After a Long Wait, FDA Approves First Anti-Addiction Implant

Probuphine promises to deliver six months of continuous buprenorphine treatment. What does this mean for the future of the opioid epidemic?

June 1, 2016 By Casey Halter

On Thursday, May 26, 2016, the U.S. Food and Drug Administration (FDA) approved probuphine, the first sub-dermal implant designed to help treat opioid addiction among adult heroin and prescription drug users.

The landmark device, developed by California-based biotech firm Titan Pharmaceuticals, and licensed for sale in North America by New Jersey-based Braeburn Pharmaceuticals, promises six months of continuous therapy with buprenorphine, currently the most widely-used medication-assisted therapy (MAT) option for treating opioid dependency in the United States.

In practice, probuphine consists of four small rods inserted by a licensed doctor under the skin of a person's arm that deliver a continuous 4 mg to 8 mg dose of buprenorphine into the bloodstream. The device is one of the first truly novel treatments for opioid addiction approved by the FDA in nearly 14 years, and arrives as the United States is contending with an opioid addiction and overdose crisis that kills nearly 80 Americans every day.

"Opioid abuse and addiction have taken a devastating toll on American families. We must do everything we can to make new, innovative treatment options available that can help patients regain control over their lives," said FDA commissioner Robert M. Califf, MD, in the agency's official announcement of its decision. "Today's approval provides the first-ever implantable option to support patients' efforts to maintain treatment as part of their overall recovery program."

However, those familiar with addiction treatment know that the path to FDA approval for probuphine has been fraught with difficulties over the last few years. Federal health authorities originally rejected the device in 2013 due to concerns over its overall safety and efficacy.

The delay in probuphine's debut to the American market raises a number of questions: Why approve the device now? What are its pros and cons for treating opioid dependency? And what does probuphine mean for the future of the anti-addiction industry?

The FDA's official decision to approve probuphine in May comes just months after its Psychopharmacologic Drugs Advisory Committee voted 12 to 5 in favor of approving the new technology. However, buprenorphine, the medication contained in the novel anti-addiction implant, has been approved and widely used by doctors to treat opioid addiction in the United States since 2002.

Today, about one quarter of the 2.8 million people estimated to have a diagnosed opioid abuse disorder in this country are prescribed buprenorphine to help them manage their addiction. Often sold under the brand names Suboxone and Subutex, or contained in other popular substance abuse treatments, such as naltrexone, buprenorphine works to suppress cravings and withdrawal symptoms in both heroin and prescription drug users, and helps to block the effects of other opioids. Until now, the anti-addiction drug has been widely available only in pill or film form, which must be taken daily and held in the mouth or under the tongue for 15 minutes for maximum efficacy.

However, expanding the use and varieties of medication-assisted therapy options, including buprenorphine treatment, was set as an official target for the FDA's Opioid Action Plan in February 2016. It was also listed as one of the U.S. Department of Health and Human Services' (HHS) top three priorities for reducing opioid- and heroin-related deaths and dependence across the country. Perhaps this is why the FDA decided to give probuphine another chance.

"There is no question that long-acting, implantable buprenorphine will have a meaningful role in the treatment of opiate addiction," said David Pickar, MD, professor of psychiatry at Johns Hopkins University, in a recent email exchange about the drug. As a member of the FDA advisory committee, Pickar voted in favor of approving the implant earlier this year. "It adds to the growing list of pharmacological interventions for this serious illness. While there are limitations to its effectiveness, it nevertheless will have a real place in treatment and likely will save lives."

Pickar says he made his decision largely in response to new data on probuphine released in a recent Phase III clinical trial, that showed 85.7 percent of people who received the probuphine implant stayed off of illicit opioids for at least four months of getting the treatment. That's compared with an efficacy rate of 71.9 percent in people who received the older, oral versions of buprenorphine.

This was a major breakthrough, said study authors, as the trial set out only to prove that probuphine could work as well as the oral form of the drug.

"We originally licensed probuphine in 2012, thinking they would approve the drug back in 2013. But the application was denied, due to what the FDA deemed a faulty trial design," explains Behshad Sheldon, CEO and executive director of Braeburn Pharmaceuticals, who spoke to us just hours before the FDA ruled to approve probuphine for use in the United States.

According to Sheldon, past clinical trials showed that probuphine performed better than a placebo in people who were new to an MAT regimen. However, federal officials said they were concerned that the drug did not contain a high enough dose of buprenorphine to be clinically meaningful. The FDA also expressed concerns over the set-up of training programs that needed to be organized for doctors to be able to implant and remove the device safely, as well as recommendations over the types of people with opioid dependence best suited for the drug.

"The original two efficacy studies conducted by Titan were in patients who were brand- new to treatment, so yesterday they were on heroin, then the next day they were in the clinical trial," explains Sheldon. "But from a common sense standpoint, it makes sense to put a six-month implant in someone who is already doing well [on buprenorphine therapy]. So we came to an agreement with the FDA on the right study design to test in a more stable patient population."

Over the next two years, Braeburn, Titan and the FDA worked together closely to bring the implant up to agency standards. In August 2015, the drugmakers re-submitted their New Drug Application (NDA) to the agency, which accepted it a month later. However, in February, just after the FDA panel recommended approval of probuphine, the agency decided to extended its decision deadline on probuphine by two months.

Throughout the waiting period, addiction advocates pushed federal authorities to hasten the approval of probuphine with letters, position papers and advocacy initiatives. According to Sheldon, at the time of the extension, thousands of doctors across the country had already signed up to become certified in inserting and removing the device. Now that probuphine is approved, the roll-out of the drug to addiction recovery facilities across the country will begin in just a few weeks.

Addiction treatment specialists and advocates who have been fighting for probuphine since 2013 say there are a few major advantages to using the implantable buprenorphine treatment over the traditional oral versions of the drug.

Obviously, there is the advantage of adherence. The probuphine implant would also spare people hoping to kick their addiction the hassle and often stigmatizing experience of having their buprenorphine prescriptions filled by a pharmacist. Plus, the implant drastically cuts back on the chances of diverting buprenorphine, which many advocates argue holds back the number of doctors willing to prescribe MAT in the first place. Currently, legal buprenorphine is the third-most confiscated opioid drug by the U.S Drug Enforcement Administration (DEA), a fact that makes many doctors wary of prescribing it to their patients over other drug-free regimens.

"Although the FDA has recently approved other buprenorphine products, none fill the specific needs that the implant can, especially one that cannot be diverted, cannot be overdose[d] on, cannot be stolen, sold or lost, cannot be abruptly stopped by the patient, and carries no risk of accidental pediatric exposure," argued activists at the National Alliance of Advocates for Buprenorphine Treatment (NAABT), a Connecticut-based nonprofit that aims to educate the public about opioid addiction and available treatments. In the months leading up to FDA approval, the

NAABT launched several letters and position papers to help open up access to probuphine across the country.

NAABT also pointed out some specific subgroups that may benefit from the probuphine implant over traditional buprenorphine therapies, such as people who need to travel abroad, or people like truck drivers, flight attendants and others who travel on the job and may not be able to fill a prescription at the same place every month. Advocates also argued that the device virtually assured medication compliance for the first six months of treatment, "arguably the most important period," and pointed out its promise in places like prisons, where buprenorphine is often diverted.

However, some addiction treatment specialists are wary of the lofty promises made by the new device. Robert Ben Mitchell, D.O., who runs an office-based opioid treatment facility in Miami, and has been working in the field of MAT for the last 15 years, says he is still going to rely on traditional buprenorphine treatment for his practice.

"It allows patients to manage individual dosages, including reducing and/or skipping dosages as they feel able to do so. This, in turn, allows patients to self-wean off the medication when they are ready. You can't do that with probuphine," argues Mitchell. No matter what, the device will deliver around 8 mg of buprenorphine into the body, which, although considered to be a "moderate" dose of the drug, can be a much higher dose than what some patients take to help manage their opioid addiction with oral forms of buprenorphine.

Another major concern among critics of probuphine is the unintended effects of having a constant dose of buprenorphine in the blood in the event of an accident or major surgery.

"Can you imagine having an emergency appendectomy or bone fractures set after a car accident and not being able to use pain medication for two to three days after your operation because you have [the] probuphine [implant] inside of you?" Mitchell asks. In fact, the FDA has voiced its own concerns about possible complications of removing and inserting the device in these scenarios. Federal health authorities have also raised concerns in the past that some patients with the probuphine treatment still needed oral buprenorphine as "rescue medication" when switching over to the implant, proof that treating addiction may not be as simple as a regimented implant.

There's also a big question going around among addiction advocates over the price of probuphine. Behshad Sheldon, CEO of Braeburn Pharmaceuticals told us that the cost of probuphine will be "competitive" with "other long-acting treatments," such as Vivitrol, a buprenorphine injection that costs around $1,000 a month. According to a recent press release from the company, probuphine will cost $4,950 for a six-month course of treatment. Comparatively, the price of traditional buprenorphine treatment is about half of that, costing around $500 a month, including doctors visits.

However, FDA approval doesn't mean that addiction treatment specialists across the country will be forced to prescribe the drug to their patients. Instead, Braeburn and Titan hope to position probuphine as yet another tool in the anti-addiction arsenal, meant for specific patients who are searching for a more tailored approach to buprenorphine treatment.

In fact, current recommendations by both drugmakers call for probuphine to be prescribed only in cases where a person has spent three months without exhibiting any evidence of illegal opioid use and at least six months taking 8 mg or less of oral buprenorphine daily. The device also must be used as part of a complete addiction treatment program, involving counseling and psychosocial support.

Common side effects of getting the probuphine implant include injection-site pain, itching and redness. From then on, the drug's effects so far seem to be similar to that of traditional buprenorphine treatments, including headache, depression, constipation, nausea, vomiting, back pain, toothache and throat pain. Studies also show that the implant may help cut back on some of the gastrointestinal distress caused by buprenorphine patches and pills.

When can we expect probuphine to make it to U.S. markets? "We'll probably need about three weeks to actually finish the packaging and print prescribing info, and then, most importantly, we will be starting the training program with physicians who need to be certified on how to implant and remove the device," says Braeburn Pharmaceuticals' Sheldon.

According to official plans set out by drugmakers, doctor trainings on the probuphine implant will last four hours and will take place on Fridays, Saturdays and Sundays, per doctors' requests. Sheldon says the trainings focus first on the states with the highest number of overdose deaths, and in areas where buprenorphine is already widely used. New York and Los Angeles currently have the largest number of pre-registered doctors for the probuphine trainings, however, a wide array of training programs in smaller cities, especially in the Midwest, have also been set up.

"We're trying to go to the people instead of making them come to us," says Sheldon. To date, Braeburn has set up 262 probuphine trainings across 55 cities, and almost 5,000 doctors have already signed up for the classes. Last weekend, Braeburn conducted its first training session, certifying the first 121 doctors in the country on how to insert and remove the implant.

Now that FDA approval is official, drugmakers are also looking at expanded uses for probuphine, including its future potential as an opioid alternative for patients with chronic pain.

"We've had a lot of interest from clinicians who told us that they already use buprenorphine for pain in some instances," says Sheldon, noting that the opioid alternative is far less addictive in many instances than traditional prescription painkillers. Braeburn aims to start talks with the FDA around probuphine's use for chronic pain immediately, but the testing involved in pushing that next approval endeavor is likely to take a few years.

So while the push to approve the new buprenorphine implant as America's next tool to combat its growing opioid crisis has been successful, it may take a few years to see probuphine's potential in this arena fully realized. In the meantime, drugmakers and advocates alike are celebrating the FDA's decision as a major move forward in the way this country is addressing the millions of people struggling with addiction.