

## Bayer introduces Kovaltry to replace Kogenate FS in Canada

*Kogenate and its successor Kogenate FS have been used in Canada to treat hemophilia A for almost a quarter-century. Their manufacturer, Bayer, is now replacing Kogenate FS with its next generation, Kovaltry, in the Canadian marketplace. First licensed by Health Canada in early 2016, the recombinant factor VIII concentrate has now also been approved by the U.S. FDA and the European Medicines Agency.*

*Hemophilia Today met with Dr. Mohammed Mahdi, medical and scientific advisor in the Hematology Branch at Bayer Canada, and Dr. Jayson Stoffman, medical director at the Manitoba Bleeding Disorders Program and past-president of the Association of Hemophilia Clinic Directors of Canada, to learn more about Kovaltry.*



**Dr. Mohammed Mahdi**



**Dr. Jayson Stoffman**

*Hemophilia Today (HT): What has led to the development of this next generation of rFVIII called Kovaltry?*

**Dr. Mahdi:** Kovaltry is not a new molecule but its development reflects Bayer's commitment to continually improving its products. Kovaltry is produced with advanced manufacturing technologies that enhance the production of rFVIII. It will be manufactured in the current site at Berkeley California and at a new manufacturing plant scheduled to come on-line in Wuppertal, Germany, which enhances global supply.

*HT: In what ways are Kogenate FS and Kovaltry similar?*

**Dr. Mahdi:** Compared to Kogenate FS, Kovaltry is similar in terms of efficacy and safety. It works just as well as Kogenate FS and the safety profile is essentially the same. Kovaltry and Kogenate FS are both made using a copy of the same natural unmodified FVIII molecule that we find in human blood. They are both recombinant molecules with an identical factor VIII amino acid sequence and molecular formula that are produced in the same baby hamster kidney cell line.

**Dr. Stoffman:** Clinically, they're the same. The efficacy and the safety are what we've come to expect from Kogenate. Kovaltry is the same molecule so it has the same clinical efficacy and it's indicated for all the same uses as Kogenate: for prophylaxis, for on-demand therapy and for surgery.

*HT: So patients shouldn't expect any difference in how it works for stopping or preventing bleeding?*

**Dr. Stoffman:** No. We've been discussing Kovaltry with patients in our clinic and it's presented to them as the same molecule that we're going to use in the same way and we expect it to work just as well. It's just going to have a different name and different packaging.

*HT: In what ways are Kogenate FS and Kovaltry different?*

**Dr. Stoffman:** One of the potential clinical benefits is that study data showed a slightly longer half-life. The studies showed that twice weekly or three times weekly prophylaxis was effective, suggesting that we're seeing is an extension of half-life that allows for better personalization of prophylaxis. That may be a clinical advantage of this new manufacturing technology.

*HT: If it's the same molecule from the same cell line, how do you explain that the half-life appears to be somewhat longer?*

**Dr. Mahdi:** While it's the same amino acid sequence, we've found that on parts of the molecule, called consensus sequences, there are areas where you have branching. On these branches you have what is called sialylation or sialic acid capping on each branch. What we've found is that there is more branching on the Kovaltry molecule than on the Kogenate molecule. Theoretically, we believe that this keeps the drug in the circulation longer. We've also introduced human heat shock protein 70, a natural chaperone protein, that's transfected or genetically inserted into the cell line. We believe this modification helps with better folding of the protein as well as reducing programmed cell death. Overall, there appears to be a favourable pharmacokinetic profile compared to Kogenate FS.

**Dr. Stoffman:** This is a different approach. A lot of the extended half-life products being developed add things onto the functional part of FVIII. Kovaltry has the same FVIII amino acid sequence but the changes happen on the outside of the protein after it's been translated from the gene into the protein. In the manufacturing of Kovaltry, all those modifications that happen afterwards are more natural, and result in a molecule that is slower to degrade. So it's a similar kind of concept to what we're trying with things like pegylation but instead Kovaltry uses great big sugars on the side of the molecule to hide the key part of the protein from the natural body systems that break down the FVIII. It's not that we change the core protein, but the modifications that happen to that protein after it's created make it a slightly bigger, more branched molecule that's slower to break down.

It's important to say that no human protein is being added into the mix. This is the gene for human heat shock protein 70 incorporated with the FVIII gene into the baby hamster kidneys.

*HT: Another recombinant gene being introduced into the baby hamster kidney cell line?*

**Dr. Stoffman:** Exactly. It's not the addition of a human protein. It's the addition of a gene for the human protein. You get all the benefits of the protein without having to add the protein itself.

*HT: You've measured an increase in mean half-life from something like 12 hours to something close to 14 hours. Are you comparing apples with apples?*

**Dr. Mahdi:** Yes, we're comparing the two products with the same group of people and seeing a slightly longer half-life.

*HT: Are there any other ways in which these two products are different?*

**Dr. Mahdi:** Kovaltry does not use any human or animal derived raw materials in the cell line, purification process or in the formulation process to manufacture Kovaltry. We replace human plasma protein solution with a proprietary medium that doesn't contain any human or animal derived raw materials as nourishment for the baby hamster kidney cells. We've gone from a so-called second generation to a third generation product.

We also introduced a 20-nanometer filtration step that reduces the theoretical risk of contamination. You can think of it as another level of safety that's introduced to the manufacturing process. It acts to ensure the purification of Kovaltry, strengthen the safety profile by removing potential viruses that might be introduced in the manufacturing of Kovaltry and filter out potential protein aggregates or the clumping of proteins during the manufacturing process. Think of it as a sieve that removes potential viruses and clumps of misfolded proteins from the final product.

*HT: What have recent clinical trials shown with regard to developing inhibitors, first in previously treated patients (PTPs) and, secondly, in previously untreated patients (PUPS)?*

**Dr. Stoffman:** The [RODIN](#) study (See *Hemophilia Today*, Vol 49, No 3, November 2014) and the more recent [SIPPET](#) study (see page 22) did not look at PTPs, so from a scientific point of view, we can't comment, but based on what we understand of inhibitors, there would be no increased risk of inhibitors in PTPs with a recombinant product like Kovaltry. These patients have been frequently treated, they haven't developed an inhibitor, and there's no concern of inhibitor development when switching from one product to another.

In terms of PUPS, there's certainly some evidence in the studies that have occurred in the last couple of years and most recently with *SIPPET* suggesting that there's an increased risk of inhibitor development with recombinant products as compared to plasma-derived FVIII containing von Willebrand factor. The *LEOPOLD* PUP studies are looking at Kovaltry, but that data is not available yet. There hasn't been any evidence that the inhibitor rate with Kovaltry is any higher than has been seen with other recombinant FVIII products, and it hasn't been any higher than with Kogenate. However, there is a real concern that previously untreated patients starting on Kovaltry, or any of the other recombinant products on the market right now are exposed to a higher risk of an inhibitor compared to starting on a plasma-derived FVIII with von Willebrand factor. At least, that's what *SIPPET* seems to suggest.

*HT: Now some more practical questions. What are the formats for Kovaltry?*

**Dr. Mahdi:** It is administered via intravenous injection after reconstitution with a diluent supplied in two pre-filled syringe volumes: 2.5 mL for the 250, 500 and 1000 IU nominal dose strengths and 5 mL for the 2000 and 3000 IU nominal dose strengths. These are the same as Kogenate FS, as is the administration device or vial adapter.

*HT: What are the storage requirements?*

**Dr. Mahdi:** Kovaltry needs to be refrigerated between 2°C to 8°C and never frozen. Once removed from the fridge, it cannot be re-refrigerated. You can store Kovaltry at room temperature up to 25°C for a single period of up to 12 months. After reconstitution it must be used within three hours. Moreover, freezing of the vials down to minus 30°C has no effect on the product.

*HT: What are the plans for making the transition from Kogenate to Kovaltry?*

**Dr. Mahdi:** The plans are to ship across the country from June to October with Atlantic Canada being the first to transition. We've left this to Canadian Blood Services and the clinics to manage. By the end of October, the transition should be finished. Once all patients have switched to Kovaltry, Kogenate FS will be discontinued in Canada.

*HT: In summary, what are some of the key benefits of Kovaltry over its predecessor?*

**Dr. Mahdi:** A slightly longer half-life may mean going from three infusions per week to twice weekly for some people, but this remains to be seen in clinical use. Kovaltry is also made with enhanced manufacturing techniques so it's a better product in that regard.

**Dr. Stoffman:** I would agree. The major benefits are to the manufacturing process. There's no human protein and there are added safety steps.

*HT: We can see half-life being a potential clinical benefit and eventually measured. It seems odd to claim, and others have done it before you, that because it's a 3<sup>rd</sup> generation, it's much safer. There's never been a safety problem with recombinant FVIII. To say Kovaltry is safer, suggests its predecessor wasn't safe and that's not true. We wonder about focusing too much on added safety.*

**Dr. Stoffman:** That's a good point. These are all added safety steps. We have a family of products that are safe and have always been safe. As a medical student I was taught about pathogen X, the thing out there that we don't know. Enhancing safety is never a bad idea, even if you haven't had a problem in the past.