ANNEX I

SUMMARY OF PRODUCT CHARACTERISTICS

▼This medicinal product is subject to additional monitoring. This will allow quick identification of new safety information. Healthcare professionals are asked to report any suspected adverse reactions. See section 4.8 for how to report adverse reactions.

1. NAME OF THE MEDICINAL PRODUCT

Kovaltry 250 IU powder and solvent for solution for injection
Kovaltry 500 IU powder and solvent for solution for injection
Kovaltry 1000 IU powder and solvent for solution for injection
Kovaltry 2000 IU powder and solvent for solution for injection
Kovaltry 3000 IU powder and solvent for solution for injection

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Kovaltry 250 IU powder and solvent for solution for injection
One mL Kovaltry 250 IU contains approximately 100 IU (250 IU / 2.5 mL) of recombinant human coagulation factor VIII (INN: octocog alfa) after reconstitution with water for injections.

Kovaltry 500 IU powder and solvent for solution for injection
One mL Kovaltry 500 IU contains approximately 200 IU (500 IU / 2.5 mL) of recombinant human coagulation factor VIII (INN: octocog alfa) after reconstitution with water for injections.

Kovaltry 1000 IU powder and solvent for solution for injection
One mL Kovaltry 1000 IU contains approximately 400 IU (1000 IU / 2.5 mL) of recombinant human coagulation factor VIII (INN: octocog alfa) after reconstitution with water for injections.

Kovaltry 2000 IU powder and solvent for solution for injection
One mL Kovaltry 2000 IU contains approximately 400 IU (2000 IU / 5 mL) of recombinant human coagulation factor VIII (INN: octocog alfa) after reconstitution with water for injections.

Kovaltry 3000 IU powder and solvent for solution for injection
One mL Kovaltry 3000 IU contains approximately 600 IU (3000 IU / 5 mL) of recombinant human coagulation factor VIII (INN: octocog alfa) after reconstitution with water for injections.

The potency (IU) is determined using the European Pharmacopoeia chromogenic assay. The specific activity of Kovaltry is approximately 4000 IU/mg protein.

Octocog alfa (Full length recombinant human coagulation factor VIII (rDNA)) is a purified protein that has 2,332 amino acids. It is produced by recombinant DNA technology in baby hamster kidney cells (BHK) into which the human factor VIII gene has been introduced. Kovaltry is prepared without the addition of any human or animal derived protein in the cell culture process, purification or final formulation.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Powder and solvent for solution for injection

Powder: solid, white to slightly yellow.
Solvent: water for injections, a clear solution.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

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

4.2 Posology and method of administration

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

Treatment monitoring

During the course of treatment, appropriate determination of factor VIII levels is advised to guide the dose to be administered and the frequency of repeated infusions. Individual patients may vary in their response to factor VIII, 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 VIII activity) is indispensable.

Posology

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

The number of units of factor VIII administered is expressed in International Units (IU), which are related to the current WHO standard for factor VIII products. Factor VIII 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 VIII in plasma).

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

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.

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 in bleeding episodes and surgery:

Table 1: Guide for dosing in bleeding episodes and 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 bleeding or oral bleeding	20 - 40	Repeat every 12 to 24 hours. At least 1 day, until the bleeding episode as indicated by pain is resolved or healing is achieved.
More extensive haemarthrosis, muscle bleeding 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 surgery including tooth extraction	30 - 60	Every 24 hours, at least 1 day, until healing is achieved.
Major surgery	80 - 100 (pre- and post-operative)	Repeat infusion every 8 - 24 hours until adequate wound healing, then 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
A safety and efficacy study has been performed in children of 012 years (see section 5.1); limited data are available for children below 1 year.
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.

Method of administration

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).
For instructions on reconstitution of the medicinal product before administration, see section 6.6 and the package leaflet.

4.3 Contraindications

- Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.
- Known allergic reactions to mouse or hamster proteins.

4.4 Special warnings and precautions for use

Traceability

In order to improve traceability of biological medicinal products, the name and the batch number of the administered product should be clearly recorded.

Hypersensitivity

Allergic type hypersensitivity reactions are possible with Kovaltry.
If symptoms of hypersensitivity occur, patients should be advised to discontinue the use of the medicinal product immediately and contact their physician.
Patients should be informed of the early signs of hypersensitivity reactions including hives, nausea, generalised urticaria, tightness of the chest, wheezing, hypotension, and anaphylaxis.

In case of shock, standard medical treatment for shock should be implemented.

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 severity of the disease as well as the exposure to factor VIII , this risk being highest within the first 20 exposure days. Rarely, inhibitors may develop after the first 50 exposure days but continues throughout life although the risk is uncommon.

The clinical relevance of inhibitor development will depend on the titre of the inhibitor, with low titre posing less of a risk of insufficient clinical response than high titre inhibitors.

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 (see section 4.2).
If the expected factor VIII activity plasma levels are not attained, or if bleeding is not controlled with an appropriate dose, testing for factor VIII inhibitor presence should be performed. In patients with high levels of inhibitor, factor VIII therapy may not be effective and other therapeutic options should be considered. Management of such patients should be directed by physicians with experience in the care of haemophilia and factor VIII inhibitors.

Cardiovascular events

Haemophilic patients with cardiovascular risk factors or diseases may be at the same risk to develop cardiovascular events as non-haemophilic patients when clotting has been normalised by treatment with factor VIII. Elevation of factor VIII levels following administration, in particular in those with existing cardiovascular risk factors, might cause a patient to have the same risk for vessel closure or myocardial infarction as for the non-haemophilic population. Consequently, patients should be evaluated for cardiac risk factors.

Catheter-related complications

If a central venous access device (CVAD) is required, risk of CVAD-related complications including local infections, bacteraemia and catheter site thrombosis should be considered. These complications have not been associated with the product itself.

Paediatric population

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

Sodium content

For 250/500/1000 IU strength
After reconstitution this medicinal product contains 0.081 mmol sodium per vial of reconstituted solution (corresponding to 1.86 mg per vial). This medicinal product contains less than 1 mmol sodium (23 mg) per dose, i.e. essentially ‘sodium-free’.

For 2000/3000 IU strength
After reconstitution this medicinal product contains 0.156 mmol sodium per vial of reconstituted solution (corresponding to 3.59 mg per vial). This medicinal product contains less than 1 mmol sodium (23 mg) per dose, i.e. essentially 'sodium-free'.

4.5 Interactions with other medicinal products and other forms of interaction

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

4.6 Fertility, pregnancy and lactation

Pregnancy

Animal reproduction studies have not been conducted with factor VIII. Based on the rare occurrence of haemophilia A in women, experience regarding the use of factor VIII during pregnancy is not available.
Therefore, factor VIII should be used during pregnancy only if clearly indicated.

Breast-feeding

It is unknown whether Kovaltry is excreted in human milk. The excretion in animals has not been studied. Therefore, factor VIII should be used during breast-feeding only if clearly indicated.

Fertility

No animal fertility studies have been conducted with Kovaltry and its effect on human fertility has not been established in controlled clinical trials. Since Kovaltry is a replacement protein of endogenous factor VIII, no adverse effects on fertility are expected.

4.7 Effects on ability to drive or use machines

If patients experience dizziness or other symptoms affecting their ability to concentrate and react, it is recommended that they do not drive or use machines until the reaction subsides.

4.8 Undesirable effects

Summary of the safety profile

Hypersensitivity or allergic reactions (which may include angioedema, burning and stinging at the infusion site, chills, flushing, generalised urticaria, headache, hives, hypotension, lethargy, nausea, restlessness, tachycardia, tightness of the chest, tingling, vomiting, wheezing) have been observed and may in some cases progress to severe anaphylaxis (including shock).
Development of antibodies to mouse and hamster protein with related hypersensitivity reactions may occur.

Development of neutralising antibodies (inhibitors) may occur in patients with haemophilia A treated with factor VIII (FVIII), including with Kovaltry. If such inhibitors occur, the condition may manifest itself as an insufficient clinical response. In such cases, it is recommended that a specialised haemophilia centre be contacted.

Tabulated list of adverse reactions

The table presented below is according to the MedDRA system organ classification (SOC and Preferred Term Level). Frequencies have been evaluated according to the following convention: very common (≥ 1/10), common (≥ 1/100 to < 1/10), uncommon (≥ 1/1,000 to < 1/100).
Within each frequency grouping, adverse reactions are presented in order of decreasing seriousness.

Table 2: Frequency of adverse drug reactions in clinical trials

MedDRA Standard System Organ Class	**Adverse reactions**	**Frequency**
Blood and lymphatic system disorders	Lymphadenopathy	common
	FVIII inhibition	very common (PUPs)* uncommon (PTPs)*
Cardiac disorders	Palpitation, sinus tachycardia	common
Gastrointestinal disorders	Abdominal pain, abdominal discomfort, dyspepsia	common
General disorders and administration site conditions	Pyrexia, chest discomfort, injection site reactions **	common
Immune system disorders	Hypersensitivity	uncommon
Nervous system disorders	Headache, dizziness	common
	Dysgeusia	uncommon
Psychiatric disorders	Insomnia	common
Skin and subcutaneous tissue disorders	Pruritus, rash***, dermatitis allergic	common
	Urticaria	uncommon
Vascular disorders	Flushing	uncommon

* Frequency is based on studies with all FVIII products which included patients with severe haemophilia A. PTPs = previously-treated patients, PUPs = previously-untreated patients
** includes injection site extravasation, hematoma, infusion site pain, pruritus, swelling
*** rash, rash erythematous, rash pruritic

Paediatric population
In completed clinical studies with 71 paediatric previously treated patients, the frequency, type and severity of adverse reactions in children were found to be similar to those 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 via the national reporting system listed in Appendix V.

4.9 Overdose

No symptoms of overdose with recombinant human coagulation factor VIII have been reported.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: antihemorrhagics: 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.

Of note, annualised bleeding rate (ABR) is not comparable between different factor concentrates and between different clinical studies.

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 rFVIII normalizes the aPTT similar to that achieved with plasma-derived factor VIII.

Clinical efficacy and safety

Control and Prevention of Bleeding
Two multi-centre, open-label, cross-over, uncontrolled, randomised studies in previously treated adults/adolescents with severe haemophilia A (< 1%) and one multi-centre, open-label, uncontrolled study in previously treated children < 12 years with severe haemophilia A were conducted.

A total of 204 subjects have been included in the clinical trial program, 153 subjects ≥ 12 years and 51 subjects < 12 years. 140 subjects were treated for at least 12 months, and 55 of these subjects for a median of 24 months.

Table 3: Consumption and overall success rates (patients treated with prophylaxis only)

	Younger children (0 <6 years)	Older children (6 <12 years)	Adolescents and adults 12-65 years			Total
			Study 1	Study 2 2 x/week dosing	Study 2 3 x/week dosing	
Study participants	25	26	62	28	31	172
Dose/prophylaxis injection, IU/kg BW median (min, max)	36 IU/kg (21; 58 IU/kg)	32 IU/kg (22; 50 IU/kg)	31 IU/kg (21; 43 IU/kg)	30 IU/kg (21; 34 IU/kg)	37 IU/kg (30; 42 IU/kg)	32 IU/kg (21; 58 IU/kg)
ABR – all bleeds (median, Q1,Q3)	2.0 (0.0; 6.0)	0.9 (0.0; 5.8)	1.0 (0.0; 5.1)	4.0 (0.0; 8.0)	2.0 (0.0; 4.9)	2.0 (0.0; 6.1)
Dose/injection for bleed treatment Median (min; max)	39 IU/kg (21;72 IU /kg)	32 IU/kg (22; 50 IU/kg)	29 IU/kg (13; 54 IU/kg)	28 IU/kg (19; 39 IU/kg)	31 IU/kg (21; 49 IU/kg)	31 IU/kg (13; 72 IU/kg)
Success rate*	92.4%	86.7%	86.3%	95.0%	97.7%	91.4%

ABR annualised bleed rate
Q1 first quartile; Q3 third quartile
BW: Body weight
*Success rate defined as % of bleeds treated successfully with ≤ 2 infusions

5.2 Pharmacokinetic properties

The Pharmacokinetic (PK) profile of Kovaltry was evaluated in PTPs with severe haemophilia A following 50 IU/kg in 21 subjects ≥ 18 years, 5 subjects ≥ 12 years and < 18 years and 19 subjects < 12 years of age.

A population PK model was developed based on all available factor VIII measurements (from dense PK sampling and all recovery samples) throughout the 3 clinical studies allowing calculation of PK parameters for subjects in the various studies. The table 4 below provides PK parameters based on the population PK model.

Table 4: PK parameters (geometric mean (%CV)) based on chromogenic assay. *

PK parameter	≥ 18 years N=109	12-<18 years N=23	6-<12 years N=27	0-<6 years N=24
$T_{1/2}$ (h)	14.8 (34)	13.3 (24)	14.1 (31)	13.3 (24)
AUC (IU.h/dL)**	1,858 (38)	1,523 (27)	1,242 (35)	970 (25)
CL (dL/h/kg)	0.03 (38)	0.03 (27)	0.04 (35)	0.05 (25)
V_{ss} (dL/kg)	0.56 (14)	0.61 (14)	0.77 (15)	0.92 (11)

* Based on population PK estimates
**AUC calculated for a dose of 50 IU/kg

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

In an international study involving 41 clinical laboratories, the performance of Kovaltry in FVIII:C assays was evaluated and compared to a marketed full length rFVIII product. Consistent results were determined for both products. The FVIII:C of Kovaltry can be measured in plasma with a one-stage coagulation assay as well as with a chromogenic assay using the routine methods of the laboratory.

The analysis of all recorded *incremental* recoveries in previously treated patients demonstrated a median rise of > 2% (> 2 IU/dL) per IU/kg body weight for Kovaltry. This result is similar to the reported values for factor VIII derived from human plasma. There was no relevant change over the 6-12 months treatment period.

Table 5: Phase III *incremental* recovery results

Study participants	N=115
Chromogenic assay results Median; (Q1; Q3) (IU/dL / IU/kg)	2.3 (1.8; 2.6)
One-stage assay results Median; (Q1; Q3) (IU/dL / IU/kg)	2.2 (1.8; 2.4)

5.3 Preclinical safety data

Non-clinical data reveal no special risk for humans based on safety pharmacology, *in vitro* genotoxicity, and short term repeat-dose toxicity studies. Repeat-dose toxicity studies longer than 5 days, reproductive toxicity studies, and carcinogenicity studies, have not been performed. Such studies are not considered meaningful due to the production of antibodies against the heterologous human protein in animals. Also factor VIII is an intrinsic protein and not known to cause any reproductive or carcinogenic effects.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Powder
Sucrose
Histidine
Glycine
Sodium chloride
Calcium chloride dihydrate
Polysorbate 80
Acetic acid, glacial (for pH adjustment)

Solvent
Water for injections

6.2 Incompatibilities

In the absence of compatibility studies, this medicinal product must not be mixed with other medicinal products.

Only the provided infusion sets should be used for reconstitution and injection because treatment failure can occur as a consequence of human recombinant coagulation factor VIII adsorption to the internal surfaces of some infusion equipment.

6.3 Shelf life

30 months

The chemical and physical in-use stability after reconstitution has been demonstrated for 3 hours at room temperature.
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.

Do not refrigerate after reconstitution.

6.4 Special precautions for storage

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 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 expiry date on the product vial, whichever is earlier. The new expiry date must be noted on the outer carton.

For storage conditions after reconstitution of the medicinal product, see section 6.3.

6.5 Nature and contents of container and special equipment for use, administration or implantation

Each single package of Kovaltry contains:
- one vial with powder (10 mL clear glass type 1 vial with grey halogenobutyl rubber blend stopper and aluminium seal)
- one pre-filled syringe with 2.5 mL (for 250 IU, 500 IU and 1000 IU) or 5 mL (for 2000 IU and 3000 IU) solvent (clear glass cylinder type 1 with grey bromobutyl rubber blend stopper)
- syringe plunger rod
- vial adapter
- one venipuncture set

Pack sizes
– 1 single pack.
– 1 multipack with 30 single packs.
Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

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

The reconstituted medicinal product is a clear and colourless solution.

Kovaltry powder should only be reconstituted with the supplied solvent (2.5 mL or 5 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.
After reconstitution the solution is clear. Parenteral medicinal 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 (vial adapter, prefilled syringe, venipuncture set) 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.
The venipuncture set provided with the product must not be used for drawing blood because it contains an in line filter.

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

7. MARKETING AUTHORISATION HOLDER

Bayer AG
51368 Leverkusen
Germany

8. MARKETING AUTHORISATION NUMBERS

EU/1/15/1076/002 1 x (Kovaltry 250 IU - solvent (2.5 mL); pre-filled syringe (3 mL))
EU/1/15/1076/012 - 1 x (Kovaltry 250 IU - solvent (2.5 mL); pre-filled syringe (5 mL))
EU/1/15/1076/004 - 1 x (Kovaltry 500 IU - solvent (2.5 mL); pre-filled syringe (3 mL))
EU/1/15/1076/014 - 1 x (Kovaltry 500 IU - solvent (2.5 mL); pre-filled syringe (5 mL))
EU/1/15/1076/006 - 1 x (Kovaltry 1000 IU - solvent (2.5 mL); pre-filled syringe (3 mL))
EU/1/15/1076/016 - 1 x (Kovaltry 1000 IU - solvent (2.5 mL); pre-filled syringe (5 mL))
EU/1/15/1076/008 - 1 x (Kovaltry 2000 IU - solvent (5 mL); pre-filled syringe (5 mL))
EU/1/15/1076/010 - 1 x (Kovaltry 3000 IU - solvent (5 mL); pre-filled syringe (5 mL))
EU/1/15/1076/017 30 x (Kovaltry 250 IU - solvent (2.5 mL); pre-filled syringe (3 mL))
EU/1/15/1076/018 - 30 x (Kovaltry 250 IU - solvent (2.5 mL); pre-filled syringe (5 mL))
EU/1/15/1076/019 - 30 x (Kovaltry 500 IU - solvent (2.5 mL); pre-filled syringe (3 mL))
EU/1/15/1076/020 - 30 x (Kovaltry 500 IU - solvent (2.5 mL); pre-filled syringe (5 mL))
EU/1/15/1076/021 - 30 x (Kovaltry 1000 IU - solvent (2.5 mL); pre-filled syringe (3 mL))
EU/1/15/1076/022 - 30 x (Kovaltry 1000 IU - solvent (2.5 mL); pre-filled syringe (5 mL))
EU/1/15/1076/023 - 30 x (Kovaltry 2000 IU - solvent (5 mL); pre-filled syringe (5 mL))
EU/1/15/1076/024 - 30 x (Kovaltry 3000 IU - solvent (5 mL); pre-filled syringe (5 mL))

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 18 February 2016

10. DATE OF REVISION OF THE TEXT

Detailed information on this medicinal product is available on the website of the European Medicines Agency http://www.ema.europa.eu.

ANNEX II

A. MANUFACTURER OF THE BIOLOGICAL ACTIVE SUBSTANCE AND MANUFACTURER RESPONSIBLE FOR BATCH RELEASE

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

A. MANUFACTURER OF THE BIOLOGICAL ACTIVE SUBSTANCE AND MANUFACTURER RESPONSIBLE FOR BATCH RELEASE

Name and address of the manufacturer of the biological active substance

Bayer HealthCare LLC
800 Dwight Way
Berkeley
CA 94710
United States

Name and address of the manufacturer responsible for batch release

Bayer AG
Kaiser-Wilhelm-Allee
51368 Leverkusen
Germany

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

Medicinal product subject to restricted medical prescription (see Annex I: Summary of Product Characteristics, section 4.2).

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

- **Periodic safety update reports (PSURs)**

The requirements for submission of PSURs for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

- **Risk management plan (RMP)**

The marketing authorisation holder (MAH) shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the marketing authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:

- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

- **Obligation to conduct post-authorisation measures**

The MAH shall complete, within the stated timeframe, the below measures:

Description	Due date
Post-authorisation Efficacy Study: In order to investigate the safety and efficacy of Kovaltry in previously untreated patients, the MAH should submit the results of the ongoing study “13400 - Leopold Kids Part B”	12/2022
Post-authorisation Efficacy Study: In order to investigate the safety and efficacy of long term treatment with Kovaltry, the MAH should submit the results of the ongoing study “13400 - Leopold Kids extension”	12/2022

ANNEX III

LABELLING AND PACKAGE LEAFLET

A. LABELLING

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

OUTER CARTON OF A SINGLE PACK (INCLUDING BLUE BOX)

1. NAME OF THE MEDICINAL PRODUCT

Kovaltry 250 IU powder and solvent for solution for injection

recombinant human coagulation factor VIII (octocog alfa)

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Kovaltry 250 IU contains (250 IU / 2.5 mL) = 100 IU octocog alfa per mL after reconstitution.

3. LIST OF EXCIPIENTS

Sucrose, histidine, glycine, sodium chloride, calcium chloride dihydrate, polysorbate 80, acetic acid glacial and water for injections.

4. PHARMACEUTICAL FORM AND CONTENTS

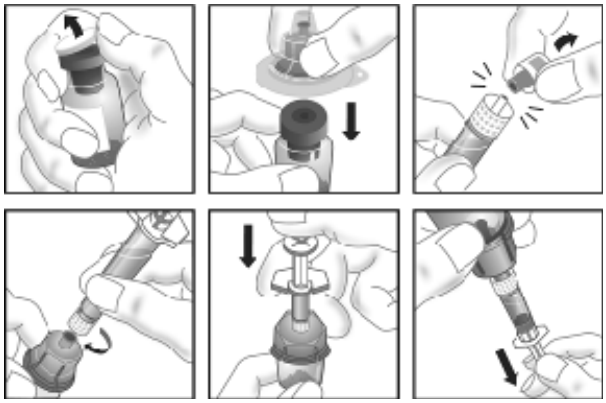
powder and solvent for solution for injection

1 vial with powder, 1 pre-filled syringe with water for injections, 1 vial adapter and 1 venipuncture set.

5. METHOD AND ROUTE(S) OF ADMINISTRATION

For intravenous use. Single dose administration only.
Read the package leaflet before use.

For reconstitution read package leaflet before use.



6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP
EXP (End of the 12 month period, if stored up to 25 °C): .....
Do not use after this date.

May be stored at temperatures up to 25 °C for up to 12 months within the expiry date indicated on the label. Note the new expiry date on the carton.
After reconstitution, the product must be used within 3 hours. **Do not refrigerate after reconstitution.**

9. SPECIAL STORAGE CONDITIONS

Store in a refrigerator. Do not freeze.

Keep the vial and the pre-filled syringe in the outer carton in order to protect from light.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

Any unused solution must be discarded.

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Bayer AG
51368 Leverkusen
Germany

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/15/1076/002 – 1 x (Kovaltry 250 IU - solvent (2.5 mL); pre-filled syringe (3 mL))
EU/1/15/1076/012 – 1 x (Kovaltry 250 IU - solvent (2.5 mL); pre-filled syringe (5 mL))

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Kovaltry 250

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC
SN
NN

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

OUTER LABEL OF MULTIPACK WITH 30 SINGLE PACKS (INCLUDING BLUE BOX)

1. NAME OF THE MEDICINAL PRODUCT

Kovaltry 250 IU powder and solvent for solution for injection

recombinant human coagulation factor VIII (octocog alfa)

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Kovaltry 250 IU contains (250 IU / 2.5 mL) = 100 IU octocog alfa per mL after reconstitution.

3. LIST OF EXCIPIENTS

Sucrose, histidine, glycine, sodium chloride, calcium chloride dihydrate, polysorbate 80, acetic acid glacial and water for injections.

4. PHARMACEUTICAL FORM AND CONTENTS

powder and solvent for solution for injection

Multipack with 30 single packs, each containing:

1 vial with powder, 1 pre-filled syringe with water for injections, 1 vial adapter and 1 venipuncture set.

5. METHOD AND ROUTE(S) OF ADMINISTRATION

For intravenous use. Single dose administration only.
Read the package leaflet before use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP
EXP (End of the 12 month period, if stored up to 25 °C): .....
Do not use after this date.

May be stored at temperatures up to 25 °C for up to 12 months within the expiry date indicated on the label. Note the new expiry date on the carton.
After reconstitution, the product must be used within 3 hours. **Do not refrigerate after reconstitution.**

9. SPECIAL STORAGE CONDITIONS

Store in a refrigerator.
Do not freeze.
Keep the vial and the pre-filled syringe in the outer carton in order to protect from light.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

Any unused solution must be discarded.

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Bayer AG
51368 Leverkusen
Germany

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/15/1076/017 – 30 x (Kovaltry 250 IU - solvent (2.5 mL); pre-filled syringe (3 mL))
EU/1/15/1076/018 – 30 x (Kovaltry 250 IU - solvent (2.5 mL); pre-filled syringe (5 mL))

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Kovaltry 250

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC
SN
NN

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

INNER CARTON OF A MULTIPACK (WITHOUT BLUE BOX)

1. NAME OF THE MEDICINAL PRODUCT

Kovaltry 250 IU powder and solvent for solution for injection

recombinant human coagulation factor VIII (octocog alfa)

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Kovaltry 250 IU contains (250 IU / 2.5 mL) = 100 IU octocog alfa per mL after reconstitution.

3. LIST OF EXCIPIENTS

Sucrose, histidine, glycine, sodium chloride, calcium chloride dihydrate, polysorbate 80, acetic acid glacial and water for injections.

4. PHARMACEUTICAL FORM AND CONTENTS

powder and solvent for solution for injection

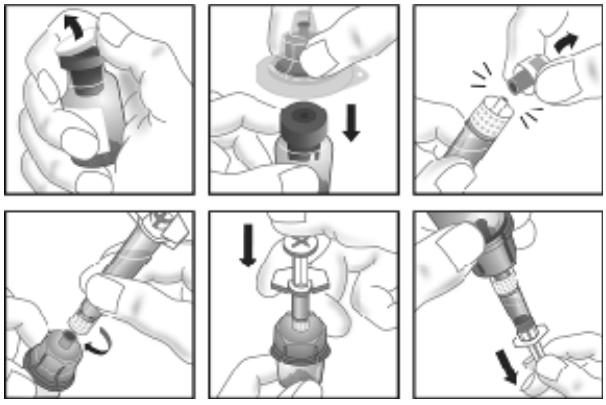
Component of a multipack, can't be sold separately.

1 vial with powder, 1 pre-filled syringe with water for injections, 1 vial adapter and 1 venipuncture set.

5. METHOD AND ROUTE(S) OF ADMINISTRATION

For intravenous use. Single dose administration only.
Read the package leaflet before use.

For reconstitution read package leaflet before use.



6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP
EXP (End of the 12 month period, if stored up to 25 °C): .....
Do not use after this date.

May be stored at temperatures up to 25 °C for up to 12 months within the expiry date indicated on the label. Note the new expiry date on the carton.
After reconstitution, the product must be used within 3 hours. **Do not refrigerate after reconstitution.**

9. SPECIAL STORAGE CONDITIONS

Store in a refrigerator. Do not freeze.

Keep the vial and the pre-filled syringe in the outer carton in order to protect from light.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

Any unused solution must be discarded.

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Bayer AG
51368 Leverkusen
Germany

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/15/1076/017 – 30 x (Kovaltry 250 IU - solvent (2.5 mL); pre-filled syringe (3 mL))
EU/1/15/1076/018 – 30 x (Kovaltry 250 IU - solvent (2.5 mL); pre-filled syringe (5 mL))

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Kovaltry 250

17. UNIQUE IDENTIFIER – 2D BARCODE

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

VIAL WITH POWDER FOR SOLUTION FOR INJECTION

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION

Kovaltry 250 IU powder for solution for injection

recombinant human coagulation factor VIII (octocog alfa)
Intravenous use.

2. METHOD OF ADMINISTRATION

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

250 IU (octocog alfa) (100 IU/mL after reconstitution).

6. OTHER

Bayer-Logo

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

OUTER CARTON OF A SINGLE PACK (INCLUDING BLUE BOX)

1. NAME OF THE MEDICINAL PRODUCT

Kovaltry 500 IU powder and solvent for solution for injection

recombinant human coagulation factor VIII (octocog alfa)

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Kovaltry 500 IU contains (500 IU / 2.5 mL) = 200 IU octocog alfa per mL after reconstitution.

3. LIST OF EXCIPIENTS

Sucrose, histidine, glycine, sodium chloride, calcium chloride dihydrate, polysorbate 80, acetic acid glacial and water for injections.

4. PHARMACEUTICAL FORM AND CONTENTS

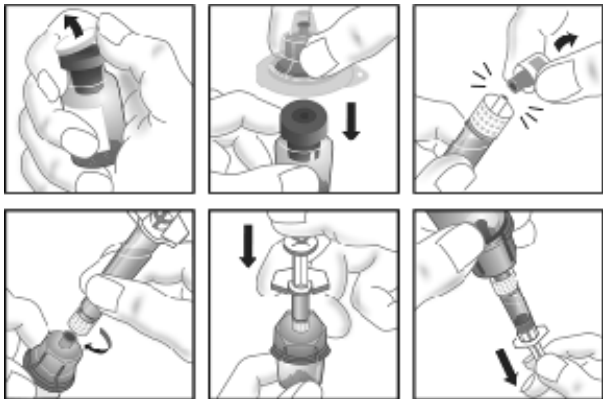
powder and solvent for solution for injection

1 vial with powder, 1 pre-filled syringe with water for injections, 1 vial adapter and 1 venipuncture set.

5. METHOD AND ROUTE(S) OF ADMINISTRATION

For intravenous use. Single dose administration only.
Read the package leaflet before use.

For reconstitution read package leaflet before use.



6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP
EXP (End of the 12 month period, if stored up to 25 °C): .....
Do not use after this date.

May be stored at temperatures up to 25 °C for up to 12 months within the expiry date indicated on the label. Note the new expiry date on the carton.
After reconstitution, the product must be used within 3 hours. **Do not refrigerate after reconstitution.**

9. SPECIAL STORAGE CONDITIONS

Store in a refrigerator. Do not freeze.

Keep the vial and the pre-filled syringe in the outer carton in order to protect from light.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

Any unused solution must be discarded.

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Bayer AG
51368 Leverkusen
Germany

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/15/1076/004 – 1 x (Kovaltry 500 IU - solvent (2.5 mL); pre-filled syringe (3 mL))
EU/1/15/1076/014 – 1 x (Kovaltry 500 IU - solvent (2.5 mL); pre-filled syringe (5 mL))

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Kovaltry 500

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC
SN
NN

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

OUTER LABEL OF MULTIPACK WITH 30 SINGLE PACKS (INCLUDING BLUE BOX)

1. NAME OF THE MEDICINAL PRODUCT

Kovaltry 500 IU powder and solvent for solution for injection

recombinant human coagulation factor VIII (octocog alfa)

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Kovaltry 500 IU contains (500 IU / 2.5 mL) = 200 IU octocog alfa per mL after reconstitution.

3. LIST OF EXCIPIENTS

Sucrose, histidine, glycine, sodium chloride, calcium chloride dihydrate, polysorbate 80, acetic acid glacial and water for injections.

4. PHARMACEUTICAL FORM AND CONTENTS

powder and solvent for solution for injection

Multipack with 30 single packs, each containing:

1 vial with powder, 1 pre-filled syringe with water for injections, 1 vial adapter and 1 venipuncture set.

5. METHOD AND ROUTE(S) OF ADMINISTRATION

For intravenous use. Single dose administration only.
Read the package leaflet before use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP
EXP (End of the 12 month period, if stored up to 25 °C): .....
Do not use after this date.

May be stored at temperatures up to 25 °C for up to 12 months within the expiry date indicated on the label. Note the new expiry date on the carton.
After reconstitution, the product must be used within 3 hours. **Do not refrigerate after reconstitution.**

9. SPECIAL STORAGE CONDITIONS

Store in a refrigerator.
Do not freeze.
Keep the vial and the pre-filled syringe in the outer carton in order to protect from light.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

Any unused solution must be discarded.

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Bayer AG
51368 Leverkusen
Germany

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/15/1076/019 – 30 x (Kovaltry 500 IU - solvent (2.5 mL); pre-filled syringe (3 mL))
EU/1/15/1076/020 – 30 x (Kovaltry 500 IU - solvent (2.5 mL); pre-filled syringe (5 mL))

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Kovaltry 500

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC
SN
NN

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

INNER CARTON OF A MULTIPACK (WITHOUT BLUE BOX)

1. NAME OF THE MEDICINAL PRODUCT

Kovaltry 500 IU powder and solvent for solution for injection

recombinant human coagulation factor VIII (octocog alfa)

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Kovaltry 500 IU contains (500 IU / 2.5 mL) = 200 IU octocog alfa per mL after reconstitution.

3. LIST OF EXCIPIENTS

Sucrose, histidine, glycine, sodium chloride, calcium chloride dihydrate, polysorbate 80, acetic acid glacial and water for injections.

4. PHARMACEUTICAL FORM AND CONTENTS

powder and solvent for solution for injection

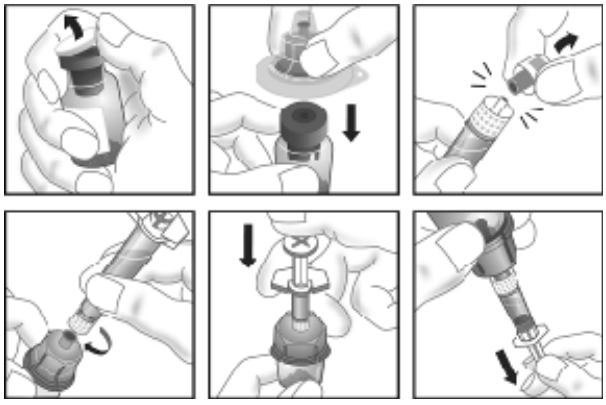
Component of a multipack, can't be sold separately.

1 vial with powder, 1 pre-filled syringe with water for injections, 1 vial adapter and 1 venipuncture set.

5. METHOD AND ROUTE(S) OF ADMINISTRATION

For intravenous use. Single dose administration only.
Read the package leaflet before use.

For reconstitution read package leaflet before use.



6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP
EXP (End of the 12 month period, if stored up to 25 °C): .....
Do not use after this date.

May be stored at temperatures up to 25 °C for up to 12 months within the expiry date indicated on the label. Note the new expiry date on the carton.
After reconstitution, the product must be used within 3 hours. **Do not refrigerate after reconstitution.**

9. SPECIAL STORAGE CONDITIONS

Store in a refrigerator. Do not freeze.

Keep the vial and the pre-filled syringe in the outer carton in order to protect from light.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

Any unused solution must be discarded.

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Bayer AG
51368 Leverkusen
Germany

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/15/1076/019 – 30 x (Kovaltry 500 IU - solvent (2.5 mL); pre-filled syringe (3 mL))
EU/1/15/1076/020 – 30 x (Kovaltry 500 IU - solvent (2.5 mL); pre-filled syringe (5 mL))

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Kovaltry 500

17. UNIQUE IDENTIFIER – 2D BARCODE

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

VIAL WITH POWDER FOR SOLUTION FOR INJECTION

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION

Kovaltry 500 IU powder for solution for injection

recombinant human coagulation factor VIII (octocog alfa)
Intravenous use.

2. METHOD OF ADMINISTRATION

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

500 IU (octocog alfa) (200 IU/mL after reconstitution).

6. OTHER

Bayer-Logo

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

OUTER CARTON OF A SINGLE PACK (INCLUDING BLUE BOX)

1. NAME OF THE MEDICINAL PRODUCT

Kovaltry 1000 IU powder and solvent for solution for injection

recombinant human coagulation factor VIII (octocog alfa)

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Kovaltry 1000 IU contains (1000 IU / 2.5 mL) = 400 IU octocog alfa per mL after reconstitution.

3. LIST OF EXCIPIENTS

Sucrose, histidine, glycine, sodium chloride, calcium chloride dihydrate, polysorbate 80, acetic acid glacial and water for injections.

4. PHARMACEUTICAL FORM AND CONTENTS

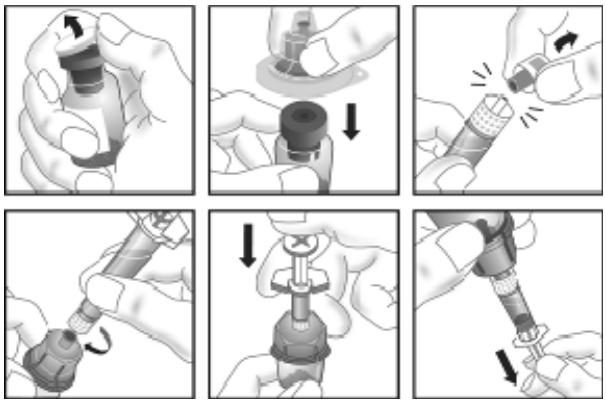
powder and solvent for solution for injection

1 vial with powder, 1 pre-filled syringe with water for injections, 1 vial adapter and 1 venipuncture set.

5. METHOD AND ROUTE(S) OF ADMINISTRATION

For intravenous use. Single dose administration only.
Read the package leaflet before use.

For reconstitution read package leaflet before use.



6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP
EXP (End of the 12 month period, if stored up to 25 °C): .....
Do not use after this date.

May be stored at temperatures up to 25 °C for up to 12 months within the expiry date indicated on the label. Note the new expiry date on the carton.
After reconstitution, the product must be used within 3 hours. **Do not refrigerate after reconstitution.**

9. SPECIAL STORAGE CONDITIONS

Store in a refrigerator. Do not freeze.

Keep the vial and the pre-filled syringe in the outer carton in order to protect from light.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

Any unused solution must be discarded.

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Bayer AG
51368 Leverkusen
Germany

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/15/1076/006 – 1 x (Kovaltry 1000 IU - solvent (2.5 mL); pre-filled syringe (3 mL))
EU/1/15/1076/016 – 1 x (Kovaltry 1000 IU - solvent (2.5 mL); pre-filled syringe (5 mL))

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Kovaltry 1000

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC
SN
NN

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

OUTER LABEL OF MULTIPACK WITH 30 SINGLE PACKS (INCLUDING BLUE BOX)

1. NAME OF THE MEDICINAL PRODUCT

Kovaltry 1000 IU powder and solvent for solution for injection

recombinant human coagulation factor VIII (octocog alfa)

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Kovaltry 1000 IU contains (1000 IU / 2.5 mL) = 400 IU octocog alfa per mL after reconstitution.

3. LIST OF EXCIPIENTS

Sucrose, histidine, glycine, sodium chloride, calcium chloride dihydrate, polysorbate 80, acetic acid glacial and water for injections.

4. PHARMACEUTICAL FORM AND CONTENTS

powder and solvent for solution for injection

Multipack with 30 single packs, each containing:

1 vial with powder, 1 pre-filled syringe with water for injections, 1 vial adapter and 1 venipuncture set.

5. METHOD AND ROUTE(S) OF ADMINISTRATION

For intravenous use. Single dose administration only.
Read the package leaflet before use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP
EXP (End of the 12 month period, if stored up to 25 °C): .....
Do not use after this date.

May be stored at temperatures up to 25 °C for up to 12 months within the expiry date indicated on the label. Note the new expiry date on the carton.
After reconstitution, the product must be used within 3 hours. **Do not refrigerate after reconstitution.**

9. SPECIAL STORAGE CONDITIONS

Store in a refrigerator.
Do not freeze.
Keep the vial and the pre-filled syringe in the outer carton in order to protect from light.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

Any unused solution must be discarded.

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Bayer AG
51368 Leverkusen
Germany

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/15/1076/021 – 30 x (Kovaltry 1000 IU - solvent (2.5 mL); pre-filled syringe (3 mL))
EU/1/15/1076/022 – 30 x (Kovaltry 1000 IU - solvent (2.5 mL); pre-filled syringe (5 mL))

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Kovaltry 1000

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC
SN
NN

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

INNER CARTON OF A MULTIPACK (WITHOUT BLUE BOX)

1. NAME OF THE MEDICINAL PRODUCT

Kovaltry 1000 IU powder and solvent for solution for injection

recombinant human coagulation factor VIII (octocog alfa)

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Kovaltry 1000 IU contains (1000 IU / 2.5 mL) = 400 IU octocog alfa per mL after reconstitution.

3. LIST OF EXCIPIENTS

Sucrose, histidine, glycine, sodium chloride, calcium chloride dihydrate, polysorbate 80, acetic acid glacial and water for injections.

4. PHARMACEUTICAL FORM AND CONTENTS

powder and solvent for solution for injection

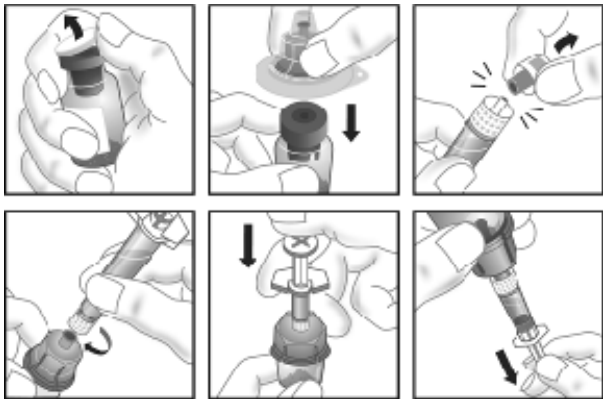
Component of a multipack, can't be sold separately.

1 vial with powder, 1 pre-filled syringe with water for injections, 1 vial adapter and 1 venipuncture set.

5. METHOD AND ROUTE(S) OF ADMINISTRATION

For intravenous use. Single dose administration only.
Read the package leaflet before use.

For reconstitution read package leaflet before use.



6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP
EXP (End of the 12 month period, if stored up to 25 °C): .....
Do not use after this date.

May be stored at temperatures up to 25 °C for up to 12 months within the expiry date indicated on the label. Note the new expiry date on the carton.
After reconstitution, the product must be used within 3 hours. **Do not refrigerate after reconstitution.**

9. SPECIAL STORAGE CONDITIONS

Store in a refrigerator. Do not freeze.

Keep the vial and the pre-filled syringe in the outer carton in order to protect from light.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

Any unused solution must be discarded.

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Bayer AG
51368 Leverkusen
Germany

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/15/1076/021 – 30 x (Kovaltry 1000 IU - solvent (2.5 mL); pre-filled syringe (3 mL))
EU/1/15/1076/022 – 30 x (Kovaltry 1000 IU - solvent (2.5 mL); pre-filled syringe (5 mL))

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Kovaltry 1000

17. UNIQUE IDENTIFIER – 2D BARCODE

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

VIAL WITH POWDER FOR SOLUTION FOR INJECTION

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION

Kovaltry 1000 IU powder for solution for injection

recombinant human coagulation factor VIII (octocog alfa)
Intravenous use.

2. METHOD OF ADMINISTRATION

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

1000 IU (octocog alfa) (400 IU/mL after reconstitution).

6. OTHER

Bayer-Logo

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

OUTER CARTON OF A SINGLE PACK (INCLUDING BLUE BOX)

1. NAME OF THE MEDICINAL PRODUCT

Kovaltry 2000 IU powder and solvent for solution for injection

recombinant human coagulation factor VIII (octocog alfa)

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Kovaltry 2000 IU contains (2000 IU / 5 mL) = 400 IU octocog alfa per mL after reconstitution.

3. LIST OF EXCIPIENTS

Sucrose, histidine, glycine, sodium chloride, calcium chloride dihydrate, polysorbate 80, acetic acid glacial and water for injections.

4. PHARMACEUTICAL FORM AND CONTENTS

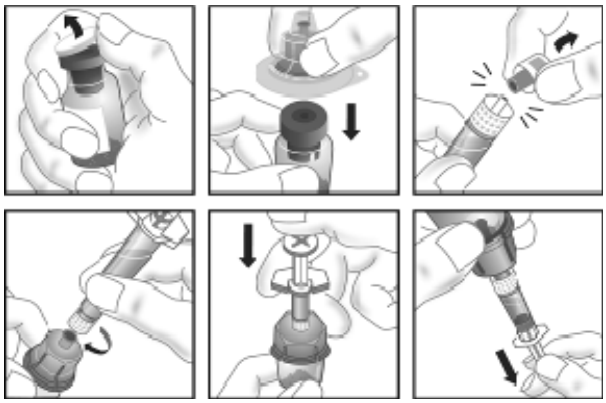
powder and solvent for solution for injection

1 vial with powder, 1 pre-filled syringe with water for injections, 1 vial adapter and 1 venipuncture set.

5. METHOD AND ROUTE(S) OF ADMINISTRATION

For intravenous use. Single dose administration only.
Read the package leaflet before use.

For reconstitution read package leaflet before use.



6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP
EXP (End of the 12 month period, if stored up to 25 °C): .....
Do not use after this date.

May be stored at temperatures up to 25 °C for up to 12 months within the expiry date indicated on the label. Note the new expiry date on the carton.
After reconstitution, the product must be used within 3 hours. **Do not refrigerate after reconstitution.**

9. SPECIAL STORAGE CONDITIONS

Store in a refrigerator. Do not freeze.

Keep the vial and the pre-filled syringe in the outer carton in order to protect from light.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

Any unused solution must be discarded.

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Bayer AG
51368 Leverkusen
Germany

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/15/1076/008 – 1 x (Kovaltry 2000 IU - solvent (5 mL); pre-filled syringe (5 mL))

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Kovaltry 2000

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC
SN
NN

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

OUTER LABEL OF MULTIPACK WITH 30 SINGLE PACKS (INCLUDING BLUE BOX)

1. NAME OF THE MEDICINAL PRODUCT

Kovaltry 2000 IU powder and solvent for solution for injection

recombinant human coagulation factor VIII (octocog alfa)

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Kovaltry 2000 IU contains (2000 IU / 5 mL) = 400 IU octocog alfa per mL after reconstitution.

3. LIST OF EXCIPIENTS

Sucrose, histidine, glycine, sodium chloride, calcium chloride dihydrate, polysorbate 80, acetic acid glacial and water for injections.

4. PHARMACEUTICAL FORM AND CONTENTS

powder and solvent for solution for injection

Multipack with 30 single packs, each containing:

1 vial with powder, 1 pre-filled syringe with water for injections, 1 vial adapter and 1 venipuncture set.

5. METHOD AND ROUTE(S) OF ADMINISTRATION

For intravenous use. Single dose administration only.
Read the package leaflet before use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP
EXP (End of the 12 month period, if stored up to 25 °C): .....
Do not use after this date.

May be stored at temperatures up to 25 °C for up to 12 months within the expiry date indicated on the label. Note the new expiry date on the carton.
After reconstitution, the product must be used within 3 hours. **Do not refrigerate after reconstitution.**

9. SPECIAL STORAGE CONDITIONS

Store in a refrigerator.
Do not freeze.
Keep the vial and the pre-filled syringe in the outer carton in order to protect from light.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

Any unused solution must be discarded.

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Bayer AG
51368 Leverkusen
Germany

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/15/1076/023 – 30 x (Kovaltry 2000 IU - solvent (5 mL); pre-filled syringe (5 mL))

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Kovaltry 2000

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC
SN
NN

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

INNER CARTON OF A MULTIPACK (WITHOUT BLUE BOX)

1. NAME OF THE MEDICINAL PRODUCT

Kovaltry 2000 IU powder and solvent for solution for injection

recombinant human coagulation factor VIII (octocog alfa)

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Kovaltry 2000 IU contains (2000 IU / 5 mL) = 400 IU octocog alfa per mL after reconstitution.

3. LIST OF EXCIPIENTS

Sucrose, histidine, glycine, sodium chloride, calcium chloride dihydrate, polysorbate 80, acetic acid glacial and water for injections.

4. PHARMACEUTICAL FORM AND CONTENTS

powder and solvent for solution for injection

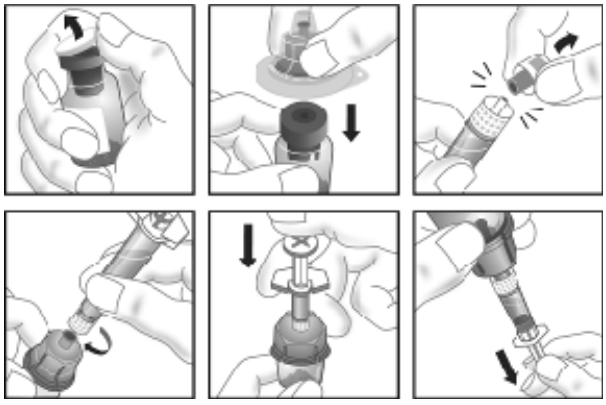
Component of a multipack, can't be sold separately.

1 vial with powder, 1 pre-filled syringe with water for injections, 1 vial adapter and 1 venipuncture set.

5. METHOD AND ROUTE(S) OF ADMINISTRATION

For intravenous use. Single dose administration only.
Read the package leaflet before use.

For reconstitution read package leaflet before use.



6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP
EXP (End of the 12 month period, if stored up to 25 °C): .....
Do not use after this date.

May be stored at temperatures up to 25 °C for up to 12 months within the expiry date indicated on the label. Note the new expiry date on the carton.
After reconstitution, the product must be used within 3 hours. **Do not refrigerate after reconstitution.**

9. SPECIAL STORAGE CONDITIONS

Store in a refrigerator. Do not freeze.

Keep the vial and the pre-filled syringe in the outer carton in order to protect from light.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

Any unused solution must be discarded.

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Bayer AG
51368 Leverkusen
Germany

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/15/1076/023 – 30 x (Kovaltry 2000 IU - solvent (5 mL); pre-filled syringe (5 mL))

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Kovaltry 2000

17. UNIQUE IDENTIFIER – 2D BARCODE

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

VIAL WITH POWDER FOR SOLUTION FOR INJECTION

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION

Kovaltry 2000 IU powder for solution for injection

recombinant human coagulation factor VIII (octocog alfa)
Intravenous use.

2. METHOD OF ADMINISTRATION

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

2000 IU (octocog alfa) (400 IU/mL after reconstitution).

6. OTHER

Bayer-Logo

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

OUTER CARTON OF A SINGLE PACK (INCLUDING BLUE BOX)

1. NAME OF THE MEDICINAL PRODUCT

Kovaltry 3000 IU powder and solvent for solution for injection

recombinant human coagulation factor VIII (octocog alfa)

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Kovaltry 3000 IU contains (3000 IU / 5 mL) = 600 IU octocog alfa per mL after reconstitution.

3. LIST OF EXCIPIENTS

Sucrose, histidine, glycine, sodium chloride, calcium chloride dihydrate, polysorbate 80, acetic acid glacial and water for injections.

4. PHARMACEUTICAL FORM AND CONTENTS

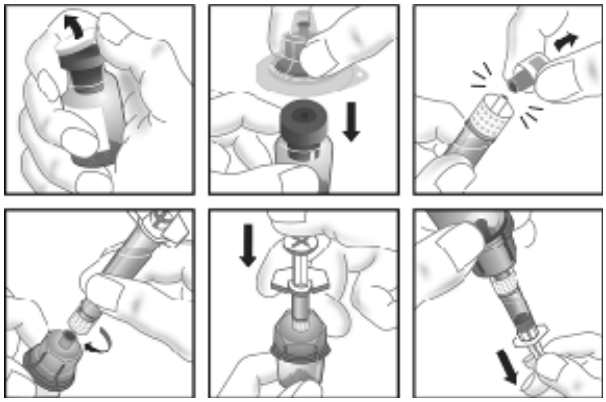
powder and solvent for solution for injection

1 vial with powder, 1 pre-filled syringe with water for injections, 1 vial adapter and 1 venipuncture set.

5. METHOD AND ROUTE(S) OF ADMINISTRATION

For intravenous use. Single dose administration only.
Read the package leaflet before use.

For reconstitution read package leaflet before use.



6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP
EXP (End of the 12 month period, if stored up to 25 °C): .....
Do not use after this date.

May be stored at temperatures up to 25 °C for up to 12 months within the expiry date indicated on the label. Note the new expiry date on the carton.
After reconstitution, the product must be used within 3 hours. **Do not refrigerate after reconstitution.**

9. SPECIAL STORAGE CONDITIONS

Store in a refrigerator. Do not freeze.

Keep the vial and the pre-filled syringe in the outer carton in order to protect from light.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

Any unused solution must be discarded.

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Bayer AG
51368 Leverkusen
Germany

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/15/1076/010 – 1 x (Kovaltry 3000 IU - solvent (5 mL); pre-filled syringe (5 mL))

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Kovaltry 3000

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC
SN
NN

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

OUTER LABEL OF MULTIPACK WITH 30 SINGLE PACKS (INCLUDING BLUE BOX)

1. NAME OF THE MEDICINAL PRODUCT

Kovaltry 3000 IU powder and solvent for solution for injection

recombinant human coagulation factor VIII (octocog alfa)

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Kovaltry 3000 IU contains (3000 IU / 5 mL) = 600 IU octocog alfa per mL after reconstitution.

3. LIST OF EXCIPIENTS

Sucrose, histidine, glycine, sodium chloride, calcium chloride dihydrate, polysorbate 80, acetic acid glacial and water for injections.

4. PHARMACEUTICAL FORM AND CONTENTS

powder and solvent for solution for injection

Multipack with 30 single packs, each containing:

1 vial with powder, 1 pre-filled syringe with water for injections, 1 vial adapter and 1 venipuncture set.

5. METHOD AND ROUTE(S) OF ADMINISTRATION

For intravenous use. Single dose administration only.
Read the package leaflet before use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP
EXP (End of the 12 month period, if stored up to 25 °C): .....
Do not use after this date.

May be stored at temperatures up to 25 °C for up to 12 months within the expiry date indicated on the label. Note the new expiry date on the carton.
After reconstitution, the product must be used within 3 hours. **Do not refrigerate after reconstitution.**

9. SPECIAL STORAGE CONDITIONS

Store in a refrigerator.
Do not freeze.
Keep the vial and the pre-filled syringe in the outer carton in order to protect from light.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

Any unused solution must be discarded.

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Bayer AG
51368 Leverkusen
Germany

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/15/1076/024 – 30 x (Kovaltry 3000 IU - solvent (5 mL); pre-filled syringe (5 mL))

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Kovaltry 3000

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC
SN
NN

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

INNER CARTON OF A MULTIPACK (WITHOUT BLUE BOX)

1. NAME OF THE MEDICINAL PRODUCT

Kovaltry 3000 IU powder and solvent for solution for injection

recombinant human coagulation factor VIII (octocog alfa)

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Kovaltry 3000 IU contains (3000 IU / 5 mL) = 600 IU octocog alfa per mL after reconstitution.

3. LIST OF EXCIPIENTS

Sucrose, histidine, glycine, sodium chloride, calcium chloride dihydrate, polysorbate 80, acetic acid glacial and water for injections.

4. PHARMACEUTICAL FORM AND CONTENTS

powder and solvent for solution for injection

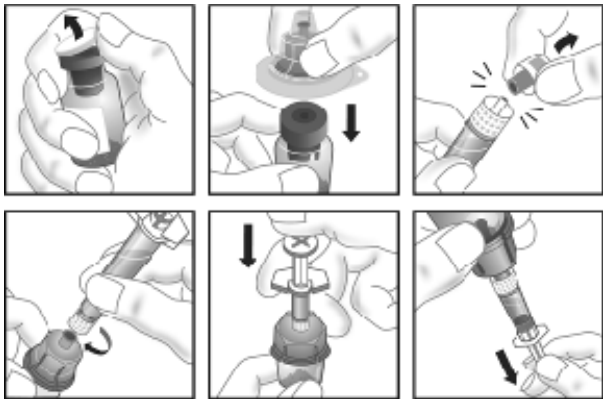
Component of a multipack, can't be sold separately.

1 vial with powder, 1 pre-filled syringe with water for injections, 1 vial adapter and 1 venipuncture set.

5. METHOD AND ROUTE(S) OF ADMINISTRATION

For intravenous use. Single dose administration only.
Read the package leaflet before use.

For reconstitution read package leaflet before use.



6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP
EXP (End of the 12 month period, if stored up to 25 °C): .....
Do not use after this date.

May be stored at temperatures up to 25 °C for up to 12 months within the expiry date indicated on the label. Note the new expiry date on the carton.
After reconstitution, the product must be used within 3 hours. **Do not refrigerate after reconstitution.**

9. SPECIAL STORAGE CONDITIONS

Store in a refrigerator. Do not freeze.

Keep the vial and the pre-filled syringe in the outer carton in order to protect from light.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

Any unused solution must be discarded.

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Bayer AG
51368 Leverkusen
Germany

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/15/1076/024 – 30 x (Kovaltry 3000 IU - solvent (5 mL); pre-filled syringe (5 mL))

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Kovaltry 3000

17. UNIQUE IDENTIFIER – 2D BARCODE

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

VIAL WITH POWDER FOR SOLUTION FOR INJECTION

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION

Kovaltry 3000 IU powder for solution for injection

recombinant human coagulation factor VIII (octocog alfa)
Intravenous use.

2. METHOD OF ADMINISTRATION

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

3000 IU (octocog alfa) (600 IU/mL after reconstitution).

6. OTHER

Bayer-Logo

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

PRE-FILLED SYRINGE WITH WATER FOR INJECTIONS

1. NAME OF THE MEDICINAL PRODUCT AND IF NECESSARY ROUTE(S) OF ADMINISTRATION

water for injections

2. METHOD OF ADMINISTRATION

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

2.5 mL [for reconstitution of strengths 250/500/1000 IU]

6. OTHER

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

PRE-FILLED SYRINGE WITH WATER FOR INJECTIONS

1. NAME OF THE MEDICINAL PRODUCT AND IF NECESSARY ROUTE(S) OF ADMINISTRATION

water for injections

2. METHOD OF ADMINISTRATION

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

5 mL [for reconstitution of strengths 2000/3000 IU]

6. OTHER

B. PACKAGE LEAFLET

Package Leaflet: Information for the user

Kovaltry 250 IU powder and solvent for solution for injection
Kovaltry 500 IU powder and solvent for solution for injection
Kovaltry 1000 IU powder and solvent for solution for injection
Kovaltry 2000 IU powder and solvent for solution for injection
Kovaltry 3000 IU powder and solvent for solution for injection
recombinant human coagulation factor VIII (octocog alfa)

▼This medicine is subject to additional monitoring. This will allow quick identification of new safety information. You can help by reporting any side effects you may get. See the end of section 4 for how to report side effects.

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 any further questions, ask your doctor or pharmacist.
- 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 or pharmacist. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet

1. What Kovaltry is and what it is used for

Kovaltry contains the active substance human recombinant coagulation factor VIII, also called octocog alfa. Kovaltry is prepared by recombinant technology without addition of any human- or animal derived components in the manufacturing process. Factor VIII is a protein naturally found in the blood that helps to clot it.

Kovaltry is used to **treat and prevent bleeding** in adults, adolescents and children of all ages with haemophilia A (hereditary factor VIII deficiency).

2. What you need to know before you use Kovaltry

Do not use Kovaltry if you are
- allergic to octocog alfa or to any of the other ingredients of this medicine (listed in section 6 and end of section 2).
- allergic to mouse or hamster proteins.

Warnings and precautions
Talk to your doctor or pharmacist if you have:
- tightness in the chest, dizziness (including when you get up from sitting or lying down), itchy nettle-rash, wheezing, feeling sick or faint. These may be signs of a rare severe sudden allergic

reaction to Kovaltry. **Stop administering the product** immediately and seek medical advice if this occurs.

- bleeding that is not being controlled with your usual dose of Kovaltry. The formation of inhibitors (antibodies) is a known complication that can occur during treatment with all Factor VIII medicines. These inhibitors, especially at high levels, stop the treatment working properly and you or your child will be monitored carefully for the development of these inhibitors. If your or your child's bleeding is not being controlled with Kovaltry, tell your doctor immediately.
- previously developed factor VIII inhibitors to a different product. If you switch factor VIII products, you may be at risk of your inhibitor coming back.
- a heart disease or are at risk of heart disease.
- to use a central venous access device for the administration of Kovaltry. You may be at risk of device related complications where the catheter is inserted including:
    - local infections
    - bacteria in the blood
    - a blood clot in the blood vessel.

Children and adolescents
The listed warnings and precautions apply to patients of all ages, adults and children.

Other medicines and Kovaltry
Tell your doctor or pharmacist if you are using, have recently used or might use 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 for advice before using this medicine.

Kovaltry is not likely to affect the fertility in male or female patients, as the active substance is naturally occurring in the body.

Driving and using machines
If you experience dizziness or any other symptoms affecting your ability to concentrate and react, do not drive or use machines until the reaction subsides.

Kovaltry contains sodium
This medicine contains less than 1 mmol (23 mg) sodium per dose, and is therefore considered essentially 'sodium-free'.

3. How to use Kovaltry

Treatment with Kovaltry will be started by a doctor who is experienced in the care of patients with haemophilia A. Always use this medicine exactly as described in this leaflet and as your doctor or pharmacist has told you. Check with your doctor or pharmacist if you are not sure.
The number of factor VIII units is expressed in International Units (IU).

Treatment of bleeding
To treat a bleed, your doctor will calculate and adjust your dose and how often it should be given, depending on factors such as:

- your weight
- the severity of your haemophilia A
- where the bleed is and how serious it is
- whether you have inhibitors and how high their level is
- the factor VIII level that is needed.

Prevention of bleeding
If you are using Kovaltry to prevent bleeding, your doctor will calculate the dose for you. This will usually be in the range of 20 to 40 IU of octocog alfa per kg of body weight, injected two or three times per week. However, in some cases, especially for younger patients, shorter dose intervals or higher doses may be necessary.

Laboratory tests
Laboratory tests at suitable intervals help to ensure you always have adequate factor VIII levels. For major surgery in particular, your blood clotting must be closely monitored.

Use in children and adolescents
Kovaltry can be used in children of all ages. In children below the age of 12 higher doses or more frequent injections than in adults may be needed.

Patients with inhibitors
If you have been told by your doctor that you have developed factor VIII inhibitors you may need to use a larger dose of Kovaltry to control bleeding. If this dose does not control your bleeding your doctor may consider giving you another product.
Speak to your doctor if you would like further information on this.
Do not increase the dose of Kovaltry to control your bleeding without checking with your doctor.

Duration of treatment
Usually, Kovaltry treatment for haemophilia is needed life-long.

How Kovaltry is given
Kovaltry is injected into a vein over 2 to 5 minutes depending on the total volume and your comfort level and should be used within 3 hours after reconstitution.

How Kovaltry is prepared for administration
Use only the components (vial adapter, pre filled syringe containing solvent and venipuncture set) provided with each package of this medicine. Please contact your doctor if these components cannot be used. Do not use if any component of the package is opened or damaged.

The reconstituted product **must be filtered by using the vial adapter** before administration to remove any possible particles in the solution.

Do not use the venipuncture set provided for drawing blood because it contains an in-line filter.

This medicine must **not** be mixed with other infusion solutions. Do not use solutions containing visible particles or that are cloudy. Follow the instructions for use given by your doctor **and provided at the end of this leaflet.**

If you use more Kovaltry than you should
Tell your doctor if this occurs. No cases of overdose have been reported.

If you forget to use Kovaltry
Administer your next dose immediately and continue at regular intervals as advised by your doctor.
Do not use a double dose to make up for a forgotten dose**.**

If you stop using Kovaltry
Do not stop using Kovaltry without checking with your doctor.

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

4. Possible side effects

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

The most **serious** side effects are **allergic reactions** or severe allergic reaction.**Stop injecting Kovaltry immediately and speak to your doctor at once if such reactions occur.** The following symptoms **could** be an early warning of these reactions:

- chest tightness/general feeling of being unwell
- dizziness
- a reduction in blood pressure, which may make you feel faint upon standing)
- feeling sick (nausea)

For children not previously treated with factor VIII medicines, inhibitor antibodies (see section 2) may form very commonly (more than 1 in 10 patients). For patients who have received previous treatment with factor VIII (more than 150 days of treatment) inhibitor antibodies (see section 2) may form uncommonly (less than 1 in 100 patients). If this happens your medicine may stop working properly and you may experience persistent bleeding. If this happens, please contact your doctor immediately.

Other possible side effects:

Common (may affect up to 1 in 10 users):

- lymph nodes enlarged (swelling under the skin of the neck, armpit or groin)
- heart palpitations (feeling your heart beating hard, rapidly, or irregularly)
- rapid heartbeat
- stomach pain or discomfort
- indigestion
- fever
- chest pain or discomfort
- local reactions where you injected the medicine (e.g. bleeding under the skin, intense itching, swelling, burning sensation, temporary redness)
- headache
- dizziness
- trouble falling asleep
- rash/itchy rash

Uncommon (may affect up to 1 in 100 users):

- allergic reactions including severe sudden allergic reaction
- dysgeusia (strange taste)
- urticaria (itchy rash)
- flushing (redness of the face)

Reporting of side effects
If you get any side effects, talk to your doctor. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via the national reporting system listed in Appendix V. By reporting side effects, you can help provide more information on the safety of this medicine.

5. How to store Kovaltry

Keep this medicine out of the sight and reach of children.

Do not use this medicine after the expiry date which is stated on labels and cartons. The expiry date refers to the last day of that month.

Store in a refrigerator (2 °C – 8 °C). Do not freeze.

Keep the medicine in original package in order to protect from light.

This medicine may be stored at room temperature (up to 25 °C) for up to 12 months when you keep it in its outer carton. If you store it at room temperature it expires after 12 months or at the expiry date if this is earlier.
The new expiry date must be noted on the outer carton when the medicine is removed from the refrigerator.

Do not refrigerate the solution after reconstitution. The reconstituted solution must be used within 3 hours. This product is for single use only. Any unused solution must be discarded.

Do not use this medicine if you notice any particles in the solution or if the solution is cloudy.

Do not throw away any medicines via wastewater or household waste. Ask your pharmacist how to throw away medicines you no longer use. These measures will help protect the environment.

6. Contents of the pack and other information

What Kovaltry contains

The **active** substance is human coagulation factor VIII (octocog alfa). Each vial of Kovaltry contains nominally 250, 500, 1000, 2000 or 3000 IU octocog alfa.
The **other** ingredients are sucrose, histidine, glycine, sodium chloride, calcium chloride dihydrate, polysorbate 80, acetic acid glacial and water for injections.

What Kovaltry looks like and contents of the pack

Kovaltry is provided as a powder and solvent for solution for injection. The powder is dry and white to slightly yellow . The solvent is a clear liquid.

Each single pack of Kovaltry contains
- a glass vial of powder
- a pre filled syringe
- a separate plunger rod
- a vial adapter
- a venipuncture set (for injection into a vein).

Kovaltry is available in pack sizes of:
– 1 single pack
– 1 multipack with 30 single packs
Not all pack sizes may be marketed.

Marketing Authorisation Holder
Bayer AG
51368 Leverkusen
Germany

Manufacturer
Bayer AG
Kaiser-Wilhelm-Allee
51368 Leverkusen
Germany

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

België/Belgique/Belgien
Bayer SA-NV
Tél/Tel: +32-(0)2-535 63 11
България
Байер България ЕООД
Тел.: +359-(0)2-424 72 80
Česká republika
Bayer s.r.o.
Tel: +420 266 101 111
Danmark
Bayer A/S
Tlf: +45 45 23 50 00
Deutschland
Bayer Vital GmbH
Tel: +49 (0)214-30 513 48
Eesti
Bayer OÜ
Tel: +372 655 8565
Ελλάδα
Bayer Ελλάς ABEE
Τηλ: +30-210-61 87 500
España
Bayer Hispania S.L.
Tel: +34-93-495 65 00
France
Bayer HealthCare
Tél (N° vert): +33-(0)800 87 54 54
Hrvatska
Bayer d.o.o.
Tel: +385-(0)1-6599 900
Ireland
Bayer Limited
Tel: +353 1 2999313
Ísland
Icepharma hf.
Sími: +354 540 8000
Italia
Bayer S.p.A.
Tel: +39 02 397 81
Κύπρος
NOVAGEM Limited
Τηλ: +357 22 48 38 58
Latvija
SIA Bayer
Tel: +371 67 84 55 63
Lietuva
UAB Bayer
Tel. +37 05 23 36 868
Luxembourg/Luxemburg
Bayer SA-NV
Tél/Tel: +32-(0)2-535 63 11
Magyarország
Bayer Hungária KFT
Tel:+36 14 87-41 00
Malta
Alfred Gera and Sons Ltd.
Tel: +35 621 44 62 05
Nederland
Bayer B.V.
Tel: +31-(0)297-28 06 66
Norge
Bayer AS
Tlf: +47 23 13 05 00
Österreich
Bayer Austria Ges.m.b.H.
Tel: +43-(0)1-711 46-0
Polska
Bayer Sp. z o.o.
Tel: +48 22 572 35 00
Portugal
Bayer Portugal, Lda.
Tel: +351 21 416 42 00
România
SC Bayer SRL
Tel: +40 21 529 59 00
Slovenija
Bayer d. o. o.
Tel: +386 (0)1 58 14 400
Slovenská republika
Bayer spol. s r.o.
Tel. +421 2 59 21 31 11
Suomi/Finland
Bayer Oy
Puh/Tel: +358- 20 785 21
Sverige
Bayer AB
Tel: +46 (0) 8 580 223 00
United Kingdom
Bayer plc
Tel: +44-(0)118 206 3000

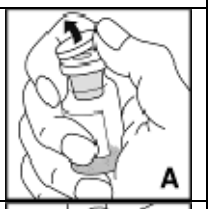
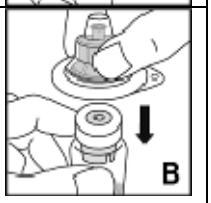
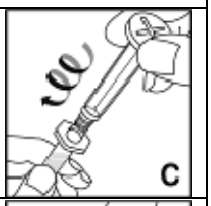
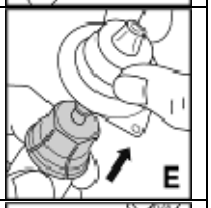
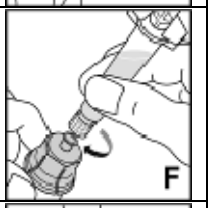
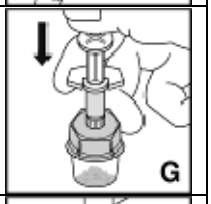
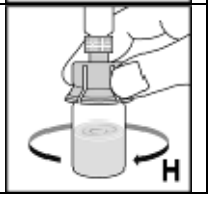
This leaflet was last revised in {**MM/YYYY**}

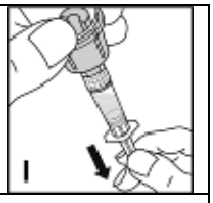
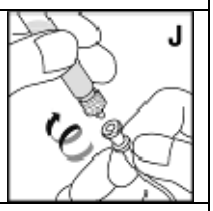
Detailed information on this medicine is available on the website of the European Medicines Agency http://www.ema.europa.eu

---

Detailed instructions for reconstitution and administration of Kovaltry

You will need alcohol swabs, gauze pads, plasters and tourniquet. These items are not included in the Kovaltry package.

1.	Wash your hands thoroughly using soap and warm water.	
2.	Hold an unopened vial and also a syringe in your hands to warm it to a comfortable temperature (do not exceed 37 °C).	
3.	Remove the protective cap from the vial **(A).**Wipe the rubber stopper on the vial with an alcohol swab and allow the stopper to air dry before use.	
4.	Place **the powder vial** on a firm, non slip surface. Peel off the paper cover on the plastic housing of the vial adapter. **Do not remove** the adapter from the plastic housing. Holding the adapter housing, place over the product vial and firmly press down **(B)**. The adapter will snap over the vial cap. **Do not remove** the adapter housing at this point.	
5.	Hold the pre filled syringe of solvent upright. Grasp the plunger rod as per the diagram and attach the rod by turning it firmly clockwise into the threaded stopper **(C)**.	
6.	Holding the syringe by the barrel, snap the syringe cap off the tip **(D)**. Do not touch the syringe tip with your hand or any surface. Set the syringe aside for further use.	
7.	Now remove and discard the adapter housing **(E)**.	
8.	Attach the pre filled syringe to the threaded vial adapter by turning clockwise **(F).**	
9.	Inject the solvent by slowly pushing down on the plunger rod **(G)**.	
10.	Swirl vial gently until all material is dissolved **(H)**. Do not shake vial. Be sure that the powder is completely dissolved. Look to check there are no particles or discoloration before you use the solution. Do not use solutions containing visible particles or that are cloudy.	

11.	Hold the vial on end above the vial adapter and syringe **(I)**. Fill the syringe by drawing the plunger out slowly and smoothly. Ensure that the full content of the vial is drawn into the syringe. Hold the syringe upright and push the plunger until no air is left in the syringe.	
12.	Apply a tourniquet to your arm.	
13.	Determine the point of injection and clean the skin with an alcohol swab.	
14.	Puncture the vein and secure the venipuncture set with a plaster.	
15.	Holding the vial adapter in place, remove the syringe from the vial adapter (the adapter should remain attached to the vial). Attach the syringe to the venipuncture set (**J**).Ensure that no blood enters the syringe.	
16.	Remove tourniquet.	
17.	Inject the solution into a vein over 2 to 5 minutes, keeping an eye on the position of the needle. The speed of injection should be based on your comfort, but should not be faster than 2 mL per minute.	
18.	If a further dose is needed, use a new syringe with product reconstituted as described above.	
19.	If no further dose is required, remove the venipuncture set and syringe. Hold a pad firmly over the injection site on your outstretched arm for about 2 minutes. Finally, apply a small pressure dressing to the injection site and consider if a plaster is necessary.	
20.	It is recommended that every time you use Kovaltry, you note down the name and batch number of the product.	
21.	Do not throw away any medicines via wastewater or household waste. Ask your pharmacist or physician how to throw away medicines you no longer use. These measures will help protect the environment	