Parental Quest Bears Fruit in a Kidney Disease Treatment

By **ANDREW POLLACK** APRIL 30, 2013

Nancy Stack and her daughter Natalie in Washington, where they awaited word about federal approval for Procysbi. Daniel Rosenbaum for The New York Times

Reluctant to say it aloud, Natalie Stack wrote her 12th birthday wish on a restaurant napkin: “To have my disease go away forever.”

A decade later, her wish is a step closer to being realized.

On Tuesday, the Food and Drug Administration approved a new drug developed with early financing from a foundation that Natalie’s parents established in response to that plea. The drug, which will be sold by the Raptor Pharmaceutical Corporation under the name Procysbi, is for nephropathic cystinosis, an extremely rare inherited disease that, if untreated, typically destroys the kidneys by age 10 and even with a kidney transplant can lead to death by early adulthood.

The story behind Procysbi’s development is yet another example of the important role that determined parents and disease foundations can play in supporting drug development, particularly for rare diseases.

But Procysbi’s approval could also raise troubling questions about whether society can afford to pay extremely high prices for drugs that treat rare diseases. That is because Procysbi is not a new chemical entity, but rather a more convenient and more tolerable version of an existing drug. The existing drug costs about $8,000 a year, whereas Procysbi will cost $250,000 on average.

High prices are typical for drugs to treat so-called orphan diseases. The health care system has tolerated that because, given the small numbers of patients, the overall cost is not that high. But as the orphan drug business model becomes increasingly popular among pharmaceutical companies, the collective cost of the drugs is beginning to mount.

The market research firm EvaluatePharma recently predicted that orphan drugs will constitute 15.9 percent of spending on prescription drugs by 2018, up from 5.1 percent in 1998. And a survey of 50 insurers and pharmacy benefit managers by J. P. Morgan found that drugs for rare diseases would be one of the areas increasingly subject to scrutiny and possible restrictions on use.

While many medicines are unpleasant to take, the existing drug for cystinosis — Cystagon, from Mylan Inc. — literally stinks. It has a strong rotten-egg smell that causes bad breath and body odor. It also causes nausea, vomiting and other abdominal problems. Moreover, it must be taken every six hours, which means patients have to get up in the middle of the night, or their parents must wake them.

Procysbi has the same ingredient as Cystagon but consists of enteric-coated spheres for delayed release. It can be taken every 12 hours instead of every six. The gastrointestinal side effect, halitosis and body odor, are reduced, though not eliminated, according to the parents of children with the disease.

Christopher M. Starr, co-founder and chief executive of Raptor, said he expected it would take time to persuade insurers to bear the extra cost.

“I get it,” he said. “It seems trivial when you first look at this.” He said doubters would think: “You’re dying of a disease. Take it every six hours if that is what you need to do.”

But Dr. Starr argued that the “subtle advantages” of Procysbi “add up to a significant benefit.” He said as many as 80 percent of patients skip doses of Cystagon, which studies have shown can lead to more rapid deterioration of the kidneys, eyes and other organs. The more tolerable Procysbi should allow people to better take their medicines.

Dr. Starr said the price reflected the value of the drug and the need to recoup Raptor’s development costs. The company’s regulatory filings show it has spent $37.4 million on research and development of the cystinosis drug from the company’s inception in 2005 through the end of 2012. Total corporate expenses in that period were $110 million.

Procysbi is the first drug approved for Raptor, which is based in Novato, Calif. Analysts expect sales could exceed $100 million annually. Shares of Raptor closed at $6.90 Tuesday, up 5 percent.

Procysbi treats a very rare disease. Only about 500 people in the United States, and 3,000 worldwide, are estimated to have cystinosis, according to the F.D.A. The disease is characterized by a buildup in cells of the amino acid cystine. The buildup damages the kidneys and eyes and eventually the thyroid gland, muscles and other organs.

Procysbi works by breaking down cystine. Its active ingredient is cysteamine, the same as in Cystagon. Cysteamine was first shown to work in the 1970s by a team led by Dr. Jerry A. Schneider at the University of California, San Diego. The F.D.A. approved Cystagon in 1994.

Mylan said Cystagon was not a financially meaningful product to the company. “We will monitor the market acceptance of new treatments for cystinosis and continue to provide access to Cystagon as long as it continues to fill an unmet need and patient demand for it exists,” Mylan said in a statement Tuesday.

When Natalie Stack was born in 1991, “we were told we’d be lucky if Natalie lived to graduate from high school,” said her mother, Nancy Stack, who lives in Corona del Mar in Southern California. But it was not until reading Natalie’s birthday wish in 2003 that Ms. Stack and her husband, Geoffrey, a real estate developer, formed the Cystinosis Research Foundation, raising almost $400,000 at an initial cocktail party.

At about the same time, Dr. Ranjan Dohil, a pediatric gastroenterologist at the University of California, San Diego, who was exploring why Cystagon was so hard to tolerate, stumbled upon something. Testing a child who had a feeding tube, Dr. Dohil accidentally delivered the drug to the child’s small intestine rather than the stomach. He found the drug was absorbed better.

To investigate further, Dr. Dohil, who had been one of Natalie's doctors, received almost $350,000 from the Stacks' new foundation to test more children, delivering the drug alternately to their stomachs or intestines through a tube that started in the nose.

"It was actually a real leap of faith on their part," Dr. Dohil said of the Stacks.

Dr. Dohil observed that delivering the drug into the intestine every 12 hours seemed as effective as putting it into the stomach every six hours. So with more than $600,000 in additional money from the foundation, he had some Cystagon pills coated so they would pass through the stomach and reach the intestine. Seven children, including Natalie, began taking them.

"Once they took it twice a day, it was hard to stop," Dr. Dohil said. The university licensed the patents to Raptor in exchange for payments and royalties. The Cystinosis Research Foundation will not receive any proceeds from sales of Procysbi since it did not stipulate profit-sharing when it gave its grants to Dr. Dohil.

To win approval, Raptor ran a six-week trial involving 43 patients whose disease was already being well controlled by Cystagon. The trial showed that Procysbi, which was called RP103 during its development, was no worse than Cystagon in controlling the amount of cystine in white blood cells.

The trial was too short, however, to demonstrate that RP103 made patients take their medicine more faithfully or preserved kidney function better than Cystagon. But Dr. Starr of Raptor said most patients have continued taking Procysbi since the trial ended and kidney function has been preserved.

Teresa Partington of Sacramento, whose 8-year-old twins took Procysbi in the clinical trial, said the new drug was a godsend, eliminating not only the nighttime awakenings but the midday dose taken at school. She said she had talked to her children's classes when they were taking Cystagon to explain why the children might smell bad.

With Procysbi, "I can't smell it on my son anymore at all," she said. "I still smell it occasionally on my daughter." She said her daughter no longer vomits, though her son occasionally does.

Ms. Partington, who is on the board of the foundation, said patients and their parents owed gratitude to Ms. Stack. "She pretty much made all this happen," she said.

Natalie — who declined, through her mother, to be interviewed — is a senior at Georgetown University interested in becoming a social worker. She is still taking the enteric-coated Cystagon she started taking in 2006 as part of Dr. Dohil's study, but she will soon switch to Procysbi.

Her kidneys have held steady and she is one of the few patients her age not to have undergone a kidney transplant, Ms. Stack said. Still, studies have shown that even those who take their medicine religiously can suffer organ damage eventually.

Ms. Stack said Procysbi should be covered by insurers.

"It does seem extreme to have it that high," she said. "But as a community, our bottom line is getting better treatment for our children. And we know

that this will change our kids' lives."

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