Long Wait For HIV Diarrhea Drug Inspires Lawsuit

Even after receiving priority review from the Food and Drug Administration, Fulyzaq, the first drug to treat diarrhea related to HIV meds, has been slow to market. A lawsuit by the biotech firm that developed Fulyzaq accuses its pharma partner of impeding the drug's progress, possibly on purpose.

June 6, 2013 By Benjamin Ryan

Christopher goes through 24 rolls of toilet paper a week. At 55, the Los Angeles resident, who is retired and on disability and who asked to go by only his middle name because he prefers to keep his serostatus private, has been living with HIV since the 1980s. Over the past decade or so, he has grappled with the increasingly debilitating gastrointestinal side effects of his HIV meds.

The only effective remedy for his constant diarrhea is a tincture of opium, which leaves him sluggish and depressed and which is hard on his stomach. Without it though, he says, he couldn't leave the house.

On December 31, 2012, the U.S. Food and Drug Administration approved what appeared to be the answer to Christopher's prayers: Fulyzaq (crofelemer), the first drug approved to treat diarrhea in people taking HIV antiretrovirals (ARVs).

Fulyzaq's history began with Napo Pharmaceuticals, a San Francisco biotech company, which discovered and initially developed the drug. In 2008, Napo signed a collaboration agreement with Salix Pharmaceuticals, a company specializing in therapies for gastrointestinal disorders, in the quest to bring Fulyzaq to market: completing clinical trials, applying to the FDA, then handling manufacturing, marketing, sales and distribution.

While diarrhea among HIV-positive people the United States is not as epidemic as it was in the pre-ARV era, it remains a major detriment to the lives of a substantial proportion of those living with the virus. The FDA recognized this significant and unmet need when it granted Fulyzaq priority review status at the end of 2011, which in theory would have given the drug a speedier approval process.

The actual release of the drug has hardly been prompt. By May 9, Salix explained in a press statement that the company was "working with the FDA to finalize the release specifications" of

Fulyzaq and would “expedite the commercial launch” of the drug once that process was complete—they hoped “in the very near future.”

Finally, in a June 6 statement, Michael Freeman, Salix’s head of investor relations and corporate communications, said, “Fulyzaq is currently stocked and available to patients with a prescription through Walgreens Specialty Pharmacy, select Walgreens HIV Centers of Excellence and other select pharmacies. Fulyzaq can be made available to most any pharmacy in the country within a 24 to 48 hour timeframe.”

“Prescriptions are being filled as we speak,” says Salix’s attorney, Benjamin J. Razi, a partner at Covington & Burling LLP in Washington, DC. “It’s just happened in the recent days, recent weeks.”

In keeping with the running disagreements between these two companies entangled in a partnership concerning Fulyzaq, Napo representative William Ohlemeyer, a partner at Boies, Schiller & Flexner in Armonk, New York, contradicts Salix’s claim about the drug’s availability.

“Notwithstanding assertions by Salix to the contrary,” he responded in his own June 6 statement, “Napo has been told by physicians who have written Fulyzaq prescriptions and patients interested in filing those prescriptions, that the drug is not yet available from Walgreens or elsewhere."

Despite repeated requests on the part of POZ, Walgreens has yet to produce an answer as to the drug’s availability.

In the pharmaceutical industry, time is money. The patent on Fulyzaq expires in January 2018, although Napo does expect to receive a four-year extension. So Fulyzaq’s absence on pharmacy shelves has done more than just frustrate people such as Christopher waiting anxiously for relief. A lawsuit over the drug is brewing between Napo and Salix.

Napo has accused Salix of breach of contract for deliberately, or unreasonably, holding up the drug’s progress, and also of diverting resources to and favoring another drug in Salix’s portfolio, Xifaxan.

Fulyzaq is unique in that it acts locally in the intestine as a mass and is not appreciably absorbed into the rest of the body. Consequently, it has no known drug-drug interactions. It also doesn’t paralyze the gut as with narcotic-based therapies like Imodium; rather the drug blocks the secretion of chloride into the gut, which in turn lowers the amount of water excreted into the gut, thus reducing diarrhea. Also, Fulyzaq is not addictive, as are opiate therapies.

“It’s a life-changing drug,” says Jerry Ernst, MD, medical director of ACRIA in New York City, one of the major clinical trial sites where Fulyzaq was studied. He predicts it could, for example, help inexpensively save lives of those around the world who are affected by cholera, which is a major cause of potentially fatal diarrhea.

Meanwhile, Salix’s Xifaxan is an antibiotic approved to treat traveler’s diarrhea and is also

approved to lower the risk of worsened brain function as a result of overt hepatic encephalopathy, a condition found in those with advanced liver damage in which the liver cannot properly process toxins. Napo alleges that after Salix acquired licensed rights to Fulyzaq doctors began prescribing Xifaxan off-label for irritable bowel syndrome (IBS)—an indication that, as Salix is on record stating, comprised about half of Xifaxan's sales by 2011. According to Napo, this period is when the two drugs' futures began to clash, since Fulyzaq shows promise as a possible drug to treat IBS.

The potential financial earnings for Fulyzaq's use in the HIV market is perhaps $150 million to $200 million a year in peak sales in the United States. Meanwhile, IBS represents the possibility for a billion dollar market.

"Xifaxan became their priority at the expense of [Fulyzaq]," Ohlemeyer says of Salix's business decisions over the past few years, "and we think that's a violation of the contract."

Napo's CEO, Lisa Conte, has spent more than two decades and over $300 million of investors' money in her quest to use a botanical element as the source of a major pharmaceutical drug. After years of investigating possible agents, her team honed its sights on crofelemer (Fulyzaq's generic name), which is a chemical entity isolated and purified from the bark latex of a tree in the South American rain forest, and which is being sustainably harvested to support drug development.

An at-times unflattering 2011 Forbes article portrays Conte as an ironic hybrid of crafty businessperson and financial ticking time bomb: incinerating cash and guiding Napo's predecessor, Shaman Pharmaceuticals, through bankruptcy, all while pulling off slick financing maneuvers to keep her ship afloat—feats worthy of MBA case study reports.

Whether Conte indeed boasts the right stuff in the cutthroat business of biotech depends on the side of the lawsuit doing the talking. In its recently filed response to Napo's suit, Salix portrays the company as a flailing enterprise in need of rescue. The legal response claims that Napo, with its lack of experience in bringing a drug to the fore, placed unrealistic expectations on Salix and second-guessed the company's business decisions without just cause.

In a recent interview, Conte rejoins that her company approached Salix not to save Napo from ruin, but to take Fulyzaq, finish its development process and then commercialize it with the wherewithal naturally lacking in a relatively small biotech firm.

"They seemed like a pretty good match," says Napo's Ohlemeyer of the initial partnership between the two companies. "The problem, of course, is that [Salix has] refused to accept the advice of, or collaborate with, Napo. They squandered the skill and experience that Napo possessed in this area. And they really, in simple terms, didn't put the time and the money that was necessary into manufacturing the drug in commercial quantities soon enough."

"Napo is dismayed at the disregard for the patient community, poor communication, and unavailability of this important new medicine since its approval," Conte said in a June 6 statement.

Salix, which has spent more than $50 million to license, develop and begin the manufacturing process for Fulyzaq, maintains in its recent court filing that there is no evidence supporting Napo's claim that the company dragged its heels in completing the clinical trials and in submitting a new drug application to the FDA.

Outside of that bone of contention and the more than $160 million in damages Napo is seeking, there is a disagreement between the two parties over what their contract says in regards to Salix's obligation to pursue the drug for other indications. According to Napo, Salix is required to commercialize Fulyzaq for use in people with IBS, and for pediatrics and infectious diarrhea. Salix insists its contractual responsibility ends with HIV and that pursuing the other indications is at the company's discretion.

"Salix is following the same development strategy that Napo followed, which was to pursue approval of Fulyzaq for the treatment of diarrhea in HIV patients, first, and to get that on the market, which we've done," Razi says. "And we're now at the period where other options can be considered and can be addressed."

Razi would not comment on whether there was research and development under way at Salix to pursue Fulyzaq for other indications.

Ultimately, Napo wants to sever ties with Salix and handle the sales and distribution of the drug itself until the biotech can get up and running with a new partner that, in the company's view, can more effectively deliver Fulyzaq into the medicine cabinets of those who need it. Whether Napo may void its contract with Salix is up for the courts to decide.

As for the reasons why the drug is apparently only just now making it to market, Razi declined to elaborate beyond pointing to Salix's $20 million investment in a manufacturing plant as an indication of the company's commitment and stating:

"Salix has reasonably and appropriately timed its very significant manufacturing expenditures and investment to the development on the clinical and regulatory front. That prudent timing and planning is today bearing fruit for patients. Salix is doing everything in its power to get product to patients who need it, and patients who need it are receiving it."

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http://beta.docker.poz.com/article/Napo-Salix-24051-8383