Kogenate® FS (Antihemophilic Factor [Recombinant]) is indicated:  
• for the treatment of classical hemophilia (hemophilia A), in which there is a demonstrated deficiency of activity of the plasma clotting factor, factor VIII (FVIII). Kogenate® FS provides a means of temporarily replacing the missing clotting factor in order to correct or prevent bleeding episodes, or in order to perform emergency or elective surgery in patients with hemophilia.  
• to prevent the occurrence of spontaneous hemorrhagic episodes and to prevent joint damage in children with no pre-existing joint damage, when used as a regular prophylactic treatment  
• to prevent or reduce the frequency of bleeding episodes in adults with hemophilia A, when used as a regular prophylactic treatment  
Kogenate® FS does not contain von Willebrand Factor and therefore, is not indicated for the treatment of von Willebrand disease.

Kovaltry™ (Antihemophilic Factor [Recombinant]) is indicated for use in adults and children with hemophilia A for:  
• Routine prophylactic treatment to prevent or reduce the frequency of bleeding episodes  
• Control and prevention of episodic bleeding  
• Peri-operative management (surgical prophylaxis)  
Kovaltry™ does not contain von Willebrand factor and is not indicated for the treatment of von Willebrand disease.

* Data from separate Product Monographs. Comparative clinical significance unknown. Please refer to the respective Product Monographs for complete information.
**Kogenate® FS**

***Antihemophilic Factor (Recombinant)***

**Product characteristics**

- Kogenate® FS is produced by Baby Hamster Kidney (BHK) cells into which the human factor VIII (FVIII) gene has been introduced.
- The BHK cell culture medium, which is used during manufacturing contains Human Plasma Protein Solution (HPPS) and recombinant insulin, but does not contain any proteins derived from animal sources.
- No human or animal proteins, such as albumin, are added during the purification and formulation processes of Kogenate® FS.
- Kogenate® FS is a highly purified glycoprotein consisting of multiple peptides including an 80 kDa and various extensions of the 90 kDa subunit.
- Studies to further elucidate the carbohydrate structure of rFVIII, indicated that both pdFVIII and rFVIII contain mainly high mannose type and complex-type sugar chains.

**Viral inactivation**

- The purification process includes an effective solvent/detergent virus inactivation step in addition to the use of the purification methods of ion exchange chromatography, monoclonal antibody immunoaffinity chromatography, along with other chromatographic steps designed to purify recombinant FVIII (rFVIII) and remove contaminating substances.

**Pharmacokinetic parameters** (Half-life at beginning of study)

- 12.2 hours

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**Kovaltry™**

***Antihemophilic Factor (Recombinant)***

**Product characteristics**

- Kovaltry™ is produced by genetically engineered Baby Hamster Kidney (BHK) cells into which the human Factor VIII gene has been introduced.
- Kovaltry™ has the identical FVIII amino acid sequence, the same molecular formula, proteolytic processing and similar post translational modifications (glycosylation and sulfation) as the licensed Kogenate® FS.
- Oligosaccharide characterization of the final product has shown superior glycosylation, better branching, and sialylation capping of terminal galactose residues.
- Kovaltry™ has the same biological activity as Factor VIII derived from human plasma.
- Human- and animal-derived raw materials are not used in the cell culture, purification, and formulation processes.
- The BHK cell line has been modified with the human heat shock protein 70 (HSP70) to enhance proper protein folding and resistance to apoptosis.
- The cell culture process employs a continuous perfusion process and is followed by an automated continuous cell separation process.

**Viral inactivation**

- To achieve a high virological safety level, the manufacturing process incorporates dedicated viral clearance steps which include a detergent virus inactivation step, and a 20-nm filtration step for removal of viruses and potential protein aggregates.
- The purification process includes methods of ion exchange chromatography, monoclonal antibody immunoaffinity chromatography, and other chromatographic steps, designed to purify recombinant Factor VIII and remove process and product-related impurities.

**Pharmacokinetic parameters** (Half-life at beginning of study)

- 13.4 hours
- Geometric mean ratio (95%CI)
  - 1.10 (1.02–1.17)

* Data from separate Product Monographs. Comparative clinical significance unknown. Please refer to the respective Product Monographs for complete information.
† The pharmacokinetic (PK) properties of Kovaltry™ were investigated in one clinical trial with adult/adolescent previously treated patients (PTPs) (12–62 years of age) with severe hemophilia A. At the beginning of the study, PK was evaluated in 26 subjects following injection of 50 IU/kg of Kovaltry™ or Kogenate® FS with at least 3 days washout. After 6–12 months routine prophylactic treatment of Kovaltry™, 19 out of 26 subjects had a second PK evaluation following injection of 50 IU/kg of Kovaltry™. Serial blood samples were collected over 48 hours. Both Kovaltry™ and Kogenate® FS were released using chromogenic assay for this PK evaluation.

Adapted from Kovaltry™ Product Monograph and Kogenate® FS Product Monograph.
**Kogenate™ FS®**

**Indications**

Kogenate™ FS (Antihemophilic Factor [Recombinant]) is indicated for the treatment of classical hemophilia (hemophilia A), in which there is a demonstrated deficiency of activity of the plasma clotting factor, factor VIII (FVIII). Kogenate™ FS provides a means of temporarily replacing the missing clotting factor in order to correct or prevent bleeding episodes, or in order to perform emergency or elective surgery in persons with hemophilia.

When used as a regular prophylactic treatment, Kogenate™ FS is indicated:

- to prevent the occurrence of spontaneous hemorrhagic episodes and to prevent joint damage in children with no pre-existing joint damage
- to prevent or reduce the frequency of bleeding episodes in adults with hemophilia A

Kogenate™ FS does not contain von Willebrand Factor and therefore, is not indicated for the treatment of von Willebrand disease.

**Dosage**

**Dosage required for hemostasis**

- The in vivo percent increase in FVIII level can be estimated by multiplying the dose of rFVIII-FS per kilogram of body weight (IU/kg) by 2%
- Dosage necessary to achieve hemostasis depends upon type and severity of bleeding episode, according to the following general guidelines:
  - **Minor hemorrhage:** 20–40% therapeutically necessary plasma level of FVIII activity; 10–20 IU/kg; repeat if further bleeding
  - **Moderate to major hemorrhage** and **minor surgical procedures:** 30–40% therapeutically necessary plasma level of FVIII activity; 15–30 IU/kg; repeat one dose at 12–24 hrs if needed
  - **Major to life-threatening hemorrhage,** **fractures and head trauma:** 80–100% therapeutically necessary plasma level of FVIII activity; 40–50 IU/kg initial dose; repeat dose 20–25 IU/kg every 8–12 hrs
  - **Major surgical procedures:** 100% therapeutically necessary plasma level of FVIII activity
    - **By bolus infusions:** preoperative dose 50 IU/kg until 100% activity; repeat as needed after 6–12 hrs initially and for 10–14 days until healing is complete
    - **By continuous infusion:** initial bolus infusion pre-surgery, immediately followed by continuous infusion (in IU/h/kg), adjusting according to patient’s daily clearance and desired FVIII levels for ≥7 days

**Routine prophylaxis**

- Adults: 25 IU/kg of body weight 3 x per week
- Children: 25 IU/kg of body weight every other day

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**Kovaltry™**

**Indications**

Kovaltry™ (Antihemophilic Factor [Recombinant]) is indicated for use in adults and children with hemophilia A for:

- Routine prophylactic treatment to prevent or reduce the frequency of bleeding episodes
- Control and prevention of episodic bleeding
- Peri-operative management (surgical prophylaxis)

Kovaltry™ does not contain von Willebrand factor and is not indicated for the treatment of von Willebrand disease.

**Dosage**

**On-demand treatment**

- The in vivo percent increase in FVIII level can be estimated by multiplying the dose of rFVIII per kilogram of body weight (IU/kg) by 2%
- Usual single dose: 10–30 IU/kg of body weight
- Higher dosages are recommended for life-threatening or major hemorrhages
- Under certain circumstances larger amounts than those calculated may be required, especially for the initial dose
- Dosage necessary to achieve hemostasis depends upon type and severity of bleeding episode, according to the following general guidelines:
  - **Minor hemorrhage:** 30–60% FVIII level required (IU/dL); repeat every 12–24 hrs for ≥3–4 days until bleeding resolved
  - **Moderate to major hemorrhage:** 40–60% FVIII level required (IU/dL); repeat every 12–24 hrs for ≥3–4 days until bleeding resolved
  - **Life-threatening hemorrhage:** 60–100 FVIII level required (IU/dL); repeat every 8–24 hrs until threat resolved
  - **Minor surgery:** 30–60 FVIII level required (IU/dL); repeat every 24 hrs for ≥1 day until hemostasis achieved
  - **Major surgery:** 60–100 (pre- and post-operative) FVIII level required (IU/dL); repeat every 8–24 hrs until adequate wound healing, then continue for ≥7 days to maintain FVIII activity of 30–60% (IU/dL)

**Routine prophylaxis**

- Adults and adolescents (>12 years of age): 20–40 IU/kg of body weight 2–3 x per week
- Children ≤12 years old: 20–50 IU/kg of body weight 2–3 x per week or every other day according to individual requirements

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* Data from separate Product Monographs. Comparative clinical significance unknown. Please refer to the respective Product Monographs for complete information.

† Minor hemorrhage includes superficial, early hemorrhages, hemorrhages into joints.

‡ Moderate to major hemorrhage includes hemorrhages into muscle, hemorrhages into the oral cavity, diffuse hemorrhages, known trauma.

¶ Major to life-threatening hemorrhage includes intracranial, intra-abdominal or intra thoracic hemorrhages, gastrointestinal bleeding, central nervous system bleeding, bleeding in the retropharyngeal or retro peritoneal spaces or hip dislocation.

§ Minor surgery includes tooth extraction.

Adapted from Kovaltry™ Product Monograph and Kogenate™ FS Product Monograph.
**Kogenate® FS™**
Antihemophilic Factor (Recombinant)

### Dosage form, strength
- Lyophilized powder for injection
- 250, 500, 1,000, 2,000, 3,000 IU/vial

### Administration
- **Kogenate® FS (Antihemophilic Factor [Recombinant]) with vial adapter is a needle-less system that prevents needlestick injuries during reconstitution**
- **Rate of administration**
  - Data from clinical trials, including patients between 0–68 years old, shows that the entire dose is administered in a median of 5 minutes. The rate of administration, however, should be adapted to the response of each patient.
  - Kogenate® FS can be infused by continuous infusion. The infusion rate should be calculated based on the clearance and the desired FVIII level.
  - For calculation of mL/h, multiply infusion rate in IU/h/kg by kg bw/concentration of solution (IU/mL)
  - Higher infusion rates may be required in conditions with accelerated clearance during major bleeds and extensive tissue damage during surgical interventions
  - Subsequent infusion rates should be calculated based on the actual FVIII levels and recalculated clearance for each day post surgery based on the equation: clearance = infusion rate/actual FVIII level

### Storage and stability
- **Kogenate® FS (Antihemophilic Factor [Recombinant]) should be stored under refrigeration (2°C–8°C)**
- Do not use beyond the expiration date indicated on the bottle
- Storage of lyophilized powder at room temperature up to 25°C for 12 months, such as in home storage situations, may be done
- If the product is stored outside the refrigerator, please add the date removed from refrigeration and note a new expiry date on the carton and vial
- The new expiry date should be 12 months from the date product is removed from the refrigerator, or the previously stamped expiry date, whichever is shorter
- Once product is removed from refrigeration, it cannot be returned to the refrigerator
- Freezing must be avoided
- Protect from extreme exposure to light and store the lyophilized powder in the carton prior to use
- After reconstitution, the product should be used immediately (within 3 hours) for direct syringe injection
- For continuous infusion, stability has been demonstrated for 24 hours at 30°C in polyvinyl chloride (PVC) bags

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**Kovaltry™**
Antihemophilic Factor (Recombinant)

### Dosage form, strength
- Lyophilized powder for injection
- 250, 500, 1,000, 2,000, 3,000 IU/vial

### Administration
- **Kovaltry™ (Antihemophilic Factor [Recombinant]) supplied with Vial Adapter is a self-contained system that prevents needlestick injuries during reconstitution**
- **Rate of administration**
  - Administer Kovaltry™ over several minutes
  - Adapt the rate of administration to the response of each individual patient
- Determine the pulse rate before and during administration of Kovaltry™
- If there is a significant increase in pulse rate, reduce the rate of administration or temporarily halt the infusion allowing the symptoms to disappear promptly

### Storage and stability
- **Kovaltry™ (Antihemophilic Factor [Recombinant]) should be stored under refrigeration (2°C–8°C)**
- Do not use beyond the expiration date indicated on the vial
- Storage of lyophilized powder at room temperature up to 25°C for 12 months, such as in home storage situations, may be done
- If the product is stored outside the refrigerator, please add the date removed from refrigeration and note a new expiry date on the carton and vial
- The new expiry date should be 12 months from the date product is removed from the refrigerator, or the previously stamped expiry date, whichever is shorter
- Once product is removed from refrigeration, it cannot be returned to the refrigerator
- Freezing must be avoided
- Protect from extreme exposure to light and store the lyophilized powder in the carton prior to use
- After reconstitution, the product should be used immediately (within 3 hours)

* Data from separate Product Monographs. Comparative clinical significance unknown. Please refer to the respective Product Monographs for complete information.
KOVANATE<sup>®</sup> FS

**Indications and clinical use**
- Kovanate<sup>®</sup> FS (Antihemophilic Factor [Recombinant]) is indicated:
  - for the treatment of classical hemophilia A, in which there is a demonstrated deficiency of activity of the plasma clotting factor, factor VIII (FVIII). Kovanate<sup>®</sup> FS provides a means of temporarily replacing the missing clotting factor in order to correct or prevent bleeding episodes, or in order to perform emergency or elective surgery in patients with hemophilia.
  - to prevent the occurrence of spontaneous hemorrhagic episodes and to prevent joint damage in children with no pre-existing joint damage, when used as a regular prophylactic treatment.
  - to prevent or reduce the frequency of bleeding episodes in adults with hemophilia A, when used as a regular prophylactic treatment.
- Kovanate<sup>®</sup> FS does not contain von Willebrand factor and therefore, is not indicated for the treatment of von Willebrand disease.
- As with any patient receiving Kovanate<sup>®</sup> FS, dose selection for an elderly patient should be individualized.

**Contraindications**
- Hypersensitivity to this drug or to any ingredient in the formulation or component of the container.
- Known hypersensitivity to mouse or hamster protein.

**Most serious warnings and precautions**
- Development of circulating neutralizing antibodies: The development of circulating neutralizing antibodies to FVIII may occur during the treatment of patients with hemophilia A. Patients should be carefully monitored for development of antibodies.

**Other relevant warnings and precautions**
- Percutaneous puncture with a needle contaminated with blood can transmit infectious viruses including HIV (AIDS) and hepatitis.
- Carcinogenesis and mutagenesis.
- Formation of antibodies to mouse and hamster proteins.
- Pregnant women.
- Nursing women: Kovanate<sup>®</sup> FS should not be used during lactation unless the benefits clearly outweigh any potential risks.
- Monitoring and laboratory tests: dosage requirement for FVIII is variable when an inhibitor is present and the dosage can be determined only by the clinical response.

**For more information**
Please consult the Product Monograph at [http://oms.bayer.ca/oms/online/kovanate-fs-pm-en-vial-adapter.pdf](http://oms.bayer.ca/oms/online/kovanate-fs-pm-en-vial-adapter.pdf) for important information relating to adverse reactions, drug interactions and dosing information which have not been discussed in this piece.

The Product Monograph is also available by calling 1-800-265-7382.

KOVALTRY<sup>™</sup>

**Indications and clinical use**
- Kovaltry™ (Antihemophilic Factor [Recombinant]) is indicated for use in adults and children with hemophilia A for:
  - Routine prophylactic treatment to prevent or reduce the frequency of bleeding episodes.
  - Control and prevention of episodic bleeding.
  - Peri-operative management (surgical prophylaxis).
- Kovaltry™ does not contain von Willebrand factor and is not indicated for the treatment of von Willebrand disease.
- Clinical studies with Kovaltry™ did not include patients aged 65 and over to be able to determine whether they respond differently from younger adults. As with any patient receiving recombinant FVIII (rFVIII), dose selection for an elderly patient should be individualized.

**Contraindications**
- Hypersensitivity to this drug or to any ingredient in the formulation or component of the container.
- Known hypersensitivity to mouse or hamster protein.

**Most serious warnings and precautions**
- Development of circulating neutralizing antibodies: The development of circulating neutralizing antibodies (inhibitors) to Factor VIII (FVIII) may occur during the treatment of patients with hemophilia A. Patients should be carefully monitored for development of inhibitors.

**Other relevant warnings and precautions**
- Percutaneous puncture with a needle contaminated with blood can transmit infectious viruses including HIV (AIDS) and hepatitis.
- Carcinogenesis and mutagenesis.
- Formation of antibodies to mouse and hamster proteins.
- Pregnant women.
- Nursing women: Kovaltry™ should not be used during lactation unless the benefits clearly outweigh any potential risks.
- Monitoring and laboratory tests: dosage requirement for rFVIII is extremely variable when an inhibitor is present and the dosage can be determined only by the clinical response.

**For more information**
Please consult the Product Monograph at [www.bayer.ca/kovaltry-pm-en](http://www.bayer.ca/kovaltry-pm-en) for important information relating to adverse reactions, drug interactions and dosing information, which have not been discussed in this piece.

The Product Monograph is also available by calling 1-800-265-7382.

References: