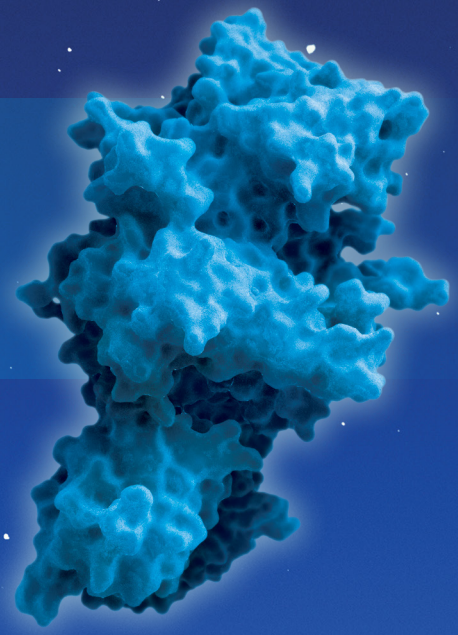
The science of KOVALTRY®



KOVALTRY® is an unmodified, full length rFVIII[1]

- KOVALTRY® has a primary protein structure that has been in use for over 20 years
- Posttranslational modifications of KOVALTRY® are similar to those of endogenous FVIII

INDICATIONS

- KOVALTRY® Antihemophilic Factor (Recombinant) is a recombinant human DNA sequence derived, full length Factor VIII concentrate indicated for use in adults and children with hemophilia A for:
  - On-demand treatment and control of bleeding episodes
  - Perioperative management of bleeding
  - Routine prophylaxis to reduce the frequency of bleeding episodes
- KOVALTRY® is not indicated for the treatment of von Willebrand disease.

SELECTED IMPORTANT SAFETY INFORMATION

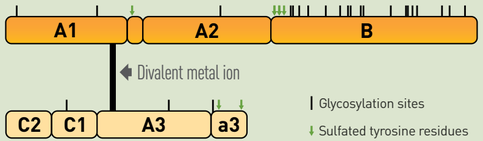
- KOVALTRY® is contraindicated in patients who have a history of hypersensitivity reactions to the active substance, to any of the excipients, or to mouse or hamster proteins.

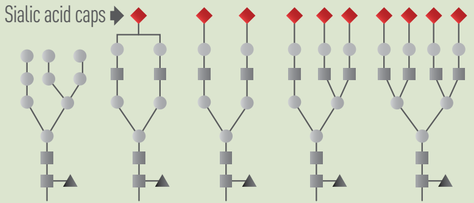
Please see additional Important Safety Information throughout and the accompanying full Prescribing Information.

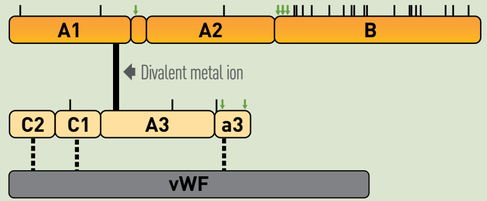
Kovaltry®

Antihemophilic Factor (Recombinant)

The structure of natural FVIII







1 Protein composition and posttranslational modifications

Endogenous FVIII is a heterodimeric protein consisting of a heavy chain with the domains A1, A2, and B, and a light chain with the domains A3, C1, and C2.[2-4]

During biosynthesis, endogenous FVIII undergoes complex **posttranslational modifications** including glycosylation, sialylation, and tyrosine sulfation.[2,5]

- **Glycosylation** is the attachment of glycans to a protein; in FVIII, most attach to the B domain[2,5]

2 The role of sialylation

At least 80% of glycans on endogenous FVIII are capped with **sialic acid**, which helps prevent FVIII from being recognized by carbohydrate-binding clearance proteins.[5]

- This helps to ensure that FVIII is not prematurely cleared by the liver, and instead can be released into circulation[5,6]

3 The role of tyrosine sulfation

Additionally, the tyrosine residues in the acidic regions between the major A domains undergo sulfation.[7,8]

- **Tyrosine sulfation** is needed for the binding of FVIII to the carrier protein, von Willebrand factor (vWF)[7,8]

SELECTED IMPORTANT SAFETY INFORMATION

- Hypersensitivity reactions, including anaphylaxis, are possible with KOVALTRY®. Early signs of hypersensitivity reactions, which can progress to anaphylaxis, may include chest or throat tightness, dizziness, mild hypotension and nausea. Discontinue KOVALTRY® if symptoms occur and seek immediate emergency treatment.

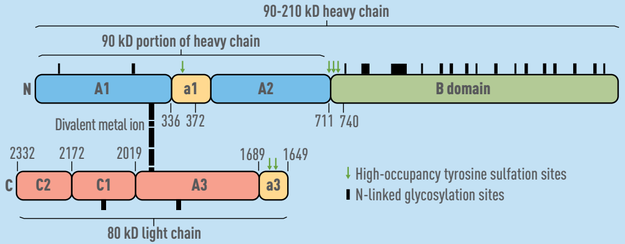
SELECTED IMPORTANT SAFETY INFORMATION

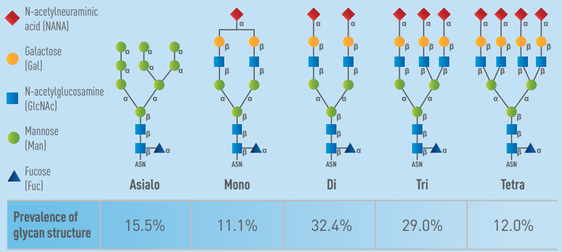
- KOVALTRY® may contain trace amounts of mouse and hamster proteins. Patients treated with this product may develop hypersensitivity to these non-human mammalian proteins.

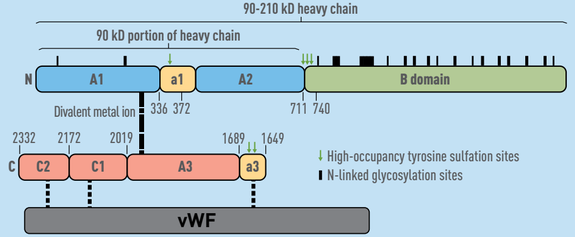
Please see additional Important Safety Information throughout and the accompanying full Prescribing Information.

Kovaltry®
Antihemophilic Factor (Recombinant)

KOVALTRY®: A molecule designed to be similar to endogenous FVIII







1 Protein composition and posttranslational modifications

KOVALTRY® is an **unmodified, full length rFVIII, containing all 6 FVIII domains**.[1,2]

Posttranslational modifications of KOVALTRY® are similar to those of endogenous FVIII.[1]

- As in endogenous FVIII, the KOVALTRY® molecule demonstrates consistent **glycosylation**, predominantly on the B domain. Multiple N-linked and O-linked glycans are present on the B domain of the KOVALTRY® molecule[1,9]

2 The role of sialylation

KOVALTRY® demonstrates consistent glycosylation and a high level of **sialylation**.[9,10]

- 96% of the terminal galactose residues on a KOVALTRY® molecule are sialylated[9]
- As in endogenous FVIII, sialylation helps to ensure that KOVALTRY® is not prematurely cleared by the liver and instead can be released into circulation[5,6]

3 The role of tyrosine sulfation

The KOVALTRY® molecule is sulfated on **6 tyrosine sites**.[9]

- The sulfation of tyrosine sites on the KOVALTRY® molecule is similar to that of endogenous FVIII[1,7,8]
- **Tyrosine sulfation** is needed for binding to the carrier protein, von Willebrand factor[1,7,8]

SELECTED IMPORTANT SAFETY INFORMATION

- Neutralizing antibody (inhibitor) formation has occurred following administration of KOVALTRY®. Previously untreated patients (PUPs) are at greatest risk for inhibitor development with all Factor VIII products. Carefully monitor patients for the development of Factor VIII inhibitors, using appropriate clinical observations and laboratory tests. If expected plasma Factor VIII activity levels are not attained or if bleeding is not controlled as expected with administered dose, suspect the presence of an inhibitor.

SELECTED IMPORTANT SAFETY INFORMATION

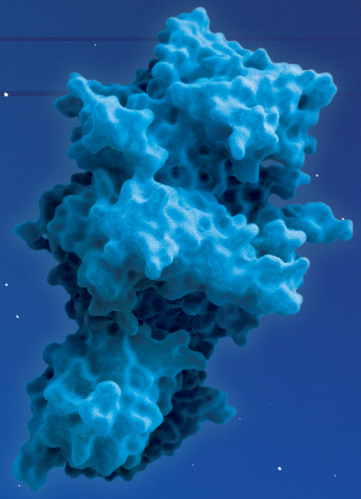
- Hemophilic patients with cardiovascular risk factors or diseases may be at the same risk to develop cardiovascular events as non-hemophilic patients when clotting has been normalized by treatment with Factor VIII.

Please see additional Important Safety Information throughout and the accompanying full Prescribing Information.

Kovaltry®
Antihemophilic Factor (Recombinant)

The science of KOVALTRY®

- An unmodified, full length FVIII[1]
- A primary protein structure with more than 20 years of clinical use[1]
- Posttranslational modifications similar to endogenous FVIII[1]
  - Consistent glycosylation[9]
    - Multiple N-linked and O-linked glycosylation sites are present on the B domain of the KOVALTRY® molecule
  - High level of sialylation[5,6,10]
    - Helps to ensure that KOVALTRY® is not prematurely cleared by the liver and instead can be released into circulation
  - Sulfation of 6 tyrosine sites[7-9]
    - Helps to facilitate binding to the carrier protein, von Willebrand factor



SELECTED IMPORTANT SAFETY INFORMATION

- Catheter-related infections may occur when KOVALTRY® is administered via central venous access devices (CVADs). These infections have not been associated with the product itself.
- The most frequently reported adverse reactions in clinical trials (≥3%) were inhibitors in previously untreated patients (PUPs)/minimally treated patients (MTPs), and headache, pyrexia, and pruritus.

Please see additional Important Safety Information throughout and the accompanying full Prescribing Information.

You are encouraged to report negative side effects or quality complaints of prescription drugs to the FDA. Visit www.fda.gov/medwatch or call 1-800-FDA-1088.

References: 1. KOVALTRY® [prescribing information]. Whippany, NJ: Bayer HealthCare LLC; 2016. **2.** Pipe SW. Functional roles of the factor VIII B domain. *Haemophilia.* 2009;15(6):1187-1196. **3.** Saenko EL, Shima M, Sarafanov AG. Role of activation of coagulation factor VIII in interaction with vWF, phospholipid, and functioning within the factor Xase complex. *Trends Cardiovasc Med.* 1999;9(7):185-192. **4.** Santagostino E. A new recombinant factor VIII: from genetics to clinical use. *Drug Design Dev Ther.* 2014;8:2507-2515. **5.** Lenting PJ, Pegon JN, Christophe OD, Denis CV. Factor VIII and von Willebrand factor—too sweet for their own good. *Haemophilia.* 2010;16(suppl 5):194-199. **6.** Bovenschen N, Rijken DC, Havekes LM, van Vlijmen BMJ, Mertens K. The B domain of coagulation factor VIII interacts with the asialoglycoprotein receptor. *J Thromb Haemost.* 2005;3(6):1257-1265. **7.** Lenting PJ, van Mourik JA, Mertens K. The life cycle of coagulation factor VIII in view of its structure and function. *Blood.* 1998;92(11):3983-3996. **8.** Leyte A, van Schijndel HB, Niehrs C, et al. Sulfation of Tyr^{1680} of human blood coagulation factor VIII is essential for the interaction of factor VIII with von Willebrand factor. *J Biol Chem.* 1991;266(2):740-746. **9.** Garger S, Severs J, Regan L, et al. BAY 81-8973, a full-length recombinant factor VIII: manufacturing processes and product characteristics. *Haemophilia.* 2017;23(2):e67-e78. **10.** Teare J, Sim D, Shah A, et al. Increased branching and sialylation of N-linked glycans of recombinant factor VIII leads to an improved pharmacokinetic profile for BAY 81-8973. Poster presented at the European Association for Haemophilia and Allied Disorders. 10th Annual Congress. February 1-3, 2017. Paris, France.

Kovaltry®

Antihemophilic Factor (Recombinant)