

PRODUCT INFORMATION

Kovaltry[®] (with vial adapter)

Octocog alfa (bhk) (recombinant Factor VIII)

NAME OF THE MEDICINE

International Non-proprietary Name (INN):	Octocog alfa
Chemical name(s):	Recombinant Human Coagulation Factor VIII
Other non-proprietary name(s) (e.g., national name, BAN):	Antihæmophilic Factor (Recombinant)
CAS number:	139076-62-3
Pharmacotherapeutic group:	Antihæmorrhagics, blood coagulation factor VIII
ATC-Code:	B02BD02
Molecular formula:	2332 amino acids
Molecular weight:	Approx. 330-360 kDa
Structural formula:	heavy chain C8241H12908N2264O2528S50 and light chain C3553H5408N956O1026S33

DESCRIPTION

Kovaltry is a sterile, stable, purified, non-pyrogenic, dried concentrate that has been manufactured using recombinant DNA technology. It is produced by Baby Hamster Kidney (BHK) cells into which the human factor VIII gene has been introduced. The active ingredient, octocog alfa (full length recombinant human coagulation factor VIII (rDNA)), is a purified protein that has 2332 amino acids.

Kovaltry is available in the following dose strengths:

Table 1 Available dose strengths

Kovaltry dose strengths	Diluent (mL)	Colour code
250 IU	2.5	Blue
500 IU	2.5	Green
1000 IU	2.5	Red
2000 IU	5	Yellow
3000 IU	5	Gray

Each vial of Kovaltry is labeled with actual recombinant factor VIII activity expressed in IU determined using the chromogenic assay. This potency assignment employs a factor VIII concentrate standard that is referenced to a WHO International Standard for factor VIII concentrates, and is evaluated by appropriate methodology to ensure accuracy of the results.

Each single-use vial of Kovaltry powder for injection contains:

Active ingredient: octocog alfa (bhk) (nominal dose strengths of 250 IU, 500 IU, 1000 IU, 2000 IU, or 3000 IU).

Excipients: sucrose, histidine, glycine, sodium chloride, calcium chloride and polysorbate 80.

[Trace amounts of mouse and hamster protein are also present.]

The liquid diluent for reconstitution is supplied in a pre-filled syringe. Each single-use prefilled diluent syringe for parenteral use contains water for injections, sterilised (2.5 mL for 250 IU, 500 IU, 1000 IU; 5 mL for 2000 IU, 3000 IU).

PHARMACOLOGY

Pharmacodynamic properties

Pharmacotherapeutic group: antihaemorrhagics: blood coagulation factor VIII, ATC code B02BD02.

Mechanism of action

The factor VIII/von Willebrand factor (vWF) complex consists of two molecules (factor VIII and vWF) with different physiological functions. When infused into a haemophiliac patient, factor VIII binds to vWF in the patient's circulation. Activated factor VIII acts as a cofactor for activated factor IX, accelerating the conversion of factor X to activated factor X. Activated factor X converts prothrombin into thrombin. Thrombin then converts fibrinogen into fibrin and a clot can be formed. Haemophilia A is a sex-linked hereditary disorder of blood coagulation due to decreased levels of factor VIII:C 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 VIII are increased, thereby enabling a temporary correction of the factor deficiency and correction of the bleeding tendencies.

Kovaltry does not contain von Willebrand factor.

Pharmacodynamic effects

The activated partial thromboplastin time (aPTT) is prolonged in people with haemophilia. Determination of aPTT is a conventional in vitro assay for biological activity of factor VIII. Treatment with recombinant Factor VIII (rFVIII) normalises the aPTT similar to that achieved with plasma-derived factor VIII.

Pharmacokinetics

The pharmacokinetic (PK) properties of Kovaltry were investigated in three studies in previously-treated patients (PTPs), adults and children, in comparison to Kogenate FS. For all PK evaluations, 50 IU/kg of Kovaltry or Kogenate FS (octocog alfa (bhk)) was injected. Serial blood samples were collected over 48 hours in adults and 24 hours in children <12 years of age.

Adolescents and Adults

Pharmacokinetics was evaluated in 26 PTPs (ages 12 to 61 years) with severe haemophilia A following 50 IU/kg of Kogenate FS or Kovaltry in a randomised cross-over study with at least a ≥ 3 day washout. Both products were released using chromogenic assay for this PK evaluation.

The analysis of plasma samples was conducted using both the one-stage clotting assay and the chromogenic assay. The results are presented in Table 2 and Table 3.

Table 2 Pharmacokinetic Parameters [Geometric Mean (%CV)] for Kovaltry Compared to Kogenate FS, One-Stage Assay Results

Parameter [unit]	Kovaltry			Kogenate FS		
	12 to 17 yrs (N=5)	≥18 yrs (N=21)	Total (N=26)	12 to 17 yrs (N=5)	≥18 yrs (N=21)	Total (N=26)
AUC [IU*h/dL]	979.6 (30.6)	1520.8 (34.2)	1397.5 (37.9)	932.8 (33.7)	1242.3 (38.9)	1175.7 (39.2)
C _{max} [IU/dL]	88.4 (30.8)	98.6 (15.1)	96.6 (18.8)	107.2 (20.3)	99.9 (20.1)	101.3 (19.9)
t _½ [h]	11.7 (9.8)	13.8 (27.7)	13.4 (26.0)	10.9 (21.3)	12.5 (25.4)	12.2 (24.9)
MRT _{IV} [h]	16.1 (4.9)	19.0 (31.1)	18.4 (28.6)	14.3 (13.8)	16.6 (29.5)	16.1 (27.6)
V _{ss} [dL/kg]	0.82 (27.7)	0.63 (17.0)	0.66 (21.8)	0.77 (27.4)	0.67 (27.8)	0.69 (27.7)
CL [dL/h/kg]	0.051 (30.6)	0.033 (34.2)	0.036 (37.9)	0.054 (33.7)	0.040 (38.9)	0.043 (39.2)

Table 3 Pharmacokinetic Parameters [Geometric Mean (%CV)] for Kovaltry Compared to Kogenate FS, Chromogenic Assay Results

Parameter [unit]	Kovaltry			Kogenate FS		
	12 to 17 yrs (N=6)	≥18 yrs (N=20)	Total (N=26)	12 to 17 yrs (N=5)	≥18 yrs (N=21)	Total (N=26)
AUC [IU*h/dL]	1519.5 (30.1)	1989.8 (35.9)	1889.2 (36.1)	1347.6 (38.8)	1646.0 (40.0)	1583.9 (39.9)
C _{max} [IU/dL]	124.0 (46.4)	131.6 (15.8)	130.1 (23.0)	113.2 (38.1)	142.3 (17.7)	136.2 (23.8)
t _½ [h]	13.7 (35.9)	13.8 (27.0)	13.8 (28.0)	13.0 (17.3)	11.8 (30.3)	12.0 (28.2)
MRT _{IV} [h]	19.2 (28.4)	19.3 (27.2)	19.3 (26.8)	18.2 (19.9)	16.1 (28.8)	16.5 (27.4)
V _{ss} [dL/kg]	0.63 (57.6)	0.49 (21.1)	0.51 (31.0)	0.67 (51.5)	0.49 (23.46)	0.52 (32.0)
CL [dL/h/kg]	0.033 (30.1)	0.025 (35.9)	0.026 (36.1)	0.037 (38.8)	0.030 (40.0)	0.032 (39.9)

The AUC was about 19% higher and CL 16% lower (p<0.0005) and t_½ was about 10% higher (p<0.05) for Kovaltry as compared to Kogenate FS. With both assays, the 90% CIs for the ratio Kovaltry / Kogenate FS of the C_{max} were within the bioequivalency criteria of 0.80 to 1.25. The bioavailability of Kovaltry was non-inferior to that of Kogenate FS. For AUC, the 90% CI was 1.13 to 1.25 when the one-stage assay was used and 1.11 to 1.28 when the chromogenic assay was used for FVIII determinations in plasma. Overall, the data demonstrate non-inferiority of PK for Kovaltry as compared to Kogenate FS.

Repeated PK measurements in 19 subjects following 6 to 12 months of prophylaxis treatment with Kovaltry did not indicate any relevant changes in PK characteristics after long-term treatment.

Children 12 Years of Age and Younger

Pharmacokinetic parameters calculated from 15 subjects <12 years of age are available for 5 subjects in age group 0 to <6 years and 10 subjects in age group 6 to 12 years as shown in Table 4.

Table 4 Pharmacokinetic Parameters (Geometric Mean [%CV]) for Kovaltry in Children <12 Years of age Based on Chromogenic Assay Results

Parameter [unit]	Geometric mean (% CV)		
	PTPs 0 to <6 yrs (N=5)	PTPs 6 to 12 yrs (N=10)	PTPs Total (N=15)
AUC [IU*h/dL]	1334.3 (29.4)	1155.4 (34.7)	1203.9 (32.8)
C _{max} [IU/dL]	74.2 (40.5)	79.8 (23.5)	77.9 (28.7)
t _{1/2} [h] ^a	11.8 (27.0)	11.9 (16.6)	11.9 (18.9)
CL [dL/h/kg] ^a	0.037 (25.1)	0.043 (34.8)	0.041 (32.2)
MRT _{IV} [h] ^a	17.3 (24.9)	17.6 (15.5)	17.5 (17.6)
V _{ss} [dL/kg] ^a	0.64 (20.6)	0.76 (28.6)	0.72 (27.1)

^an=4 for PTPs 0 to <6 years

Children <12 years of age have lower plasma concentrations as compared to PTPs >12 years of age. The t_{1/2} across the age groups is similar.

The PK of Kovaltry is best described by a two compartment model. The population PK model was developed using the PK and recovery data from 183 subjects who participated in PK evaluations in the three phase III studies. Age, height, weight, body mass index (BMI), lean body weight (LBW) and race were investigated as covariates since they were considered to be of clinical interest. LBW explained a large part of the variability for both clearance and volume of distribution as expected for a compound mainly distributed in plasma.

Incremental Recovery

The analysis of all recorded incremental recovery in adult/adolescent PTPs, using one-stage and chromogenic assays, demonstrated a median rise of factor VIII clotting activity (FVIII:C) >2 IU/dL per IU/kg body weight of Kovaltry administered. This result is similar to the reported values for factor VIII derived from human plasma. In children 12 years of age and younger, the median incremental recovery values were 1.62 kg/dL for the younger age group (0 to <6 years) and 1.80 kg/dL for the older age group (6 to 12 years). There was no relevant change over the treatment period of 6 to 12 months.

Table 5 Incremental Recovery in Adult PTPs

	LEOPOLD I	LEOPOLD II	Pooled Analysis
Study participants	N=59	N=56	N=115
Chromogenic assay results Median (Q1; Q3) (IU/dL per IU/kg)	2.5 (2.1; 2.8)	2.1 (1.7; 2.4)	2.3 (1.8; 2.6)
One-stage assay results Median (Q1; Q3) (IU/dL per IU/kg)	2.2 (1.9; 2.5)	2.1 (1.7; 2.3)	2.2 (1.8; 2.4)

Table 6 Incremental Recovery in Paediatric PTPs

	LEOPOLD Kids	
	PTPs 0 to <6 yrs	PTPs 6 to 12 yrs
Study participants	N=24	N=25
Start of study: Chromogenic assay results Median (Q1; Q3) (IU/dL per IU/kg)	1.6 (1.3; 1.9)	1.7 (1.4; 2.0)
	N=23	N=25
After 6 months: Chromogenic assay results Median (Q1; Q3) (IU/dL per IU/kg)	1.8 (1.4; 2.0)	1.8 (1.2; 2.1)

CLINICAL TRIALS

The safety and efficacy of Kovaltry for routine prophylaxis, control and prevention of bleeding episodes, and perioperative management of patients with severe haemophilia A (<1% FVIII) was evaluated in three clinical studies: two multi-centre, open-label, cross-over, uncontrolled, randomised studies in adolescent and adult PTPs (age ≥ 12 years to <65 years) and one multi-centre, two-part, open-label, uncontrolled study in paediatric patients ≤ 12 years of age.

A total of 204 subjects have been included in the completed clinical trials, 153 subjects ≥ 12 years of age and 51 subjects <12 years of age. One hundred-forty (140) subjects were treated for at least 12 months, and 55 of these subjects for a median of 24 months. In addition, 9 previously untreated patients (PUPs) have been exposed in the ongoing PUP trial.

Routine Prophylaxis

Adolescents and Adults

The efficacy and safety of routine prophylaxis treatment with Kovaltry was demonstrated in LEOPOLD I. LEOPOLD II demonstrated the superiority of prophylaxis treatment over on-demand treatment with Kovaltry during a one-year treatment period. In both studies, the primary efficacy variable was annualised bleeding rate (ABR) (bleeds/subject/year) (see [Table 7](#)).

In LEOPOLD I, the prophylactic regimen was 20 to 50 IU/kg two or three times per week in which the dose frequency was assigned by the investigator based on the patient's individual requirements. In LEOPOLD II, the prophylactic regimen was 20 to 30 IU/kg two times per week or 30 to 40 IU/kg three times per week and the treatment group was assigned by randomisation.

A total of 140 subjects were treated with Kovaltry for at least 12 months with median exposure days (ED) of 157 (305 inclusive of extension phase) in LEOPOLD I and 153 ED in LEOPOLD II. In both studies, subjects in the Intent-to-Treat (ITT) population were adherent to >95% to 100% of prescribed number of prophylaxis infusions.

Table 7 Overview of LEOPOLD I and LEOPOLD II

	LEOPOLD I (N=62) ^a	LEOPOLD II (N=80)
Age (mean±SD) (years)	31.5±12.7	29.6±11.0
Previous treatment	Prophylaxis: 80.6%	On-demand: 100%
# of Target joints (mean; SD)	1.4±1.3	3.0±2.1
Joint haemorrhage history (mean #; SD of joint bleeds during 12 months prior study)	8.0±11.9	32.1±23.8
Median nominal prophylaxis dose/ injection (range)		
All	31.2 IU/kg (21-43 IU/kg)	31.7 IU/kg (21-42 IU/kg)
Prophylaxis 2 times per week	35.0 IU/kg (21-42 IU/kg)	30.4 IU/kg (21-34 IU/kg)
Prophylaxis 3 times per week	31.1 IU/kg (24-43 IU/kg)	37.4 IU/kg (30-42 IU/kg)
Treatment duration	1 year main study 1 year extension	1 year

LEOPOLD I: All (n=62); 2x/week (n=18); 3x/week (n=44)

LEOPOLD II: All (n=59); 2x/week (n=28); 3x/week (n=31); on-demand (n=21)

^aLEOPOLD I included PK, safety and efficacy of prophylaxis treatment and hemostasis during surgeries. Prophylaxis treatment phase data are presented.

The median ABR for the ITT population in LEOPOLD I was 1.0 bleeds/year. In LEOPOLD II, comparison of the bleeding rates between subjects receiving on-demand therapy versus prophylaxis treatment in an ANOVA demonstrated a statistically significant difference ($p < 0.0001$) in the median ABR in subjects receiving on-demand therapy (60 bleeds per year) as compared to subjects receiving prophylaxis treatment (2 bleeds per year). The mean ABR in LEOPOLD I was 3.79 ± 5.21 . In LEOPOLD II, mean ABR in subjects receiving on-demand therapy was 57.69 ± 24.56 versus 4.94 ± 6.81 in the subjects receiving prophylaxis treatment.

Table 8 Annualised Bleeding Rate in Adolescent and Adult Patients

Treatment Regimen	LEOPOLD I	LEOPOLD II
All Bleeding Episodes [ABR median (IQR ^a Q1; Q3)]		
Prophylaxis (All)	1.0 (0.0; 5.1)	2.0 (0.0; 7.0)
2 times per week	1.0 (0.0; 8.0)	4.0 (0.0; 8.0) (First 6 months of study: 4.1; Second 6 months of study: 1.1)
3 times per week	2.0 (0.5; 5.0)	2.0 (0.0; 4.9) (First 6 months of study: 2.0; Second 6 months of study: 2.0)
On-demand	N/A	60 (41.7; 76.3)
Spontaneous Bleeding Episodes [ABR median (IQR Q1; Q3)]		
Prophylaxis (All)	1.0 (0.0; 3.9)	1.0 (0.0; 4.0)
2 times per week	-	2.0 (0.0; 6.5)
3 times per week	-	0.0 (0.0; 3.0)
On-demand	N/A	42.1 (24.3; 61.3)
Joint Bleeding Episodes [ABR median (IQR Q1; Q3)]		
Prophylaxis (All)	1.0 (0.0; 3.0)	2.0 (0.0; 6.0)
2 times per week	-	2.5 (0.0; 7.5)
3 times per week	-	1.0 (0.0; 4.0)
On-demand	N/A	38.8 (24.3; 60.0)
% Patients with Zero Bleeding Episodes ^b (n)		
Prophylaxis (All)	25.8% (16)	27.1% (16)
2 times per week	-	28.6% (8)
3 times per week	-	25.8% (8)

LEOPOLD I: All (n=62); 2 x/week (n=18); 3 x/week (n=44)

LEOPOLD II: All (n=59); 2 x/week (n=28); 3 x/week (n=31); on-demand (n=21)

^aIQR = Interquartile Range

^bObservation of one-year treatment period

Children 12 Years of Age and Younger

Efficacy of prophylaxis treatment with Kovaltry in PTPs age 0 to 12 years was demonstrated in a multi-centre, open-label, uncontrolled study (LEOPOLD Kids). Primary efficacy variable was annualised number of total bleeds during prophylaxis treatment that occurred within 48 hours of previous prophylaxis treatment. Annualised number of total bleeds during prophylaxis treatment, independent of time of injection, was also analysed.

Kovaltry was administered at frequencies of either 2 times per week, 3 times per week or every other day. The frequency as well as dose (20–50 IU/kg) was adapted to individual subject's need (see Table 9).

Table 9 Overview of LEOPOLD Kids for PTPs Children 12 Years of Age or Younger

	LEOPOLD Kids	
	PTPs 0 to <6 yrs (N=25)	PTPs 6 to 12 yrs (N=26)
Age (mean±SD) (years)	3.8±1.3	8.8±1.8
Previous treatment	Prophylaxis: 92.0%	Prophylaxis: 65.4%
# of Target joints (mean; SD)	0.2±0.4	0.7±1.1
Treatment regimen during study (6 months)		
2x/week	36%	50%
3x/week or every other day	64%	50%

The median ABR within 48 hour after prophylactic injection was 0.00 bleeds/year (IQR: 0.00–3.95) [mean; 2.04±2.91]; the median ABR at any time during prophylaxis treatment was 1.90 bleeds/year (IQR: 0.00–6.02) [mean; 3.75±4.98]. Majority (32/53) of bleeds that occurred within 48 hours after a previous prophylaxis injection were trauma related. Twenty-three (45.1%) subjects reported no bleeds during the six-month treatment period.

Table 10 Annualised Bleeding Rate in Children 12 Years of Age or Younger

ABR Median (IQR ^a Q1; Q3)	LEOPOLD Kids		
	PTPs 0 to <6 yrs (N=25)	PTPs 6 to 12 yrs (N=26)	PTPs (Total) (N=51)
	Within 48 h after prophylactic injection		
All bleeds	1.9 (0.0; 4.0)	0.0 (0.0; 2.0)	0.0 (0.0; 4.0)
Spontaneous bleeds	0.0 (0.0; 0.0)	0.0 (0.0; 0.0)	0.0 (0.0; 0.0)
Joint bleeds	0.0 (0.0; 0.0)	0.0 (0.0; 0.0)	0.0 (0.0; 0.0)
	During prophylaxis treatment independent of time of injection		
All bleeds	2.0 (0.0; 6.0)	0.9 (0.0; 5.8)	1.9 (0.0; 6.0)
Spontaneous bleeds	0.0 (0.0; 0.0)	0.0 (0.0; 0.0)	0.0 (0.0; 0.0)
Joint bleeds	0.0 (0.0; 1.9)	0.0 (0.0; 2.1)	0.0 (0.0; 2.0)
% Patients with Zero Bleeding Episodes	10 (40%)	13 (50%)	23 (45.1%)

^aIQR = Interquartile Range

Paediatric Prophylaxis for Joint Damage Risk Reduction

Kovaltry and Kogenate FS have comparable PK and efficacy in preventing joint bleeds in children 12 years and younger. The same protective effect on joints observed with Kogenate FS in children with haemophilia A without pre-existing joint disease can be expected with Kovaltry.

In a clinical study with Kogenate FS, a total of 65 boys less than 30 months of age with severe ($\leq 2\%$ Factor VIII) haemophilia A and with ≤ 2 bleeds into each index joint and normal baseline joint imaging, were observed for up to 5.5 years in a multi-centre, open-label, prospective, randomised, controlled clinical study. Patients received either 25 IU/kg every other day (primary prophylaxis; n=32) or at least 3 doses totalling a minimum of 80 IU/kg at the time of a bleeding episode (enhanced episodic; n=33). Joint damage was evaluated by magnetic resonance imaging (MRI) or radiography, as well as the frequency of bleeding episodes. Joint damage detected by MRI or radiography in the ankles, knees, and elbows (i.e. index joints) was statistically significantly lower (p=0.002) for subjects receiving prophylactic therapy (7%) than for subjects receiving episodic therapy (42%). This corresponds to a 6.29-fold relative risk of joint damage for subjects treated with enhanced episodic therapy compared to prophylaxis. The mean rate of index joint haemorrhages for subjects on episodic therapy was 4.89 bleeds per year, versus 0.63 bleeds per year observed in the prophylaxis arm.

Three of 33 (9.1%) subjects in the episodic arm experienced recurrent life threatening bleeds (intracranial, gastrointestinal) compared to no subjects in the prophylaxis arm. On a per joint basis, joints in the prophylaxis arm were 8-fold more likely to remain damage-free than those in the episodic arm. Joint damage was most frequently observed in ankle joints and was detected at higher rates by MRI than by radiography. Ankles were also the index joint that demonstrated the highest frequency of bleeding events in this study (left ankle, mean 2.7 haemorrhages; right ankle, mean 2.6 haemorrhages).

As shown in Table 11 below, the incidence of joint damage was statistically significantly lower in the prophylaxis group as compared to the episodic group when assessed by MRI, or either MRI or radiography, using predefined criteria for establishing joint damage. However, there was no statistically significant difference between the two groups when joint damage was assessed by radiography alone.

Table 11 Subjects with joint damage (subjects with available baseline and endpoint data)

Endpoint	Prophylaxis		Episodic therapy		p-value
	Incidence (%)	Relative risk (95% CI)	Incidence (%)	Relative risk (95% CI)	
MRI	2/27 (7%)	0.17 (0.04, 0.67)	13/29 (45%)	6.05 (1.50, 24.38)	0.002
Radiography	1/28 (4%)	0.19 (0.02, 1.55)	5/27 (19%)	5.19 (0.65, 41.54)	0.101
MRI or Radiography	2/30 (7%)	0.16 (0.04, 0.65)	13/31 (42%)	6.29 (1.55, 25.55)	0.002

Relative risk is the risk of damage to one or more index joints on the given therapy as compared to the other therapy. P-value is from the 2-sided Fisher Exact Test comparing the incidence of joint damage between treatment groups.

As shown in Table 12 below, the assessment of endpoints in all randomised subjects assuming that those without complete baseline and endpoint data are treatment failures (intention-to-treat analysis). The incidence of joint damage was statistically significantly lower in the prophylactic group as compared to the episodic treatment group, with similar p-values, when assessed by MRI, or either MRI or radiography.

Table 12 Subjects with joint damage (all randomised subjects assuming subjects without complete baseline and endpoint data as treatment failures)

Endpoint	Prophylaxis n=32		Episodic therapy n=33		p-value
	Incidence (%)	Relative risk (95% CI)	Incidence (%)	Relative risk (95% CI)	
MRI	7 (22%)	0.42 (0.20, 0.88)	17 (52%)	2.35 (1.13, 4.90)	0.020
Radiography	5 (16%)	0.47 (0.18, 1.20)	11 (33%)	2.13 (0.83, 5.45)	0.150
MRI or Radiography	8 (25%)	0.43 (0.22, 0.85)	19 (58%)	2.30 (1.18, 4.49)	0.012

Relative risk is the risk of damage to one or more index joints on the given therapy as compared to the other therapy. P-value is from the 2-sided Fisher Exact Test comparing the incidence of joint damage between treatment groups.

Routine prophylactic treatment in children ages 0-2.5 years with no pre-existing joint damage has been shown to be more effective in reducing spontaneous joint bleeding and the risk of joint damage, compared to an enhanced episodic treatment regimen. Evaluation of monthly index joint and other haemorrhages by subject age showed that in subjects receiving enhanced episodic therapy, the frequency of monthly index joint and non-joint bleeds increased each year, while in patients receiving routine prophylaxis, the monthly bleeding frequency for both index joint and non-joint bleeds remained low in all age groups over the duration of the study. This data can be extrapolated to ages >2.5-16 years for children who have no existing joint damage.

Control and Prevention of Bleeding Episodes

Adolescents and Adults

A total of 1892 bleeding episodes in 108 subjects were treated with Kovaltry. The majority of the bleeding episodes were spontaneous, localised in joints, and mild to moderate in severity (see [Table 13](#)).

The treatment response was assessed by the subject as “good” or “excellent” (68.2% to 80.9%), “moderate” (16.2% to 29.9%), and “poor” (1.9% to 3%) in a total of 1850 bleeds. Majority of bleeding episodes resolved with ≤ 2 injections of Kovaltry.

Table 13 Control and Prevention of Bleeding Episodes in Adolescents and Adults Treated with Kovaltry

Characteristics of Bleeding Episodes (N =Patients with bleeds)	LEOPOLD I		LEOPOLD II	
	Prophylaxis Main Study N=62	Prophylaxis Extension N=55	Prophylaxis N=59	On-demand N=21
Total number of bleeds ^a	241	154	293	1204
Spontaneous % (n/total)	63.5% (153/241)	52.7% (79/150 ^b)	73.9% (209/283 ^b)	78.5% (943/1202 ^b)
Mild/moderate % (n/total)	89.2% (215/241)	84.9% (130/153 ^b)	88.8% (260/293 ^b)	91.3% (1092/1196 ^b)
Joint bleeds % (n/total)	79.3% (191/241)	77.9% (120/154)	87.0% (255/293 ^b)	77.2% (924/1197 ^b)
Median number of injections/bleed treatment (range)	1.0 (0-48)		1.0 (0-7)	1.0 (0-20)
% of bleeds treated with ≤2 injections	87.0%		96.2%	95.3%
Median dose/injection (range)	31.6 IU/kg (14-67 IU/kg)		29.4 IU/kg (19-49 IU/kg)	22.0 IU/kg (11-35 IU/kg)

^a Total number of bleeds is the sum of spontaneous, trauma, untreated bleeds and includes bleeds with “missing” reason for injection/untreated/bleeds.

^b Total number of bleeds for the percentages calculations [% (n/total)] excludes the “missing” from the ^a Total number of bleeds

Children 12 Years of Age and Younger

A total of 97 bleeding episodes in 28 subjects were treated with Kovaltry. Majority (96.8%) of the bleeds were mild to moderate in severity. Fifty-nine (72.8%) bleeds were trauma related. During the 6 month treatment period, the median consumption of Kovaltry for the treatment of breakthrough bleeds was 36.94 IU/kg/injection (range 20.8–71.6 IU/kg).

The hemostatic efficacy in treatment of bleeds was assessed as either “good” or “excellent” in 90.1% of cases (97.8% in the younger age group and 81.0% in the older age group). Majority of bleeds (89.7%) were successfully treated with ≤2 injections.

Table 14 Control and Prevention of Bleeding Episodes in Children Treated with Kovaltry

	LEOPOLD Kids		
	PTPs 0 to <6 years (N=25)	PTPs 6 to 12 years (N=26)	PTPs (Total) (N=51)
Location of bleeds n/total (%)	Skin/mucosa: 28/52 (53.8%) Joint: 10/52 (19.2%)	Skin/mucosa: 17/45 (37.8%) Joint: 22/45 (48.9%)	Skin/mucosa: 45/97 (46.4%) Joint: 32/97 (33.0%)
Bleed severity, n (%)	Mild: 33 (63.5%) Moderate: 17 (32.7%) Severe: 2 (3.8%)	Mild: 17 (37.8%) Moderate: 27 (60.0%) Severe: 1 (2.2%)	Mild: 50 (51.5%) Moderate: 44 (45.4%) Severe: 3 (3.1%)
Type of bleeds	Spontaneous: 18.2% Trauma: 81.8%	Spontaneous: 32.4% Trauma: 62.2% Unspecified: 5.4%	Spontaneous: 20 (24.7%) Trauma: 59 (72.8%) Unspecified: 2 (2.5%)
Median number of injections/bleed treatment (range)	1.0 (0–9)	1.0 (0–8)	1.0 (0–9)
Bleeds treated with ≤2 infusions	92.4%	86.7%	89.7%
Response to treatment of bleeds (excellent, good, moderate, poor)	Excellent/good: 97.8% Moderate: 0% Poor: 2.3%	Excellent/good: 81.0% Moderate: 18.9% Poor: 0%	Excellent/good: 90.1% Moderate: 8.6% Poor: 1.2%
Median dose/injection (range)	38.7 IU/kg (20.8–71.6 IU/kg)	32.4 IU/kg (21.7–50.0 IU/kg)	36.9 IU/kg (20.8–71.6 IU/kg)

Peri-operative Management

A total of 14 major and 46 minor surgeries were performed in 44 previously treated subjects (adults and children) with severe haemophilia A. Seven of the 14 major surgeries were orthopedic procedures, including joint replacement. Approximately 51% of the minor surgeries were dental extractions. All subjects received Kovaltry as bolus injections. In the adolescent and adult subjects, the initial Kovaltry doses administered ranged between 3000–5000 IU (nominal dose). In a single subject younger than 12 years of age who underwent a major surgery, the total initial Kovaltry dose administered was 2500 IU (108.7 IU/kg).

The blood loss, during and after surgery, was within expected ranges. Hemostatic control was assessed by surgeons as “good” or “excellent”.

INDICATIONS

Treatment and prophylaxis of bleeding in patients with haemophilia A (congenital factor VIII deficiency). Kovaltry can be used for all age groups. (See Clinical Trials section)

Kovaltry does not contain von Willebrand factor and is not indicated in von Willebrand disease.

CONTRAINDICATIONS

Hypersensitivity to the active substance or to any of the excipients.

Known allergic reactions to mouse or hamster protein.

PRECAUTIONS

Hypersensitivity and anaphylactic reactions

Hypersensitivity to mouse or hamster protein. Allergic type hypersensitivity reactions are possible with Kovaltry. The product may contain traces of hamster or mouse proteins which in some patients may cause allergic reactions.

Patients should be made aware that the potential occurrence of chest tightness, dizziness, mild hypotension and nausea during infusion could constitute an early warning for hypersensitivity and anaphylactic reactions. Symptomatic treatment and therapy for hypersensitivity should be instituted as appropriate. If allergic or anaphylactic reactions occur, the injection/infusion should be stopped immediately. In case of anaphylaxis, the current medical standards for treatment should be observed.

Inhibitors

The formation of neutralising antibodies (inhibitors) to factor VIII is a known complication in the management of individuals with haemophilia A. These inhibitors are usually IgG immunoglobulins directed against the factor VIII procoagulant activity, which are quantified in Bethesda Units (BU) per mL of plasma using the modified assay. The risk of developing inhibitors is correlated to the exposure to factor VIII, this risk being highest within the first 20 exposure days and to other genetic and environmental factors. Rarely, inhibitors may develop after the first 100 exposure days.

The risk for inhibitor development depends on a number of factors relating to the characteristics of the patient, e.g. type of the Factor VIII gene mutation, family history, ethnicity, which are believed to represent the most significant risk factors for inhibitor formation. Risk factors include non-caucasians, polymorphisms in TNF- α or IL-10, intensive high dose treatments and surgery.

In general, all patients treated with coagulation factor VIII products should be carefully monitored for the development of inhibitors by appropriate clinical observations and laboratory tests.

Monitoring Laboratory Tests

Monitor plasma factor VIII activity levels to confirm that adequate factor VIII levels have been achieved and maintained, when clinically indicated.

Catheter-related infections

Catheter-related infections may be observed when Kovaltry is administered via central venous access devices (CVADs). These infections have not been associated with the product itself.

Cardiovascular disorder

Haemophiliac patients with cardiovascular risk factors or diseases may be at the same risk of developing cardiovascular events as non-haemophiliac patients when clotting has been normalised by treatment with FVIII.

Effects on fertility

The effects of Kovaltry on fertility have not been investigated in animals.

No effect on male reproductive organs was seen in repeated administration toxicity studies of up to 400 IU/kg/day Kovaltry for 5 days in rats and rabbits. Factor VIII is an endogenous protein, and no effect on fertility has been seen in humans with this protein.

Use in pregnancy: Category B2*

Animal reproduction studies have not been conducted with Kovaltry. It is also not known whether Kovaltry can cause fetal harm when administered to a pregnant woman or affect reproductive capacity. Kovaltry should be given to a pregnant woman only if clearly needed.

Use in lactation

It is not known whether Kovaltry is excreted into human milk. Because many drugs are excreted into human milk, caution should be exercised if Kovaltry is administered to a breastfeeding woman.

Paediatric Use

Safety and efficacy studies have been performed in previously treated paediatric patients. Children, in comparison to adults, present higher factor VIII clearance values and, thus, lower half-life and recovery of factor VIII. This may be due to differences in body composition. Account for this difference in clearance when dosing or following factor VIII levels in the paediatric population, as higher or more frequent dosing may be needed in children.

Routine prophylactic treatment with Kogenate FS (Antihemophilic Factor [Recombinant]) in children starting prophylaxis treatment at ages 0 to 2.5 years with no pre-existing joint damage has been shown to reduce spontaneous joint bleeding and the risk of joint damage. This data can be extrapolated to ages >2.5 to 16 years for children who have no existing joint damage.

Use in the elderly

Clinical studies did not include patients aged 65 years or more. As with any patient receiving recombinant factor VIII, dose selection for an elderly patient should be individualised.

Genotoxicity

Kovaltry is not expected to be genotoxic as biotechnology-derived pharmaceuticals are unlikely to directly interact with DNA or other chromosomal material. Kovaltry was not genotoxic in a mouse lymphoma assay.

Carcinogenicity

Carcinogenic studies in animals have not been performed. As factor VIII is an endogenous replacement protein it is not expected to be carcinogenic.

Effects on ability to drive or use machinery

Kovaltry has no influence on the ability to drive or to use machines.

* Drugs which have been taken by only a limited number of pregnant women and women of childbearing age, without an increase in the frequency of malformation or other direct or indirect harmful effects on the human foetus having been observed. Studies in animals are inadequate or may be lacking, but available data show no evidence of an increased occurrence of foetal damage.

INTERACTIONS WITH OTHER MEDICINES

No interactions of human coagulation factor VIII (rDNA) products with other medicinal products have been reported.

ADVERSE EFFECTS

The most frequently reported adverse reactions in clinical trials ($\geq 3\%$) were headache, pyrexia, and pruritus, which may be related to potential hypersensitivity reactions (see Table 15).

Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in clinical trials of another drug and may not reflect the rates observed in clinical practice.

Previously Treated Patients (PTPs)

A total of 193 PTPs (inclusive of 51 paediatric patients) were included to assess frequency of adverse reactions in the three phase III studies (see Table 15). The frequency, type, and severity of adverse reactions in children are similar to those in adults.

Table 15: Adverse Reactions in Previously Treated Patients (N=193)

MedDRA Primary System Organ Class Preferred term	Frequency N (%)
Blood and the Lymphatic System Disorders	
Lymphadenopathy	2 (1.0%)
Cardiac Disorders	
Palpitation	2 (1.0%)
Sinus tachycardia	2 (1.0%)
Gastrointestinal Disorders	
Abdominal pain	4 (2.1%)
Abdominal discomfort	3 (1.6%)
Dyspepsia	4 (2.1%)
General Disorders and Administration Site Conditions	
Pyrexia	8 (4.1%)
Chest discomfort	2 (1.0%)
Injection site reactions ^a	5 (2.6%)
Immune System Disorders	
Hypersensitivity	1 (0.5%)
Nervous System Disorders	
Dizziness	2 (1.0%)
Dysgeusia	1 (0.5%)
Headache	14 (7.3%)
Psychiatric Disorders	
Insomnia	5 (2.6%)
Skin and Subcutaneous Tissue Disorders	
Dermatitis allergic	2 (1.0%)
Pruritus	6 (3.1%)
Rash ^b	5 (2.6%)

Urticaria	1 (0.5%)
Vascular disorders	
Flushing	1 (0.5%)

^aincludes injection site extravasation and hematoma, infusion site pain, pruritus, and swelling

^bincludes rash, rash erythematous, and rash pruritic

Description of selected adverse reactions

Immunogenicity

The immunogenicity of Kovaltry was evaluated in previously treated patients. During clinical trials with Kovaltry in approximately 200 paediatric and adult patients diagnosed with severe haemophilia A (FVIII < 1%) with previous exposure to factor VIII concentrates \geq 50 exposure days (ED), no case of inhibitor development occurred.

In an actively enrolling clinical trial in previously untreated patients, three out of sixteen treated patients developed high titer inhibitor. The median number of exposure days at the time of inhibitor detection was 10 exposure days (range 6-20 exposure days).

Paediatric population

In completed clinical studies with 51 paediatric previously treated patients, the frequency, type and severity of adverse reactions in children were found to be similar to those in adults.

The clinical trial in previously untreated patients is ongoing.

DOSAGE AND ADMINISTRATION

For intravenous use. Kovaltry should be injected intravenously over 2 to 5 minutes depending on the total volume. The rate of administration should be determined by the patient's comfort level (maximal rate of infusion: 2 mL/min). Kovaltry is not intended for administration by continuous infusion.

Treatment should be initiated under the supervision of a physician experienced in the management of haemophilia.

Dosage

The dosage and duration of the substitution therapy to achieve haemostasis must be individualised according to the patient's needs (weight, severity of disorder of the haemostatic function, the site and extent/severity of the bleeding, the titre of inhibitors, and the factor VIII level desired).

The clinical effect of factor VIII is the most important element in evaluating the effectiveness of treatment. It may be necessary to administer more Kovaltry than would be estimated in order to attain satisfactory clinical results. If the calculated dose fails to attain the expected FVIII levels or if bleeding is not controlled after administration of the calculated dosage, the presence of a circulating inhibitor in the patient should be suspected. Its presence should be substantiated and the inhibitor level quantitated by an appropriate laboratory test. When an inhibitor is present, the

dosage requirement for Kovaltry is extremely variable and the dosage can be determined only by the clinical response.

Prescribed doses of Kovaltry should be expressed as International Units, written in full.

On Demand Treatment

The calculation of the required dose of factor VIII is based on the empirical finding that 1 International Unit (IU) factor VIII per kg body weight raises the plasma factor VIII activity by 1.5% to 2.5% of normal activity.

The required dose is determined using the following formulae:

Required units = body weight (kg) x desired factor VIII rise (% or IU/dL) x reciprocal of observed recovery (i.e. 0.5 for recovery of 2.0%).

The amount to be administered and the frequency of administration should always be targeted to the clinical effectiveness required in the individual case. The usual single dose is 10-30 IU/kg body weight. Higher dosages are recommended for life threatening or major haemorrhages. Under certain circumstances, larger amounts than those calculated may be required, especially in the case of the initial dose.

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

Table 16 Guide for dosing during bleeding episodes and in surgery

Degree of haemorrhage/ Type of surgical procedure	Factor VIII level required (%) (IU/dL)	Frequency of doses (hours)/ Duration of therapy (days)
Haemorrhage		
Early haemarthrosis, muscle bleed or oral bleed	20 - 40	Repeat every 12 to 24 hours for at least 1 day, until the bleeding episode as indicated by pain is resolved or healing is achieved.
More extensive haemarthrosis, muscle bleed or haematoma	30 - 60	Repeat infusion every 12 - 24 hours for 3 - 4 days or more until pain and acute disability are resolved.
Life threatening haemorrhages	60 - 100	Repeat infusion every 8 to 24 hours until threat is resolved
Surgery		
Minor including tooth extraction	30 - 60	Every 24 hours for at least 1 day, until healing is achieved.
Major	80 - 100 (pre- and post-operative)	Repeat infusion every 8 - 24 hours until adequate wound healing occurs, then continue with therapy for at least another 7 days to maintain a factor VIII activity of 30% to 60% (IU/dL).

Prophylaxis

For long term prophylaxis against bleeding in patients with severe haemophilia A, the usual doses for adolescents (> 12 years age) and adult patients are 20 to 40 IU of Kovaltry per kg body weight two to three times per week.

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

Paediatric population

Kovaltry is appropriate for use in paediatric patients. Safety and efficacy studies have been performed in children in 0-12 years. The recommended prophylaxis doses are 20-50 IU/kg twice weekly, three times weekly or every other day according to individual requirements. For paediatric patients above the age of 12 the dose recommendations are the same as for adults.

Elderly

As with any patient receiving recombinant factor VIII, dose selection for an elderly patient should be individualised.

Patients with inhibitors

Patients should be monitored for the development of factor VIII inhibitors. If the expected plasma factor VIII activity levels are not attained, or if bleeding is not controlled with an appropriate dose, an assay should be performed to determine if a factor VIII inhibitor is present. If the inhibitor is present at levels less than 10 Bethesda Units (BU) per mL, administration of additional recombinant human coagulation factor VIII may neutralise the inhibitor and permit continued clinically effective therapy with Kovaltry. However, in the presence of an inhibitor, the doses required are variable and must be adjusted according to clinical response and monitoring of plasma factor VIII activity. In patients with inhibitor titres above 10 BU or with high anamnestic response, the use of (activated) prothrombin complex concentrate (PCC) or recombinant activated factor VII (rFVIIa) preparations has to be considered. These therapies should be directed by physicians with experience in the care of patients with haemophilia.

Reconstitution and administration

Contains no antimicrobial agent. Product is for single use in one patient only.

General instructions

Detailed instructions for preparation and administration are contained in the package leaflet provided with Kovaltry.

Kovaltry powder should only be reconstituted with the supplied solvent (2.5 mL or 5.0 mL water for injections) in the prefilled syringe and the vial adapter. For infusion, the product must be prepared under aseptic conditions. If any component of the package is opened or damaged, do not use this component.

Gently rotate the vial until all powder is dissolved. After reconstitution the solution is clear. Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration. Do not use Kovaltry if you notice visible particulate matter or turbidity.

After reconstitution, the solution is drawn back into the syringe. Kovaltry should be reconstituted and administered with the components provided with each package.

The reconstituted product must be filtered prior to administration to remove potential particulate matter in the solution. Filtering is achieved by using the vial adapter.

If you have any questions about Kovaltry and compatible separate filters contact Bayer Australia Limited (1800-KOGEN8 or 1800 564 368).

Incompatibilities

This product must not be mixed with other medicinal products or solvents.

OVERDOSAGE

No case of overdose with recombinant human coagulation factor VIII has been reported.

For information on the management of overdose, contact the Poison Information Centre on 131126 (Australia).

PRESENTATION AND STORAGE CONDITIONS

Presentation

Kovaltry supplied with vial adapter for needleless reconstitution is provided with a prefilled syringe containing diluent for reconstitution.

Kovaltry 250 IU, 500 IU, 1000 IU

Packs of 1 vial of lyophilised powder for injection [250 IU, 500 IU, 1000 IU octocog alfa (bhk)] and a prefilled diluent syringe (2.5 mL Water for Injections) for reconstitution.

Kovaltry 2000 IU, 3000 IU

Packs of 1 vial of lyophilised powder for injection [2000 IU, 3000 IU octocog alfa (bhk)] and a prefilled diluent syringe (5 mL Water for Injections) for reconstitution.

Not all presentations are being distributed in Australia.

Storage conditions

Store in a refrigerator (2°C – 8°C). Do not freeze. Keep the vial and the pre-filled syringe in the outer carton in order to protect from light.

Within its overall shelf life of 30 months, the product, when kept in its outer carton, may be stored at ambient room temperature (up to 25°C) for a limited period of 12 months. In this case, the product expires at the end of this 12-month period or the expiration date on the product vial, whichever is earlier. The new expiry date must be noted on the outer carton.

Once product is removed from refrigeration, it cannot be returned to the refrigerator.

After reconstitution, from a microbiological point of view, the product should be used immediately. If not used immediately, in-use storage times and conditions prior to use are the responsibility of the user. The chemical and physical in-use stability after reconstitution has been demonstrated for 3 hours.

Do not refrigerate after reconstitution.

NAME AND ADDRESS OF THE SPONSOR

Bayer Australia Ltd
ABN 22 000 138 714
875 Pacific Highway
Pymble, NSW 2073

POISON SCHEDULE OF THE MEDICINE

Appendix A exempt

DATE OF FIRST INCLUSION IN THE ARTG

1 April 2016

® Registered Trademark of Bayer AG