Alprolix, a longer half-life factor IX, approved by Health Canada

Alprolix™, a recombinant factor IX concentrate manufactured by Biogen Idec, was approved by Health Canada March 21, 2014 and by the U.S. FDA a week later. It is indicated in adults and children (≥12 years) with hemophilia B for routine prophylactic treatment to prevent or reduce the frequency of bleeding episodes and for control of bleeding episodes.

Alprolix is the first in a new class of longer half-life coagulation products for hemophilia. Half-life is defined as the time it takes for half the clotting factor to be eliminated from circulation. Alprolix is currently being reviewed by health authorities in the provinces and territories. Decisions are expected soon as to when it will be approved for distribution by Canadian Blood Services (in all the provinces and territories except Quebec) and by Héma-Québec (in Québec). Hemophilia Today (HT) interviewed two physicians who were closely involved with the development and clinical trials of Alprolix. – David Page

Dr. Glenn Pierce is the senior vice-president for Global Medical Affairs and the chief medical officer for hemophilia at Biogen Idec, a biotechnology company based in Cambridge, Massachusetts. Dr. Pierce has been involved in hemophilia since the day he was born. He had severe factor VIII deficiency until a liver transplant five years ago cured his hemophilia. Dr. Pierce has been president of the U.S. National Hemophilia Foundation three times.

Dr. Jerry Powell is professor of medicine at the University of California and since 1990 has been centre director of the hemophilia treatment centre (HTC) at the Davis Medical Center. Since 1990 he has spent much of his time pursuing clinical trials to improve the products and care of people with hemophilia. Dr. Powell studied medicine at the University of Washington in Seattle. He did his internship and residency in internal medicine at the University of Chicago and returned to Seattle for his fellowship in hematology and oncology. He spent several years in the laboratory of Earl Davie, who is very well known in the field of clotting factors. His group purified many of the coagulation factor proteins and eventually did the genetic studies that cloned factors VIII and IX. Dr. Jerry Powell was lead author of the Phase 3 Study of Recombinant Factor IX Fc Fusion Protein in Hemophilia B, which was published in the New England Journal of Medicine on December 12, 2013. He was involved in both the Phase I/II and III clinical trials of Biogen Idec’s longer half-life factors VIII and IX.
Hemophilia Today: Biogen Idec is not a well-known company here in Canada, at least in the hemophilia community. Dr. Pierce, can you tell us about Biogen's history, especially as regards biological therapies?

Dr. Pierce: The company has a long history in biotechnology. It was founded more than 30 years ago by two Nobel laureates, Phil Sharpe and Walter Gilbert, in Cambridge, Massachusetts. It has developed an extensive portfolio in multiple sclerosis as well as in other autoimmune diseases. So it's a company that is well known for its ability to manufacture recombinant proteins and for its work in other chronic illnesses, but is new to hemophilia. I joined Biogen Idec five years ago to lead the development of long-lasting coagulation factors. This was a program that the company brought on board in 2007, based upon Fc fusion technology that came from Harvard and Brandeis University. They were in need of an individual who knew something about hemophilia drug development, which is why I joined the company.

HT: Could you please describe the Fc fusion technology behind Alprolix?

Dr. Pierce: Fc fusion is the same technology that other companies have used to develop long-lasting versions of other drugs over the past 15-20 years. It's now understood that the Fc-receptor system, which has evolved in mammals over a period of many hundreds of millions of years, is responsible for keeping immunoglobulins in the bloodstream for a prolonged period of time. The Fc fusion system slows degradation of proteins like immunoglobulins, which are antibodies needed to fight infections. This is done by recycling immunoglobulins as they go through the destructive pathways that all proteins go through. It takes them back out from the intracellular compartments where they would be destroyed and recycles them back into the circulation.

Biogen and a number of others have determined how we could exploit this process for other types of proteins that don't last very long in the circulation, like the clotting factors. And so by attaching the back end of an immunoglobulin molecule to another protein such as factor VIII or factor IX, one can take advantage of the recycling pathway. Instead of the protein getting destroyed, much of it comes back out of the cell and gets recycled back into the circulation. This technology has been exploited for seven or eight other approved drugs, including drugs like Enbrel®, which is used in rheumatoid arthritis and other autoimmune diseases.

HT: Dr. Pierce, what evidence have you been able to gather that this modified, larger molecule is equally efficacious in stopping bleeding, given the same level of factor IX in the bloodstream?

Dr. Pierce: We needed to make sure the factor IX molecule with an Fc fused to the back end was as effective in functioning as native factor IX. We did this in the laboratory with a variety of clotting factor assays as well as in factor IX-deficient mice and dogs. In these preclinical studies, we demonstrated that the factor IX Fc could stop bleeding equally well compared to BeneFIX®. And we showed that it lasted two to three times longer.
HT: That leads to the key question with extended half-life factor IX: how much it’s extended over current products. I raise the issue because we’re used to BeneFIX with a 19-hour reported half-life. This seems a bit different from the way you report half-life in your studies.

Dr. Pierce: When one applies the Fc fusion technology to different proteins, the half-life varies from protein to protein. For the factor IX Fc, now called Alprolix, we’ve been able to achieve a half-life of about 82 hours, or about three and a half days. So from the time a patient takes factor IX Fc until half of the factor IX is left, three and a half days will pass.

HT: This is a little confusing. In the Phase III study, as you’ve just said, you report a half-life of 82 hours. And in the published paper, you report 33 hours for BeneFIX while Pfizer’s own package insert claims 19 hours as the BeneFIX half-life. Do you have different ways of measuring?

Dr. Pierce: We do. When one measures half-life, one needs to go out a certain amount of time, based on that protein’s half-life in order to get an accurate measurement. BeneFIX measurements go out 48 hours. That’s not a sufficient time to accurately measure half-life. When one goes out 48 hours, the half-life is about 18 hours. When one measures BeneFIX over a more scientifically appropriate time period, such as 96 hours, the half-life is 33 hours. So it’s perhaps not useful to look at Alprolix’s half-life as a multiple of BeneFIX’s half-life; it’s useful to look at what the half-life of Alprolix actually is, that is, 82 hours.

HT: But half-life is not a straight line when plotted on a graph. It’s a curve with a quick drop in factor IX activity in the first few hours and days and a slower drop as the days go by. So you’re not seeing a 50% decrease in factor IX in the first 82 hours after infusion. That first 50% loss in activity is much quicker. Isn’t that correct?

Dr. Pierce: Yes. In the first six to nine hours, in what’s called the alpha phase, the factor IX activity is lost much more quickly. It’s even faster with BeneFIX. You’ve got a large decrease at the beginning so if you don’t measure far enough out in time, you won’t get an accurate measurement of half-life. We’ve measured Alprolix over 14 days and, if you average it out, there’s one half-life decrease every three and a half days.

HT: What happens to the factor IX in those first hours? Where does it go?

Dr. Pierce: It’s thought it goes into the extravascular spaces, outside the bloodstream. But it’s hard to do that study as it’s not possible to measure it there. The question is, “Is it useful in the extravascular spaces?” That has never been conclusively proven. There is some evidence that factor IX needs to go through this compartmentalization to be active during a bleeding episode.
**HT:** Another way to think about this that might be more useful is to look at time to 1% or time to 3% with a standard dose of 50 IUs per kilogram. Would that give a better idea on the frequency of infusions needed?

**Dr. Pierce:** If you give a dose of 50 IUs per kilogram, after seven days, models predict about 95% of patients will be above 1% with Alprolix. That contrasts with 31% treated with the same dose of BeneFIX. If you receive 100 IUs per kilogram of Alprolix every 14 days, about 53% of patients will end the period at 1% or higher, compared to 1.5% of patients treated with BeneFIX.

**Dr. Powell:** From a patient’s perspective, what he really wants to know is how long it will take before he is at risk of bleeding again. This is complex. It depends on his activity level. If a person is going to be engaged in activities that have a higher risk of bleeding, he clearly needs a higher factor IX level. If he’s at a desk job or going to school, he doesn’t have to worry so much about maintaining a high factor IX level. We’ve tried to model the data from these patients at different factor levels. With factor IX levels above 1%, we don’t expect to see any spontaneous bleeding. With factor IX levels above 3%, we don’t expect any spontaneous bleeding or bleeding from minor trauma. And so each individual patient is going to have to determine the time to the next dose based on what trough level he is willing to accept based on his activity level. That’s a pretty long answer but it does describe where we’ll be going in the clinic with dosing with this exciting drug with intervals that will be longer than 3 or 4 days. On the study, it looked like a number of patients could go 12 or 14 days between doses and maintain a factor IX level above 1%.

**HT:** And have no breakthrough bleeds?

**Dr. Powell:** Yes, and have no or rare breakthrough bleeds. We looked at those who had chronic joint damage and target joints. Would they have breakthrough bleeds at a higher rate? With factor levels above 1% we did not see target joints having problems with an increased rate of breakthrough bleeding.

**HT:** At least not a significant number of patients?

**Dr. Powell:** Right.

**HT:** Dr. Powell, you were very involved in the clinical study of Alprolix. Could you describe the clinical trial and the key results?

**Dr. Powell:** The major objective of the trial was to take the drug and study it prospectively in patients at multiple centres trying to duplicate what a clinical experience would be like. This particular Phase III clinical trial was international with over 100 patients enrolled at multiple sites. A first group of patients were followed using on-demand therapy. A second group were followed on a prospectively prescribed once-a-week regimen and a third group of patients were followed on a pharmacokinetic-guided regimen so that their factor IX levels never fell below 1%. This last group had a variable interval between dosing but the objective was to maintain the factor IX level above 1% with a defined dose of 100 IUs per kilogram. There was a fourth arm of the study in which patients who needed surgery used the study drug. Over 10 patients
underwent major surgery, primarily orthopedic joint surgery. The major outcome was pretty much as expected from the Phase I/II results. The efficacy was equal compared to the standard factor IX products in stopping bleeding and reducing pain from a bleed.

HT: How did you measure this?

Dr. Powell: There are two ways to talk about efficacy. One is to define efficacy by the factor IX level. But, more importantly, patients want to know if a product stops the pain from an acute bleed as effectively. That’s a subjective judgment but patients reported that Alprolix stopped the pain from an acute bleed as quickly as any of the other factor IX products they had used. That was important.

HT: So you saw this with the on-demand patients who were experiencing frequent bleeds?

Dr. Powell: Right. And the factor IX levels that the patients were able to obtain correlated with what we expected to see. And efficacy was tested more formally in surgery. The efficacy in stopping bleeding with Alprolix was as expected given the factor IX levels in the plasma. All of that was very reassuring. We expected to see this but it was nice to show in the study.

The patients in all these different arms were treated as they would have been in the clinic. Both those on on-demand therapy and those on prophylaxis were studied for over 50 exposure days or one year or more, and there is an extension study in addition to the Phase III study. The major reason for all of that was to see if any inhibitors developed. After repeated dosing in these previously treated patients, there were none. We also wanted to see if there were any unexpected problems. There were none. All of the medical problems that we saw in the study population were problems we would expect to see in a hemophilia population. That, too, was very reassuring.

HT: What do you see as the principal benefits of Alprolix compared to the current factor IX preparations?

Dr. Pierce: The development of a class of longer half-life products such as Alprolix offers the ability to decrease the burden of therapy. Currently patients with severe hemophilia B need to take factor IX two to three times a week prophylactically in order to prevent bleeding. With Alprolix we demonstrated that patients could prevent the majority of bleeding episodes if they infused every one to two weeks at a dose of 50 to 100 IUs per kilogram.

Dr. Powell: I see two benefits. The first is the decreased burden of dosing. We have all moved into the era where we try to keep the factor IX level above 1%. Most factor IX patients require infusions every three or four days to achieve that. With this longer half-life product, they should be able to achieve that with less frequent infusions. Clearly, infusions once a week kept their levels much higher than 1%. And some of the patients got by with infusions every 10 or 14 days. So based on these data, the expectation is that each individual patient will be able to dose somewhere between once a week and once every two
weeks, and still have no spontaneous bleeding. That’s the first major advantage.

The second major advantage that I see from these data is a little more subtle. The major problem with hemophilia is that patients bleed into joints and there is joint damage. But the more important problem is internal bleeding, such as a retroperitoneal bleed with organ damage or an intracranial bleed with neurological damage. These kinds of bleeds occur much less often but are much more severe. Even though we didn’t specifically study such rare events, the prediction is that with this longer acting drug we’ll see many fewer of those devastating bleeds.

I think those are outstanding advantages to look forward to in the next year or two.

HT: Could you put this advance in context? In terms of the last 40 years, since factor concentrates came onto the market in the late 1960s and early 1970s, how does this stack up?

Dr. Powell: There’s no other genetic disease that has seen the progress of hemophilia. It’s almost breathtaking to think that in the 1960s the life expectancy of a boy born with hemophilia was 20 years and now it’s essentially a normal life expectancy. But if you look at the severe hemophilia population, the major cause of death is still bleeding. We have more work to do. So that’s the major advantage of longer half-life factors; we should have many fewer bleeding episodes that cause illness and death. The problem with the plasma-derived products, as we all know, were the two episodes of HIV and hepatitis C, and nobody really knows what the next epidemic might be. There may be unknown viruses coming along. So that was the first big advance: recombinant technology. And this is the next major step: longer-acting factors. I see these entirely replacing current products.

However, after all my enthusiasm, I have to say the proof is in the pudding. This was a Phase III study with a little over 100 patients. We need to see what happens over the next few years with a couple of thousand patients with many thousands of infusions. I don’t expect any problems but we always have to be vigilant and follow up with good post-marketing surveillance.

HT: Could you describe Biogen’s manufacturing capacity and its ability to provide an uninterrupted supply of Alprolix once it is marketed?

Dr. Pierce: Biogen Idec is the oldest independent biotechnology company in the world. We’ve been manufacturing recombinant therapeutics for more than 30 years, and have facilities in Cambridge, Massachusetts; Research Triangle Park, North Carolina; and a duplicate facility in Hillerød, Denmark. We have developed a very large production capability, one of the largest in the pharmaceutical industry. Some of our drugs are monoclonal antibodies, used therapeutically in very large doses for chronic patients so we’ve had to develop a large capacity. We’re able to use that capacity to manufacture Alprolix.

While Biogen Idec is new to the hemophilia world, many of the people working for Biogen Idec are not new to hemophilia. We’ve also hired a number of people from the hemophilia community—patients, family members, treatment centre...
personnel—all of whom know this community well and who have instilled within Biogen Idec an understanding of what the community is all about. It’s a small community that has been through a lot in its history so it’s important that when a new company comes on the scene it does so with full knowledge of who this community is so that it can better serve the needs of all patients.