SELECT THE REQUIRED INFORMATION

PROFESSIONAL INFORMATION

PATIENT INFORMATION LEAFLET

SCHEDULING STATUS: S4

1 NAME OF THE MEDICINE

KOVALTRY® 250 IU, LYOPHILISED POWDER FOR INJECTION
KOVALTRY® 500 IU, LYOPHILISED POWDER FOR INJECTION
KOVALTRY® 1000 IU, LYOPHILISED POWDER FOR INJECTION
DILUENT FOR KOVALTRY®: Sterile Water for Injection (SWI)

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

KOVALTRY 250:

Each vial of lyophilised powder contains 250 IU recombinant antihaemophilic Factor VIII (octocog alfa)

KOVALTRY 500:

Each vial of lyophilised powder contains 500 IU recombinant antihaemophilic Factor VIII (octocog alfa)

KOVALTRY 1000:

Each vial of lyophilised powder contains 1000 IU recombinant antihaemophilic Factor VIII (octocog alfa)

Each vial is produced by recombinant DNA technology. It is a sterile, stable, purified, nonpyrogenic, 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.

3 PHARMACEUTICAL FORM

White to slightly yellow solid powder for reconstitution (before reconstitution).

Solvent: Water for injection

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Treatment and prophylaxis of bleeding in haemophilia A (congenital factor VIII deficiency) for all age groups.

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

4.2 Posology and method of administration

Posology

KOVALTRY is administered directly into the blood stream by IV injection.
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 KOVALTY 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 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.

On demand treatment
The required dose is determined using the following formula:
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 usual single dose is 10 to 30 IU/kg body weight. Higher dosages are recommended for life threatening or major haemorrhages.
For subjects with a recovery below 2 (which may occur e.g., in small children), higher dosages may be needed.
Guidance for dosing in bleeding episodes for children and adults:

Haemorrhagic Event/Type of surgery:	**FVIII Level required (IU/dL):**	**Frequency of doses (Hours)/Duration of Therapy (Days)**
Minor haemorrhage: Early haemarthrosis, minor muscle, oral bleeds.	20 to 40 %	Repeat every 12 to 24 hours. At least one day, until bleeding episode as indicated by pain is resolved or healing is achieved.
Moderate to major haemorrhage: More extensive haemarthrosis, muscle bleeding or hematoma.	30 to 60 %	Repeat infusion every 12 to 24 hours; 3 to 4 days or more until pain and acute disability are resolved.
Minor Surgery (including tooth extraction)		Every 24 hours, at least 1 day, until healing is achieved.
Life-threatening haemorrhage:	60 to 100 %	Repeat infusion every 8 to 24 hours until threat is resolved.
Major Surgery	80 to 100 % (pre- and post-operative)	Repeat dose every 8-24 hours until adequate wound healing, then therapy for at least another 7 days to maintain FVIII activity of 30-60% (IU/dL).

Prophylaxis treatment for adolescent and adult patients

For long term prophylaxis against bleeding in patients with severe haemophilia A, the recommended doses are 20 to 40 IU of factor VIII per kg body weight two or three times per week. In some cases, especially in younger patients, shorter dosage intervals or higher doses may be used.

Rate of administration:
The rate of administration should be adapted to the response of each individual patient.

Special populations
Paediatric patients
KOVALTRY is appropriate for use in paediatric patients. Safety and efficacy studies have been performed in children 0 to 12 years. The recommended prophylaxis doses are 20 to 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 patients
Clinical studies did not include patients aged 65 and over to be able to determine whether they respond differently from younger patients. However, clinical experience with other FVIII products has not identified differences between the elderly and younger patients. Dose selection for an elderly patient should be individualised.

Patients with hepatic impairment
Dose adjustment for patients with hepatic impairment has not been studied in clinical trials.

Patients with renal impairment
Dose adjustment for patients with renal impairment has not been studied in clinical trials.

Gender
No female data are available, as haemophilia rarely occurs in women, females were not included in clinical trials.

4.3 Contraindications

- Hypersensitivity to the active substance or to any of the excipients.
- Known allergic reactions to mouse or hamster protein.

4.4 Special warnings and precautions for use

Hypersensitivity

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, 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 neutralizing 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. Inhibitors may develop after the first 100 exposure days. All patients treated with coagulation factor VIII products should be carefully monitored for the development of inhibitors by appropriate clinical observations and laboratory tests.

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

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 FVIII.

Contains sucrose.

Patients with rare hereditary conditions such as fructose intolerance, glucose-galactose mal-absorption or sucrase-isomaltase insufficiency should not take KOVALTRY.

4.5 Interaction with other medicines and other forms of interaction

No interactions of human coagulation factor VIII products with other medicines have been reported.

4.6 Fertility, pregnancy and lactation

Safety in pregnancy and lactation has not been established.

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

4.7 Effects on ability to drive and 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

A total of 236 (193 PTPs, 43 PUPs/MTPs) patients constituted the pooled safety population in the three phase III studies in previously treated patients (PTPs), previously untreated patients (PUPs) and minimal treated patients (MTPs); LEOPOLD I, LEOPOLD II, LEOPOLD Kids studies). The median time on clinical trial for pooled safety population was 558 days (range 14 to 2436 days) with a median of 183 exposure days (EDs) (range 1 to 1230 EDs). Majority of patients (n= 201 of 236; 85.2 %) accumulated ≥ 100 EDs. Total number of exposure days for all treatments (prophylaxis, on-demand, perioperative management, pharmacokinetic (PK) studies and Immune Tolerance Induction (ITI) was 65029 EDs, andof which 59585 EDs were for prophylaxis treatment.
Subjects who received KOVALTRY for perioperative management (n=5) with treatment period of 2 to 3 weeks and those who received single doses of KOVALTRY for PK studies (n=6) were excluded from the pooled safety analysis.
The most frequently reported adverse reactions in the pooled population were pyrexia (9.3 %), headache (8.5 %) and rash (5.5 %). The most frequently reported adverse reaction in PUPs/MTPs was FVIII inhibition (see Description of selected Adverse Reactions- Immunogenicity).

Adverse reactions based on experiences from clinical trials for KOVALTRY are presented in the table below, sorted by System organ class (SOC). 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), rare (≥1/10,000 to <1/1,000), very rare (<1/10,000).

Standard System Organ Class	Very Common (≥1/10)	Common (≥1/100 to <1/10)	Uncommon (≥1/1,000 to <1/100)
Blood and Lymphatic System Disorders			Lymphadenopathy
Cardiac Disorders			Palpitation, sinus tachycardia
Gastrointestinal Disorders		Abdominal pain, abdominal discomfort, dyspepsia	
General Disorders and Administration Site Conditions		Pyrexia, injection site reactions *	Chest discomfort
Immune System Disorders	FVIII Inhibitor PUPs/MTPs [a]		Hypersensitivity FVIII Inhibitor PTPs[b]
Nervous System Disorders		Headache, dizziness	Dysgeusia
Psychiatric Disorders		Insomnia	
Skin and Subcutaneous Tissue Disorders		Pruritus, rash**, Urticaria	Dermatitis Allergic
Vascular Disorders			Flushing

*includes injection site extravasation and hematoma, infusion site pain, pruritus, and swelling

** includes rash, rash erythematous, rash pruritic, rash vesicular

[a] FVIII Inhibitor in PUPs/MTPs consists of Preferred Terms Anti-factor VIII antibody positive (N=22) and Factor VIII (N=1); inhibitor analysis based on 42/43 PUP/MTP patients in LEOPOLD Kids Part B, one patient was unevaluable for inhibitor analysis and thus excluded. (see 4.8.3 Description of selected Adverse Reactions- Immunogenicity).
[b] FVIII inhibitor in PTPs based on N=193 patients of the pooled three phase III studies in previously treated patients (PTPs); LEOPOLD I, LEOPOLD II and LEOPOLD Kids Part A.

Description of selected adverse reactions

Immunogenicity
The immunogenicity of KOVALTRY was evaluated in previously treated patients (PTPs and PUPs/MTPs.

During clinical trials with KOVALTRY in approximately 200 pediatric and adult patients diagnosed with severe hemophilia A (FVIII < 1%) with previous exposure to factor VIII concentrates ≥ 50 ED, one case of transient low titer inhibitor (peak titer: 1.0 BU/ml) occurred in a 13 year old PTP after 549 EDs concurrent with an acute infection and positive IgG anticardiolipin antibodies. The Factor VIII recovery was normal (2.7 IU/dL per IU/kg).
In the clinical trial that enrolled previously untreated (PUPs) and minimally treated patients (MTPs) (defined as having had up to ≤ 3 EDs to a factor VIII product at the time of enrollment), Factor VIII inhibitors were detected in 23 of 42 patients with a median (range) of 9 (4 – 42) EDs at the time of the first positive inhibitor test. Of these, 6 patients had low titer inhibitors (≤ 5.0 BU) and 17 patients had high titer inhibitors (> 5.0 BU). In patients who developed high titer inhibitors, high-risk mutations for inhibitor development were identified in 12 of 14 patients with available FVIII mutation data.

Additional information on special populations

Paediatric patients

In clinical studies with 51 paediatric PTPs, the frequency, type and severity of adverse reactions in children are similar as in adults.

In the clinical study of 43 pediatric PUPs/MTPs, the most frequently reported adverse reaction was Factor VIII inhibitors.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Healthcare providers are asked to report any suspected adverse reactions to SAHPRA via the "**6.04 Adverse Drug Reaction Reporting Form**", found online under SAHPRA's publications: https://www.sahpra.org.za/Publications/Index/8

4.9 Overdose

No information exists on symptoms of Factor VIII overdosage. Treatment is symptomatic and supportive.

5 PHARMACOLOGICAL PROPERTIES

Pharmacotherapeutic group: antihemorrhagics, blood coagulation factor VIII
ATC Code: B02BD02

5.1 Pharmacodynamic properties

Patients with haemophilia are deficient in factor VIII. Octacog alfa (recombinant antihaemophilic factor VIII) replaces that deficit and allows normal blood coagulation to occur. The activated partial thromboplastin time (aPTT) is prolonged in people with haemophilia.

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

Clinical efficacy and safety

Clinical studies

Control and Prevention of Bleeding
Two multi-center, open-label, cross-over, uncontrolled, randomized studies in PTPs, adults and adolescents with severe hemophilia A (<1%) and 1%). One multicenter, open-label, uncontrolled study in pediatric PTPs <12 years of age (Part A) and PUPs/MTPs <6 years of age (Part B) with severe hemophilia A were conducted.
LEOPOLD I (Study 1:): The objective was to demonstrate pharmacokinetics (PK), safety and efficacy of prophylaxis treatment and hemostasis during surgeries. The study duration was 1 year with an optional extension for one further year. Seventy-three (73) subjects previously treated with prophylaxis or on-demand regimen were included (Part A: 26 subjects (PK), Part B: 62 subjects (safety and efficacy) and Part C: 5 subjects only surgery (plus 5 subjects in extension for 12 surgeries). Fifty-five (55) subjects continued in the one-year extension study.

LEOPOLD II (Study 2:): The objective was to demonstrate superiority of prophylaxis over on-demand treatment during a one-year treatment period in 80 subjects previously treated with on-demand treatment. Patients were randomized to be treated with the on-demand or prophylaxis regimen.

LEOPOLD Kids (Study 3:): The objective was to assess safety and, efficacy, pharmacokinetics and perioperative management of hemostasis during surgery in children < previously treated patients (PTPs: ≥50 EDs) ≤12 years of age (Part A) and previously untreated (PUPs) and minimally treated patients (MTPs: ≤3 EDs) < 6 years of age (Part B).

Eighty two (82) subjects (46 subjects from Part A, 36 subjects from Part B continued in the extension study. A total of 247 subjects (204 PTPs and 43 PUPs/MTPs) have been exposed in the trial program, 153 subjects ≥ 12 years and 94 subjects < 12 years. Two-hundred eight (208) subjects (174 PTPs, 34 PUPs/MTPs) were treated for at least 12 months, and 98 of these subjects (78 PTPs, 20 PUPs/MTPs) for at least 24 months.

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 FVIII 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 below provides PK parameters based on the population PK model.

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 to12 months treatment period.

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

Nonclinical studies evaluating KOVALTRY in haemophilia A mouse efficacy models demonstrated restoration of hemostasis. The nonclinical safety program did not identified any concerns for humans based on safety pharmacology, acute toxicity, repeated-dose toxicity and genotoxicity studies.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Powder:

Calcium chloride,

Glycine

Histidine

Polysorbate 80

Sodium chloride

Contains sugar: sucrose

Solvent:

Water for injection: One prefilled syringe of diluent for KOVALTRY contains 2,5 mL or 5 mL Sterile Water for Injection.

6.2 Incompatibilities

- In the absence of compatibility studies, this medicine must not be mixed with other medicines.'
- This medicine must not be mixed with other medicines except those mentioned in section 6.5.

6.3 Shelf life

30 months.

Administer within 3 hours at room temperature after reconstitution.

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 the refrigerator between 2°C to 8°C. Do not freeze.

Product may be stored for up to 12 months at a temperature up to 25°C and up to 6 months at a temperature up to 30°C. Do not use beyond the expiration date indicated on the bottle.

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.

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

Protect from exposure to light and store the lyophilised powder in the carton prior to use.

KEEP OUT OF REACH OF CHILDREN.

6.5 Nature and contents of container

Each package of KOVALTRY contained in a cardboard carton contains:

• one vial with reconstitution cap (Bio-Set System), containing powder (10 mL clear glass type 1 vial with grey halogenobutyl rubber blend stopper plus lacquered aluminium seal with plastic flip-off top reconstitution cap).

• one pre-filled syringe with 2.5 mL (for 250 IU, 500 IU and 1000 IU) solvent (clear glass cylinder type 1 with grey bromobutyl rubber blend stopper).

• syringe plunger rod.

• one venipuncture set.

6.6 Special precautions for disposal of a used medicine or waste materials derived from such medicine and other handling of the product

Clear colourless liquid with no visible particulate matter (after reconstitution with water for injection).

KOVALTRY powder should only be reconstituted with the supplied solvent (2.5 mL water for injections) in the prefilled syringe and the integrated seal and liquid transfer component. 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.

7 HOLDER OF CERTIFICATE OF REGISTRATION

Bayer (Pty) Ltd

Reg. No.: 1968/011192/07

27 Wrench Road

Isando, 1609

8 REGISTRATION NUMBER(S)

KOVALTRY 250: 52/8.1/0266

KOVALTRY 500: 52/8.1/0267

KOVALTRY 1000: 52/8.1/0268

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

11 August 2020

10 DATE OF REVISION OF THE TEXT

01 November 2022

REFERENCES:

References 1	Detering E : 012a Justification Document Update of Section 4.8 Undesirable Effects Kovaltry valid as per 09 Mar 2021
Reference 2	Clinical Study Report LEOPOLD Kids Extension study. Bayer AG. Report number: PH-41325. 2021.
Reference 3	Integrated Summary of safety 2.7.4 Addendum to Summary of Clinical Safety (PH-41325 - 13400 extension)_
Reference 4	Clinical Study Report BAY 81-8973 / 13400 (part B) Addendum 1 PH-41833. 2021
Reference 5	2.7.4 Addendum to the Summary of Clinical Safety Leopold Kids Extension
Reference 6	Afonja O : 013 Justification Document Update of Section 5.1.3: Clinical Studies valid as per 09 Mar 2021