmacokinetic parameters (arithmetic mean, CV%) following a single injection of 50 IU/kg IDELVION<sup>®</sup> in 18 to 65 year old adults**

PK parameters	IDELVION <sup>®</sup> (50 IU/kg) (N = 47)
IR (IU/dL)/(IU/kg)	1.30 (23.8)
C <sub>max</sub> (IU/dL)	66.6 (26.7)
AUC <sub>0-inf</sub> (h.IU/dL)	7482 (28.4)
t <sub>1/2</sub> (h)	104.2 (25.4)
MRT (h)	142.8 (22.7)
CL (mL/h/kg)	0.731 (26.8)
V <sub>ss</sub> (dL/kg)	1.020 (27.9)
Time to 1% FIX activity (days) <sup>a</sup>	23.0
Time to 3% FIX activity (days) <sup>a</sup>	16.0
Time to 5% FIX activity (days) <sup>a</sup>	12.5

a = estimated time to median FIX activity above the pre-specified %.

IR = incremental recovery; C<sub>max</sub> = maximum concentration; AUC = area under the FIX activity time curve; t<sub>1/2</sub> = half-life; MRT = mean residence time; CL = body weight adjusted clearance; V<sub>ss</sub> = body weight adjusted volume of distribution at steady-state; time to 1% FIX activity = estimated time in days after dose when FIX activity has declined to approximately 1 IU/dL above baseline.

The PK data demonstrate that IDELVION<sup>®</sup> has an improved PK profile with a prolonged circulating half-life, increased area under the FIX activity time curve, lower clearance and an increased incremental recovery. In the pivotal study, the mean (CV%) incremental recovery

of IDELVION<sup>®</sup> was 1.30 (23.8%) which is higher than that achieved 1.00 (25.7%) with the previous FIX product (plasma-derived FIX (pdFIX) or recombinant FIX (rFIX)). Therefore, 1 IU/kg IDELVION<sup>®</sup> provides a mean increase of 1.30 IU/dL in the circulating level of FIX.

Repeat PK assessment for up to 30 weeks demonstrated a stable PK profile and incremental recovery was consistent over time.

The PK after a single dose of 75 IU/kg IDELVION<sup>®</sup> was derived from 8 evaluable subjects. The mean FIX activity at day 14 was 6.65%. The estimated time to 1% of FIX activity is approximately 27 days after a single dose of 75 IU/kg IDELVION<sup>®</sup>, based on population PK modelling simulations.

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

### ***Paediatric population***

The PK parameters of IDELVION<sup>®</sup> were evaluated in 8 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 were estimated based on the plasma FIX activity over time profile. **Table 3** summarises the PK parameters calculated from the paediatric data of 35 subjects, 1 to <18 years of age. Compared with adults, incremental recovery appeared to be slightly lower and body weight adjusted clearance appeared to be higher in children.

**Table 3: Comparison of pharmacokinetic parameters of IDELVION<sup>®</sup> by age category (arithmetic mean, CV %) following a single injection of 50 IU/kg IDELVION<sup>®</sup>**

PK parameters	1 to <6 years (N = 12)	6 to <12 years (N = 15)	12 to <18 years (N = 8)
IR (IU/dL)/(IU/kg)	0.951 (21.5)	1.06 (22.6)	1.11 (27.7)
C <sub>max</sub> (IU/dL)	48.3 (19.0)	52.9 (23.2)	55.3 (28.1)
AUC <sub>0-inf</sub> (h.IU/dL)	4583 (33.2)	5123 (31.4)	5347 (48.2)
t <sub>1/2</sub> (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)
V <sub>ss</sub> (dL/kg)	1.43 (24.1)	1.32 (19.7)	1.16 (14.0)

IR = incremental recovery; C<sub>max</sub> = maximum concentration; AUC = area under the FIX activity time curve; t<sub>1/2</sub> = half-life; MRT = mean residence time; CL = body weight adjusted clearance; V<sub>ss</sub> = body weight adjusted volume of distribution at steady-state.

### Population PK modelling

Based on population PK modelling simulations (median data), the estimated time to reach 1% and 5% plasma FIX activity following a single dose of 25 IU/kg, 50 IU/kg and 75 IU/kg IDELVION<sup>®</sup> are shown in **Table 4**.

**Table 4: Estimated time to reach 1% and 5% median plasma FIX activity following a single dose of IDELVION<sup>®</sup>**

	Estimated time to median FIX activity above specified % (days)		
	0 to <6 years	6 to <12 years	12 to <18 years
<b>Time to 1%</b>			
25 IU/kg	9	12	14
50 IU/kg	14	17	21
75 IU/kg	17	21	25
<b>Time to 5%</b>			
25 IU/kg	4	5	6
50 IU/kg	7	9	11
75 IU/kg	9	12	14

### CLINICAL TRIALS

The safety, efficacy and PK of IDELVION<sup>®</sup> were evaluated in prospective, open-label and multi-centre clinical studies. The relationship of the PK profile to the clinical response; namely the prevention of bleeding episodes with once weekly routine prophylaxis was

explored in a phase I/II study (Study 2004). The efficacy of IDELVION<sup>®</sup> that compared episodic (on demand) treatment to weekly routine prophylaxis; compared weekly routine prophylaxis to every 10 or 14 day routine prophylaxis; haemostatic efficacy in the treatment of bleeding episodes and in the perioperative setting was evaluated in a pivotal phase II/III study (Study 3001). A study in the paediatric population (Study 3002) also characterised the safety, PK, and efficacy of IDELVION<sup>®</sup> when used as routine prophylaxis (7 day dosing regimen) for the prevention of bleeding episodes and in the treatment of bleeding episodes.

The subjects enrolled had previously been treated with FIX replacement products (i.e. rFIX or pdFIX), had no confirmed history of FIX inhibitor formation, and were immunocompetent. All subjects in studies 2004 and 3001, were between the ages of 12 and 61 years and were required to have >150 exposure days (EDs) of previous FIX treatment. In Study 3002 all subjects were between 1 and 10 years (those aged <6 years were required to have >50 EDs).

### **Routine prophylaxis**

In studies 2004, 3001 and 3002, the occurrence of bleeding episodes was recorded over the prophylaxis treatment period and the annualised spontaneous bleeding rate (AsBR) was determined.

#### ***Adult and adolescent subjects (≥12 to 65 years of age)***

In Study 3001, a total of 63 male, previously treated patients (PTPs) with haemophilia B (≤2% endogenous FIX activity), between 12 and 61 years of age received IDELVION<sup>®</sup> for up to 27 months. Forty subjects in the prophylaxis arm received weekly routine prophylaxis at an initial dose of 35–50 IU/kg, with median dose of 40 IU/kg of IDELVION<sup>®</sup> at the end of the weekly prophylaxis period.

Following ≥26 weeks of a 7 day dosing interval prophylaxis regimen, 26 out of 40 subjects (26/40) switched to a longer prophylaxis dosing interval of either 10 or 14 days at a dose of 50–75 IU/kg based on meeting all of the following criteria: no dose adjustment in the previous month; currently on weekly prophylaxis of ≤50 IU/kg; did not experience a spontaneous bleeding episode in the previous month and willing to switch to a longer treatment interval. The extended interval was 10 days if the current weekly dose was >40 to ≤50 IU/kg, 14 days if the current weekly dose was ≤40 IU/kg. The median dose was 74.2 IU/kg for 14 day prophylaxis.

The median AsBR of 0.00 for subjects on a 7 day regimen was the same as that for subjects on the extended treatment intervals: 10 day regimen, 0.00; 14 day regimen, 0.00 (see **Table 5**).

**Table 5: Study 3001; Annualised bleeding rates of prophylaxis regimens and on demand treatment with IDELVION<sup>®</sup> (efficacy population)**

	<b>7 day prophylaxis regimen (N = 59)*</b>	<b>14 day prophylaxis regimen (N = 21)</b>	<b>On demand (N = 23)</b>
<b>Annualised spontaneous bleeding rate (bleeding episodes/year/subject)</b>			
Median (Q1, Q3)	0.00 (0.00, 0.75)	0.00 (0.00, 1.00)	11.57 (7.69, 17.03)
Mean (SD)	0.59 (1.139)	1.07 (2.114)	13.26 (8.613)
<b>Total annualised bleeding rate (bleeding episodes/year/subject)</b>			
Median (Q1, Q3)	0.61 (0.00, 2.57)	1.08 (0.00, 2.70)	18.65 (16.70, 25.53)
Mean (SD)	1.76 (3.209)	1.96 (2.653)	20.28 (8.616)

\* Includes 19 subjects who switched from on demand to 7 day prophylaxis.

Q1 = first quartile; Q3 = third quartile; SD = standard deviation.

In addition, based on a matched pairs design, every 14 day prophylaxis with IDELVION<sup>®</sup> was demonstrated to be as effective as every 7 day prophylaxis with IDELVION<sup>®</sup>. The AsBRs for 7 day and 14 day prophylaxis are summarised in **Table 6**.

**Table 6: Study 3001; Comparison of annualised bleeding rate by prophylaxis regimen**

<b>Bleeding episode aetiology</b>	<b>7 day prophylaxis (N = 21)</b>	<b>14 day prophylaxis (N = 21)</b>	<b>Mean difference (95% CI)*</b>
<b>Spontaneous</b>			
Median (Q1, Q3)	0 (0, 0)	0 (0, 1.00)	-0.79 (-1.780, 0.197)
Mean (SD)	0.28 (1.010)	1.07 (2.114)	

\* 95% CI based on t-test from matched pairs design.

Q1 = first quartile; Q3 = third quartile; SD = standard deviation.

In Study 3001, 23 subjects in the on demand arm received IDELVION<sup>®</sup> as needed for the treatment of bleeding episodes. Nineteen subjects subsequently crossed-over to weekly prophylaxis after approximately 26 weeks of episodic treatment. These subjects showed a statistically significant reduction in the rate of spontaneous and total bleeding episodes after switching from on demand treatment to prophylaxis. During on demand treatment, the

subjects had a median AsBR of 15.4 bleeding episodes per year per subject. After switching to weekly prophylaxis treatment, the median AsBR was 0.00 bleeding episodes per year per subject. The corresponding median and mean percent reductions in AsBR were 100% and 96.0% ( $P < 0.0001$ ), respectively. Similar results were observed in the efficacy population. A comparison of the AsBRs and ABRs in the subjects evaluable for efficacy is summarised in **Table 7**.

**Table 7: Study 3001; Comparison of annualised bleeding rates for patients switching from on demand to prophylaxis treatment**

Bleeding episode aetiology	On demand (N = 19)*	Weekly prophylaxis (N = 19)*	Percent reduction with prophylaxis (N = 19)*
<b>Spontaneous</b>			
Mean (SD)	14.57 (8.421)	0.73 (1.171)	96.0 (5.539)
Median	15.43	0.00	100
IQR	7.98, 17.96	0.00, 0.96	90.5, 100
Range	2.00, 39.50	0.00, 4.2	82.8, 100
<b>Total</b>			
Mean (SD)	20.78 (9.194)	2.87 (4.814)	88.8 (12.762)
Median	19.22	1.58	90.9
IQR	16.70, 25.84	0.00, 4.06	81.2, 100
Range	2.00, 46.1	0.00, 21.1	54.3, 100

\* Based on matched pairs design.

IQR = interquartile range, defined for 25th percentile and 75th percentile; SD = standard deviation; Subjects evaluable for efficacy are subjects who received at least 1 dose of on demand treatment, and 1 dose of prophylaxis treatment.

In Study 2004, subjects receiving weekly prophylaxis treatment had a lower AsBR (median: 1.13; N = 13) than subjects receiving on demand treatment only (median: 22.2; N = 4).

Consumption of IDELVION<sup>®</sup> was measured as a secondary endpoint in Study 3001. Adult and adolescent subjects on routine prophylaxis regimens, exhibited mean monthly consumption of IDELVION<sup>®</sup> that was approximately 50% lower than their previous FIX prophylaxis treatment; the mean consumption was reduced from 321 IU/kg of the previous FIX products to 203 IU/kg per month of IDELVION<sup>®</sup> on once weekly regimen and 157 IU/kg on once every 14 day regimen.



### ***Paediatric subjects (0 to <12 years of age)***

In Study 3002, all 27 male subjects were previously treated patients (PTPs) on a 7 day prophylaxis regimen. The overall median AsBR was 0.00 bleeds per year per subject. No differences between subjects <6 years of age and subjects 6 to <12 years of age were observed with regard to the efficacy of a 7 day routine prophylaxis regimen. These results are consistent with the AsBR derived for the adult population receiving routine prophylaxis in Study 3001.

Consumption of IDELVION<sup>®</sup> was measured as a secondary endpoint in Study 3002. In paediatric subjects on a 7 day IDELVION<sup>®</sup> routine prophylaxis regimen, consumption was similar to that of adults on the same prophylaxis regimen. In addition, the monthly prophylaxis consumption of IDELVION<sup>®</sup> administered per subject was lower than for their previous FIX; the mean (SD) monthly consumption of IDELVION<sup>®</sup> was 200 (40) IU/kg (N = 27) compared with 390 (209) IU/kg FIX (N = 24). There was no difference in IDELVION<sup>®</sup> consumption between the 2 paediatric age groups (subjects <6 years of age and subjects 6 to <12 years of age).

Clinical studies are ongoing in this patient group, investigating the safety and efficacy of extended treatment intervals of up to 14 days.

### **Control and prevention of bleeding episodes**

#### ***Adult and adolescent subjects (≥12 to 65 years of age)***

In studies 2004 and 3001, bleeding episodes were treated with IDELVION<sup>®</sup> when they occurred (i.e. on demand). Successful treatment was defined as achieving haemostasis with no more than 2 injections. In addition, Investigators evaluated the haemostatic efficacy via a 4-point scale (excellent, good, moderate, poor / no response).

Across studies 2004 and 3001, 65 subjects experienced a total of 443 bleeding episodes that were treated with IDELVION<sup>®</sup> (432 were assessed for efficacy). Of these 443 bleeding episodes, 412 (93.0%) were controlled with a single IDELVION<sup>®</sup> injection and another 26 (5.9%) were controlled with 2 injections. Five bleeding episodes (1.1%) required more than 2 injections.

For 94.6% of bleeding episodes the haemostatic efficacy rating was either excellent or good.

### ***Paediatric subjects (0 to <12 years of age)***

In Study 3002, 23/27 subjects experienced a total of 106 bleeding episodes that were treated with IDELVION<sup>®</sup>; the majority of bleeding episodes (103/106; 97.2%) were successfully treated with 1 or 2 injections of IDELVION<sup>®</sup>. For most bleeding episodes requiring treatment, the Investigator's assessment of haemostatic efficacy of IDELVION<sup>®</sup> was either excellent (78/104 bleeding episodes; 75.0%) or good (22/104 bleeding episodes; 21.2%). These results were consistent for both age groups (see **Table 8**).

**Table 8: Control of bleeding episodes (N) requiring treatment**

	<b>Studies 2004 and 3001 Adult and Adolescent (≥12 to 65 years of age) (N = 443)</b>	<b>Study 3002 Paediatric (0 to &lt;12 years of age) (N = 106*)</b>
<b>Number of injections required</b>	<b>Number (%)</b>	
1 or 2 injections	438 (98.9)	103 (97.2)
>2 injections	5 (1.1)	3 (2.8)
<b>Efficacy grading</b>	<b>Number (%)</b>	
Excellent	350 (79.0)	78 (75.0)
Good	69 (15.6)	22 (21.2)

\* 106 bleeding episodes with number of injections, 104 minor bleeding episodes with assessments for efficacy.

Note: total number of episodes (N) includes 11 bleeding episodes in adults/adolescents and 3 in paediatric subjects without an efficacy assessment.

### **Control and prevention of bleeding episodes in the perioperative setting**

There were 15 surgeries in the IDELVION<sup>®</sup> clinical development program, including 3 surgeries in children <12 years of age. Five of the surgeries were orthopaedic. A single dose of IDELVION<sup>®</sup> before surgery was sufficient to maintain haemostasis during the surgical period. Haemostasis was assessed by the Investigator/surgeon using a 4-point scale of excellent, good, fair and none. Haemostatic efficacy in the perioperative setting was excellent or good in 100% of the surgeries. During the 14 day post-operative period, subjects received between 2 and 7 injections of IDELVION<sup>®</sup>, depending on the type of surgery. The mean total consumption of IDELVION<sup>®</sup> during the surgical period ranged from 81 IU/kg (tooth extraction; Study 3002) to 380 IU/kg (total knee replacement; Study 3001). There was no clinical evidence of thrombotic complications in any of the subjects.

## **INDICATIONS**

IDELVION<sup>®</sup> is indicated in all patients with haemophilia B for:

- Routine prophylaxis to prevent or reduce the frequency of bleeding episodes
- Control and prevention of bleeding episodes
- Control and prevention of bleeding in the perioperative setting.

## **CONTRAINDICATIONS**

IDELVION<sup>®</sup> is contraindicated in patients who have a known hypersensitivity to IDELVION<sup>®</sup>, any of its components, excipients, or hamster protein (see **Table 1**).

## **PRECAUTIONS**

### **Monitoring laboratory tests**

To confirm adequate FIX levels have been achieved and maintained, monitor plasma FIX activity by performing the one-stage clotting assay.

When using an *in vitro* thromboplastin time (aPTT)-based one-stage clotting assay for determining FIX activity in patients' blood samples, plasma FIX 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 approximately 50% lower than expected recovery based on labelled potency. This is of importance particularly when changing the laboratory and/or reagents used in the assay.

### **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<sup>®</sup> and contact their physician. All FIX products have potential of allergic reactions. It is suggested that the initial administrations of FIX should, according to the treating physician's judgment, be performed under medical observation where proper medical care for allergic reactions could be provided.

## **Thromboembolism**

Because of the potential risk of thrombotic complications with the use of FIX-containing products, 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<sup>®</sup> should be weighed against the risk of these complications.

## **Inhibitors**

Formation of neutralising antibodies (inhibitors) to FIX has been reported during factor replacement therapy in the treatment of haemophilia B.

Patients should be monitored for the development of inhibitors by appropriate clinical observations and laboratory tests. If expected plasma FIX activity levels are not attained, or if the bleeding is not controlled after IDELVION<sup>®</sup> administration, the presence of an inhibitor should be suspected. A specialised haemophilia treatment centre should be contacted if a patient develops an inhibitor.

Perform a Bethesda inhibitor assay if expected FIX plasma levels are not attained or if bleeding is not controlled with the expected dose of IDELVION<sup>®</sup>. Use Bethesda Units (BU) to report inhibitor levels.

There have been reports in the literature showing a correlation between the occurrence of a FIX 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 FIX inhibitors may be at an increased risk of anaphylaxis with subsequent challenge with FIX.

The safety and efficacy of using IDELVION<sup>®</sup> for immune tolerance induction has not been established.

## **Effects on fertility**

Fertility studies in animals have not been conducted with IDELVION<sup>®</sup>.

## **Use in pregnancy**

Category B2

Animal reproduction studies have not been conducted with IDELVION<sup>®</sup>. Based on the rare occurrence of haemophilia B in women, experience regarding the use of IDELVION<sup>®</sup> during pregnancy is not available. Therefore, IDELVION<sup>®</sup> should be used during pregnancy only if clearly indicated.

## **Use in lactation**

Lactation studies in animals have not been conducted with IDELVION<sup>®</sup>. Based on the rare occurrence of haemophilia B in women, experience regarding the use of IDELVION<sup>®</sup> during lactation is not available. Therefore, IDELVION<sup>®</sup> should be used during lactation only if clearly indicated.

## **Previously untreated patients**

The safety and efficacy of IDELVION<sup>®</sup> in previously untreated patients (PUPs) have not been established.

## **Paediatric use**

The listed precautions apply both to adults and children.

## **Genotoxicity**

IDELVION<sup>®</sup> did not show evidence of genotoxicity in a reverse mutation assay in bacteria or a chromosomal aberration assay in human lymphocytes.

## **Carcinogenicity**

Carcinogenicity studies have not been conducted with IDELVION<sup>®</sup>.

## **Continuous infusion**

The safety and efficacy of IDELVION<sup>®</sup> administration by continuous infusion have not been established.

## **INTERACTIONS WITH OTHER MEDICINES**

No interactions of IDELVION<sup>®</sup> with other medicinal products have been reported.

## ADVERSE EFFECTS

During open label clinical trials with IDELVION<sup>®</sup> conducted in 107 PTPs, there were 579 adverse events reported in 94/107 (87.9%) subjects who received a total of 6480 injections. Of these 579 events, 15 were reported as related to IDELVION<sup>®</sup> in 8/107 (7.5%) subjects.

A total of 6480 injections were administered to the Overall Safety population during a median of 469.0 days (min, max: 25 to 986 days), with a median 3000 IU per injection (min, max: 139 to 10570 IU). The median total amount of IDELVION<sup>®</sup> administered was 126810 IU (min, max: 1900 to 999051).

The most frequent adverse reactions in clinical trials are headache and injection site reactions. The frequency of these events are in the common category. The adverse reactions, the frequency of which is estimated on a per-patient basis, by system organ class (SOC, and preferred term level) and frequency of occurrence, are presented in **Table 9**.

**Table 9: Frequency of adverse reactions observed in clinical studies**

MedDRA Standard System Organ Class	Adverse reactions	Frequency <sup>a</sup>
General disorders and administration site conditions	Injection site reactions	Common
Immune system disorders	Hypersensitivity	Uncommon
Nervous system disorders	Headache Dizziness	Common Uncommon
Skin and subcutaneous tissue disorders	Rash Eczema	Uncommon Uncommon

<sup>a</sup> Frequencies have been evaluated on a per-patient basis according to the following convention:

very common:  $\geq 1/10$   
common:  $\geq 1/100$  and  $< 1/10$   
uncommon:  $\geq 1/1,000$  and  $< 1/100$   
rare:  $\geq 1/10,000$  and  $< 1/1,000$   
very rare:  $< 1/10,000$   
not known (cannot be estimated from the available data).

No neutralising antibodies (inhibitors) (see **PRECAUTIONS**), or antibodies to hamster proteins have been detected in 107 PTPs in the clinical studies with IDELVION<sup>®</sup>.

One previously untreated patient (PUP) from the ongoing clinical trial reported an inhibitor against factor IX. There are insufficient data to provide information on inhibitor incidence in PUPs.

No thrombotic events were reported in 107 PTPs in the clinical studies with IDELVION<sup>®</sup>.

With the use of FIX 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 FIX inhibitors. No anaphylactic reactions have been observed in clinical studies with 107 patients for IDELVION<sup>®</sup>.

### ***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.

### **DOSAGE AND ADMINISTRATION**

Initiate treatment of IDELVION<sup>®</sup> under the supervision of a physician experienced in the treatment of haemophilia B.

It is recommended that prescribed doses of IDELVION<sup>®</sup> be expressed using 'International Units' written in full.

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.

## **Dosage**

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

The number of units of FIX administered is expressed in International Units (IU), which are related to the current WHO standard for FIX products. One IU of FIX activity is equivalent to that quantity of FIX in 1 mL of normal human plasma. FIX activity in plasma is expressed either as a percentage (relative to normal human plasma) or in IU (relative to an International Standard for factor IX in plasma).

## ***Prophylaxis***

### **Adults and adolescents ( $\geq 12$ years of age)**

For routine prophylaxis to prevent bleeding in patients  $\geq 12$  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.

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 increase dose and extend dosing interval during routine clinical management.



In some cases, especially in younger patients, and depending on individual patient pharmacokinetics, age, bleeding phenotype and physical activity, shorter dosage intervals or higher doses may be necessary.

Refer to **Pharmacokinetics** and **CLINICAL TRIALS** sections for relevant data.

### ***On demand treatment***

The calculation of the required dose of FIX is based on the empirical finding that 1 IU FIX per kg body weight is expected to increase the circulating level of FIX by an average of 1.3 IU/dL (1.3% of normal) in patients  $\geq 12$  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 FIX increase (IU/dL or % of normal) x {reciprocal of observed recovery (IU/kg per IU/dL)}

OR

Expected FIX increase (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 FIX 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 IU.

2. A dose of 1000 IU of IDELVION<sup>®</sup>, administered to a 25 kg patient, should result in a peak post-injection FIX increase of  $1000 \text{ IU}/25 \text{ kg} \times 1.0 \text{ (IU/dL per IU/kg)} = 40 \text{ IU/dL}$  (40% of normal).

*Patients  $\geq 12$  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 FIX increase (IU/dL) x 0.77 dL/kg

Example:

3. A peak level of 50% of normal is required in an 80 kg patient with severe haemophilia B. The appropriate dose would be  $80 \text{ kg} \times 50 \text{ IU/dL} \times 0.77 \text{ dL/kg} = 3080 \text{ IU}$ .
4. A dose of 2000 IU of IDELVION<sup>®</sup>, administered to an 80 kg patient, should result in a peak post-injection FIX increase of  $2000 \text{ IU} \times 1.3 \text{ (IU/dL per IU/kg)} / 80 \text{ kg} = 32.5 \text{ IU/dL}$  (32.5% of normal).

*Control and prevention of bleeding episodes and in the perioperative setting*

A guide for dosing IDELVION<sup>®</sup> in the control and prevention of bleeding episodes and in the perioperative setting is provided in **Table 10**. Ensure the FIX activity level is achieved and maintained in the corresponding period. The recommended circulating FIX level requirement for paediatric patients is the same as for adults.

**Table 10: Dosing for control and prevention of bleeding episodes and in the perioperative setting**

Degree of haemorrhage	FIX level required (%) (IU/dL)	Frequency of doses (hours)/Duration of therapy (days)
<b>Minor or moderate</b> 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.
<b>Major</b> 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.
Control and prevention of bleeding in the perioperative setting	FIX level required (%) (IU/dL)	Frequency of doses (hours)/Duration of therapy (days)
<b>Minor surgery</b> e.g. (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.
<b>Major surgery</b>	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.

### *Older people*

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

### **Monitoring advice**

Patients should be monitored to confirm adequate FIX levels have been achieved and maintained, and for the development of FIX inhibitors. See **PRECAUTIONS**.

### **General instructions**






For intravenous use only after reconstitution.



The solution should be clear or slightly opalescent, yellow to colourless. After filtering/withdrawal (see **Reconstitution**) 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

 <p>1</p>	<p>1. Bring the WFI to room temperature. Ensure IDELVION<sup>®</sup> and WFI vial flip caps are removed and the stoppers are treated with an antiseptic solution and allowed to dry prior to opening the Mix2Vial<sup>™</sup> package.</p> <p>Open the Mix2Vial<sup>™</sup> package by peeling off the lid. Do <b>not</b> remove the Mix2Vial<sup>™</sup> from the blister package!</p>
 <p>2</p>	<p>2. Place the <b>WFI vial</b> on an even, clean surface and hold the vial tight. Take the Mix2Vial<sup>™</sup> together with the blister package and push the spike of the <b>blue</b> adapter end <b>straight down</b> through the WFI vial stopper.</p>
 <p>3</p>	<p>3. Carefully remove the blister package from the Mix2Vial<sup>™</sup> set by holding at the rim, and pulling <b>vertically</b> upwards. Make sure that you only pull away the blister package and not the Mix2Vial<sup>™</sup> set. Do not touch the exposed end of the Mix2Vial<sup>™</sup> set.</p>
 <p>4</p>	<p>4. Place the <b>IDELVION<sup>®</sup> vial</b> on an even and firm surface. Invert the WFI vial with the Mix2Vial<sup>™</sup> set attached and push the spike of the <b>transparent</b> adapter end <b>straight down</b> through the IDELVION<sup>®</sup> vial stopper. The WFI will automatically flow into the IDELVION<sup>®</sup> vial.</p>
 <p>5</p>	<p>5. With one hand grasp the IDELVION<sup>®</sup> side of the Mix2Vial<sup>™</sup> set and with the other hand grasp the WFI side and unscrew the set carefully counterclockwise into two pieces.</p> <p>Discard the WFI vial with the blue Mix2Vial<sup>™</sup> adapter attached.</p>

 <p style="text-align: center;">6</p>	<p>6. Gently swirl the IDELVION<sup>®</sup> vial with the transparent adapter attached until the substance is fully dissolved. Do not shake.</p>
 <p style="text-align: center;">7</p>	<p>7. Draw air into an empty, sterile syringe. While the IDELVION<sup>®</sup> vial is upright, connect the syringe to the Mix2Vial<sup>™</sup>'s Luer Lock fitting by screwing clockwise. Inject air into the IDELVION<sup>®</sup> vial.</p>

***Withdrawal and application***

 <p style="text-align: center;">8</p>	<p>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.</p>
 <p style="text-align: center;">9</p>	<p>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<sup>™</sup> adapter from the syringe by unscrewing counterclockwise.</p>

For injection of IDELVION<sup>®</sup>, the provided administration sets are recommended to be used because treatment failure can occur as a consequence of FIX adsorption to the internal surface of some injection equipment.

Care should be taken that no blood enters the syringe filled with IDELVION<sup>®</sup>, as there is a risk that the blood could coagulate in the syringe and fibrin clots could therefore be administered to the patient. If blood enters the syringe discard and prepare a new vial of IDELVION<sup>®</sup>.

The IDELVION<sup>®</sup> solution must not be diluted.

### ***Administration***

Intravenous use.

For instructions on reconstitution of the medicinal product before administration, see **General instructions**. 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<sup>®</sup>, the rate of injection should be decreased or the application should be stopped, as required by the clinical condition of the patient. See **PRECAUTIONS**.

Use in one patient on one occasion only.

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

It is strongly recommended that every time that IDELVION<sup>®</sup> 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.

### ***Compatibility with other medicines***

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 **DESCRIPTION**.

## **OVERDOSAGE**

No symptoms of overdose with IDELVION<sup>®</sup> have been reported.

For general advice on overdose management contact the Poisons Information Centre on 131 126.

## **PRESENTATION AND STORAGE CONDITIONS**

Store at 2–25°C. Do not freeze. Keep vials in the outer carton in order to protect from light.

After reconstitution the chemical and physical in-use stability has been demonstrated for 8 hours at room temperature (below 25°C).

As IDELVION<sup>®</sup> contains no antimicrobial preservatives, the product should be used within 4 hours of reconstitution. Keep at room temperature (below 25°C).

Do not use after the expiry date.

### **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 Water for Injections 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 Water for Injections in a vial (type I glass), with a stopper (rubber) a disc (plastic) and a cap (aluminium).

### **Presentation**

#### ***One pack with 250, 500 or 1000 IU containing:***

- 1 vial with powder
- 1 vial with 2.5 mL Water for Injections
- One administration pack containing:*
  - 1 filter transfer device 20/20
  - 1 disposable 5 mL syringe
  - 1 venipuncture set
  - 2 alcohol swabs

**Attachment 1: Product information for AusPAR Idelvion albutrepenonacog alfa reh CSL Bhering Pty Ltd PM-2015-01850-1-4 Final 26 September 2017. This Product Information was approved at the time this AusPAR was published.**

1 non-sterile plaster

***One pack with 2000 IU containing:***

1 vial with powder

1 vial with 5 mL Water for Injections

***One administration pack containing:***

1 filter transfer device 20/20

1 disposable 10 mL syringe

1 venipuncture set

2 alcohol swabs

1 non-sterile plaster

Not all pack sizes may be marketed.

**NAME AND ADDRESS OF THE SPONSOR**

CSL Behring (Australia) Pty Ltd

ABN 48 160 734 761

189–209 Camp Road

Broadmeadows VIC 3047

Australia

**POISON SCHEDULE OF THE MEDICINE**

Unscheduled

**DATE OF FIRST INCLUSION IN THE AUSTRALIAN REGISTER OF THERAPEUTIC GOODS (THE ARTG)**

20 September 2016

**DATE OF MOST RECENT AMENDMENT**

04 April 2017

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**For Medical/Technical Enquiries**

TOLL FREE: 1800 642 865



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## **For Customer Service Enquiries**

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