The Blood Factor

by David Page, CHS National Executive Director

Rebinyn, an extended half-life factor IX, to be launched April 1

Interview conducted by David Page, CHS National Director of Health Policy, on behalf of Hemophilia Today.

Rebinyn, an extended half-life factor IX concentrate, manufactured by Novo Nordisk, is one of the “winners” in the recent Canadian Blood Services tender for the 2018-2020 period. (See page 10 for more information on the tender results.) It will become available across Canada, except in Quebec, starting on April 1. Hemophilia Today interviewed Dr. Manuel Carcao, pediatric hematologist and co-director of the Comprehensive Care Hemophilia Program at The Hospital for Sick Children in Toronto and lead author of the Paradigm 5 study on the use of Rebinyn in children, and Dr. Hossam Saad, Associate Director of Biopharm Medical Affairs at Novo Nordisk Canada, to learn more about this new therapy.

David Page (DP): Dr. Saad, can you tell us about the history of the development of Rebinyn?

Dr. Hossam Saad: Rebinyn, in development by Novo Nordisk for over 10 years, came about because of the need for less frequent infusions and higher trough levels in the treatment of patients with hemophilia B. Trough level is the lowest level of factor a person on prophylaxis reaches, just before his next infusion. Novo’s end goal was higher quality of life with better treatment regimens. Rebinyn was approved by the FDA in the U.S. in May 2017, by the European Medicines Agency (EMA) in June 2017 and by Health Canada in November 2017. It is currently in use in Switzerland. Novo Nordisk is preparing to begin marketing in the U.S. and Canada.

DP: What are the approved indications for use in Canada?

Dr. Saad: Health Canada has approved Rebinyn for use in patients with hemophilia B of all age groups for the control of bleeding, for the prevention of bleeding (i.e. before a risky activity) and in the perioperative setting. In addition, it is indicated for patients 18 years of age and older for routine long-term prophylaxis.

Dr. Manuel Carcao: We need to recognize that many drugs are not initially approved for use in the pediatric setting, yet pediatricians, in discussion with patients/families, may nevertheless choose to use them; hence, Rebinyn, while not indicated for prophylaxis under the age of 18 by Health Canada, may still end up being used for prophylaxis in this age group.

DP: Dr. Carcao, could you explain the concept of extended half-life?

Dr. Carcao: Half-life is the time it takes for half the product, once infused into a person, to be degraded or destroyed. The longer the half-life, the longer the product lasts in a person’s body. It generally takes about five or six half-lives to completely eliminate a product. There has been a big drive over the last 10 years to extend the half-life of factor so that patients ultimately need fewer infusions or can maintain higher trough levels to protect them from bleeds, or both. Half-life varies from individual to individual. Some patients are quite fortunate in that their half-lives are longer than normal; other patients may have shorter half-lives. Still, everyone may benefit from a product that has a longer half-life.

DP: How does the technology used to extend half-life in Rebinyn compare with other factor IX products?

Dr. Carcao: For factor IX, three technologies are currently being used to extend half-life. All three involve the concept of taking recombinant factor IX and binding something to it. The three different things that are being fused to factor IX to prolong half-life are: 1) recombinant Fc; 2) recombinant albumin and 3) polyethylene glycol (PEG). The first technology—Fc—is used in Alprolix, which has been available in Canada for the last two years. The Fc extends the half-life of Alprolix by about three-fold vs standard factor IX. The use of recombinant albumin to extend the half-life of factor IX is
used in a product called Idelvion, which is licensed in Canada but is only available in Quebec under strict criteria. Rebinyn uses PEG to shield the factor IX from degradation and extend its half-life. Idelvion and Rebinyn extend the half-life of factor IX approximately five-fold.

**DP: Rebinyn is a product that could potentially be used routinely over many years. PEG can be found in the brains of animals when it is infused at very, very high doses. This has raised some concerns among some physicians and patients alike about potential toxicity. Both EMA and Health Canada have held back from approving Rebinyn for routine prophylaxis in those under 18. What is the evidence on the safety of PEG?**

**Dr. Saad:** After reviewing all the clinical information that we have and that we submitted to Health Canada, there is no indication of any adverse effects. No neurological adverse events were reported after five years of intensive study in clinical trials.

**Dr. Carcao:** There is a lot of evidence attesting to the safety of PEG and of pegylated medicines in general. First of all, pegylated medicines have been around for over 25 years. There are many pegylated drugs in use and many more in development. This is a technology that has been well studied. Second, many children have been using Rebinyn for over five years through the clinical trial period and they have demonstrated no short or long term adverse effects. Finally, while it is true that PEG has been found in the bodies of animals following the regular use of PEG, it reaches a steady state; it doesn't continue to accumulate over time. Moreover, if one stops receiving PEG, the PEG will be completely eliminated. And finally, even in those animals who received massive doses of PEG, far higher than with Rebinyn in humans, we don't actually see any adverse effects.

**DP: Is more safety evidence needed before regulators like Health Canada will approve Rebinyn for routine prophylactic use in people under 18? How long will it take to gather that evidence?**

**Dr. Saad:** Novo Nordisk is working with Health Canada and EMA to get an indication for prophylaxis in children. This involves gathering more safety and efficacy data for these age groups. We have the PARADIGM 5 extension study in children, which is ongoing, and the PARADIGM 6 study, which involves previously untreated patients. For the most part, these are very young children, most younger than two years of age. There is no timeline.

**DP: What have you learned from clinical trials about the efficacy of Rebinyn in preventing bleeding?**

**Dr. Carcao:** The impact of a five-fold extension of half-life for patients is tremendous. Most patients using standard half-life products like Benefix or Rixubis will require two to three infusions per week of 40 IUs per kilogram. Yet even with these frequent infusions, they don't achieve trough levels higher than 1 to 5% of normal, which leaves them vulnerable to bleeding. The higher the trough level, the better the person is protected from bleeding. With Rebinyn, adults and children receiving one infusion per week are able to achieve a trough level of 25-30% in adolescents and adults, and 15-20% in younger children. These are remarkable trough levels. With such trough levels these individuals are almost completely protected from bleeds and are able to engage in most sports and work activities with almost no restrictions.

As a result of the higher trough levels, we are finding that patients on Rebinyn have less bleeding. Some adults switching to Rebinyn have reported a few bleeds but this is likely because they already had quite damaged joints prior to switching. When switched to Rebinyn, the vast majority of people, particularly children, do not experience any bleeds. Furthermore, over time these patients begin to recognize they're well protected, become less anxious about being active, and in some cases become more active. All of this results in better quality of life, which has been reported. I see all of these benefits in the patients that I have switched to Rebinyn as part of the clinical trial, and who have been using Rebinyn for five years. Not one has wanted to return to the standard product when this was offered.

**DP: Who would benefit the most from using a product like Rebinyn?**

**Dr. Carcao:** All patients can benefit. Severe hemophilia B patients who bleed a lot despite prophylaxis with standard half-life factor concentrates would benefit greatly from these higher trough levels. Patients who do not bleed as much could benefit by going to prophylaxis every 14 days. Patients who have resisted being on prophylaxis, for whatever reason, may now see the benefit of starting once-every-two-week prophylaxis. Some mild patients who don't self-infuse but occasionally bleed may also benefit from Rebinyn. Such patients can receive a dose of Rebinyn and be well protected for two weeks; this is great if they are going on a short vacation and want to be protected, or if they are planning on engaging in a lot of sports in a short period of time. For people with hemophilia B undergoing surgery, Rebinyn might shorten hospital stays and reduce the number of clinic visits needed to receive follow-up doses of factor after surgery.

**DP: What about patients who only infuse to treat a bleed?**

**Dr. Carcao:** When we treat a bleed with standard half-life products, we need to treat with two or three doses over a few days, often at the hospital. With Rebinyn, one infusion will suffice to treat most bleeds.
Dr. Saad, can you tell us about the practical side of Rebinyn?

Dr. Saad: Rebinyn comes in 500, 1,000 and 2,000 IU/1, each with 4 mL of diluent in a prefilled syringe. In all situations, Rebinyn should only be used before its expiry date on the vial. Before reconstitution, it can be stored either in the fridge at 2 to 8°C or up to 6 months one time at room temperature (up to 30°C). After reconstitution, it should be used immediately; otherwise, it can be stored for up to 24 hours in the fridge at 2 to 8°C, or at room temperature up to 30°C for up to 4 hours.

DP: What is the schedule for introduction of Rebinyn across the country?

Dr. Saad: According to the contract with CBS, Rebinyn will be introduced in all treatment centres served by CBS starting on April 1.

A plan will be developed to ensure a smooth transition and avoid any wastage of product. Patients should contact their HTC staff.

DP: In summary, Dr. Carcao, what are the key benefits of Rebinyn?

Dr. Carcao: The tremendous half-life extension. The much higher factor levels obtained between doses. The very high trough levels. All of this resulting in fewer infusions, leading to better adherence and better health outcomes.

Editor’s note: The Rebinyn product monograph is available at www.novonordisk.ca/content/dam/Canada/AFFILIATE/www-novonordisk-ca/OurProducts/PDF/rebinyn-product-monograph.pdf