If a medicine is too expensive, should a hospital make its own?

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When Marleen Kemper was a child, she watched two of her primary-school classmates get ill. One had a brain tumor, and the other contracted an infection in his gut. Both of them died. Kemper was around ten at the time, and knew that she didn't want to see another friend perish. She told her parents she wanted to do something that

would prevent others dying. She wanted to be a doctor.

But training is hypercompetitive in the Netherlands, where Kemper was growing up. She didn't quite have the grades. She liked chemistry, so chose a career in pharmacy instead. She studied for six years, and did a residency for another four. Today, she's a highly respected hospital pharmacist based at Amsterdam UMC's Academic Medical Center, a cavernous building crafted out of concrete on the south-east fringe of the Dutch capital.

To understand what happened next, you have to understand several things about Kemper. Two date back to her childhood. One was those early experiences of losing friends to illness, which ensured she'll do everything she can to make sick people better.

The second is that, though she's highly accomplished, Kemper is self-admittedly hard-headed, and has always had a rebellious streak. She once dyed her hair black to stand out from the crowd. Sometimes she likes to shock people.

Which leads into the third, more recent trait: a steely determination to do right by her patients, whatever the cost. And the cost can be great. In 2017, when the price of a drug to treat a rare genetic disorder skyrocketed, Kemper wasn't happy. The result was a dispute that's still going on today and has spread beyond the four walls of the UMC hospital. It's spread beyond the city of Amsterdam. And it's even spread beyond the borders of the Netherlands.

Most of us never have to worry about chenodeoxycholic acid (CDCA), one of the two primary bile acids produced by our livers. But for a tiny fraction of us, a rare genetic trait means we end up short.

Having this gene variant prevents the body from creating sterol

27-hydroxylase, a liver enzyme. Without it, the liver won't convert enough cholesterol into CDCA. The result is an overabundance of other bile acids and substances, which then get pumped out of the liver and through the body, causing untold damage.

The illness that results is called cerebrotendinous xanthomatosis, or CTX. It can cause cataracts, dementia, neurological problems and seizures, but it can be treated. Since the 1970s, the pharma industry has been able to produce CDCA, and so people who need it can supplement their shortage. The system worked well; the drug was relatively cheap for such a niche illness. A year's treatment cost around €30,000 per patient.

Until suddenly it didn't. In 2017, Leadiant Biosciences, which was supplying CDCA to these patients in the EU, raised the price of its version of the drug—known as CDCA Leadiant—to over €150,000 per patient per year.

The price increase soon had an effect. The Netherlands has an insurance-based health system, and in April 2018, Dutch insurers—who had been paying for 50 or so patients across the country to receive the drug—balked at the fivefold increase, refusing to pay. Patients unable to pay themselves would have gone without treatment, so Kemper—whose hospital was one of the treatment centers for CTX—stepped in. Amsterdam UMC would produce the medicine for these patients itself, at cost price.

She was upset, she admits. "Patients have a medical need. If those patients with CTX don't get their medication, they get neurological implications, they get complications with their cholesterol and dementia, epilepsy… it is an essential medicine."

Anyone wanting to manufacture a drug must get a marketing authorization to do so. But Leadiant had become the only game in town,

the owner of exclusive rights to manufacture CDCA commercially in the EU.

Yet there was a solution. Under EU rules, pharmacies can make (or "compound") a prescribed drug on a small scale for their patients.

So Kemper began researching where she could find the ingredients to make CDCA. It was difficult: in the pursuit of better margins, vast numbers of manufacturing companies have closed their factories across the world and concentrated their efforts in China, where the costs of producing pharmaceutical ingredients are lower. Just one European company manufactures the ingredients to EU standards.

Kemper approached them, and they declined to supply her the raw material. In the end, she found a Chinese manufacturer instead. She went to the hospital's executive board and gained approval to manufacture the drug. It cost the pharmacy €28,000 per patient per year—pretty much exactly the same as the price of the drug beforehand.

CDCA wasn't initially used to treat CTX. Originally it was developed to treat gallstones. This main use of the drug—which from the mid-1970s had been sold in the Netherlands as Chenofalk—became outmoded when the standard procedure to deal with troublesome gallstones became to just cut out the gallbladder entirely.

At the turn of the millennium, Dutch doctors started using Chenofalk off-label to treat CTX—a practice that carried on for several years. At this time, in the mid-2000s, a year's supply of the drug cost less than €500.

But in 2008, Leadiant acquired the rights to Chenofalk. Then, nine days before Christmas 2014, it succeeded in getting its version of CDCA classified as an "orphan medicine" for treating CTX. That classification gave Leadiant the exclusive right to manufacture its CDCA drug

commercially in Europe for the next ten years. Leadiant then took Chenofalk off the market in 2015.

Introduced by EU regulation in the year 2000, orphan drug classification is given to drugs that treat serious illnesses that affect fewer than five in every 10,000 people in the EU. Its purpose is to help companies recoup the costs of developing treatments that would otherwise be unlikely to generate a profit. Without it, the pharma industry wouldn't be incentivized to seek new drugs for the rarest diseases.

But in this case, CDCA was already known as a CTX treatment, with Chenofalk having been used off-label to treat it for years. Kemper believes that Leadiant is getting the financial benefits of orphan designation, but for a drug that had gone through development and been released to market long ago. "There were publications already in the 1980s," she says. "There's no patents, nothing. It's really bizarre."

Kemper isn't the only one concerned about the price rise and CDCA's orphan drug status. In September 2018, a lobby group, the Dutch Pharmaceutical Accountability Foundation, asked the Dutch competition authority to investigate the price increase. And this spring Test Achats, a nonprofit consumer-protection organization in neighboring Belgium, lodged a complaint against Leadiant with the Belgian Competition Authority.

"We noticed that in 2005, the price for the treatment of a patient in one year was around €500. Now it's more than €150,000," explains Laura Marcus, legal counsel to Test Achats. "It's bad for the sick person but also for the Belgian health system, which is paying most of the [cost of the] treatment."

When a drug company raises the price of its treatment, and a hospital pharmacy decides not to accept the increase but instead endeavors to

compound its own version, undercutting the drug company's price, things tend to get interesting.

In June 2018, Kemper received a phone call from the Dutch health inspectorate. It had received a letter of concern—who it came from, Amsterdam UMC doesn't know, though the health inspectorate has said it was acting in response to an enforcement request from Leadiant—with a long list of things for the investigators to check.

Kemper took the news in her stride. She had expected a rocky road. "As a pharmacist, I am a professional and I know what I'm doing, and we have standards for compounding," she explains. So she wasn't worried when a team of four inspectorate monitors turned up at the door of her pharmacy in Amsterdam that summer. Two were there to take samples of the raw materials she was using to compound CDCA, and to ensure that all the correct processes were being followed. They rifled through the reams of paperwork and procedures that Kemper had spent hours developing for her staff to follow, while the other two inspectors combed through coverage of the case to ensure that Kemper and her team weren't advertising their work, which isn't allowed for medicines that haven't been given market authorization.

The lab checked out: its processes were up to standard, and the paperwork was all in order. But in July Kemper got a phone call that floored her: the inspectorate's analysis of the raw materials her pharmacy was using to compound the CDCA had discovered that they weren't up to snuff. Two components found in it were above allowed limits.

"As a professional you think: what did I miss? It was very emotional, a bit heavy," she says. With the board of directors at the hospital, Kemper decided to immediately withdraw the product from patients; the health insurers said they'd step in and cover putting the patients back on the Leadiant version of the drug.

Kemper personally called the 50 or so patients she was providing with the drug. "The first one was hard," she admits. "I expected they'd be angry or something like that. But no, no one [was]. The patients said: "Well, please go on with this job.""

The Dutch inspectorate has said that Kemper can resume compounding CDCA provided she can find a raw material that doesn't contain impurities—something Kemper is keeping tight-lipped about.

So, if she can get the materials she needs, Kemper is hopeful to be able to continue compounding CDCA in the future.

But for now, it's back to square one—paying the full price for CDCA Leadiant.

These events have had wider consequences. What was initially a dispute inside the Netherlands has bled across borders, with Belgian patients with CTX now being affected.

It started with a conversation between the Dutch and Belgian health ministers shortly after Kemper's production of CDCA was halted, says Thomas De Rijdt, head of pharmacy at University Hospitals Leuven. The Dutch minister wanted to know from his Belgian counterpart why Belgian hospitals were able to make the same drug without any issues.

"For Belgium, we have about ten patients," De Rijdt says. "So ten patients are helped with the preparations from our hospital and the University Hospital in Antwerp."

These hospitals had been compounding CDCA capsules for CTX patients for years. Leuven had sourced raw materials that had been tested and approved by a laboratory accredited by the Belgian government. But when the case in the Netherlands started entering conversation at

diplomats' dinners, the Belgian government wanted to double-check that its raw materials were OK.

It ran a second battery of tests—with a different accredited laboratory—which came back with a problem. A single impurity was found. The government ordered a quarantine of the raw material and recalled all the CDCA it had made.

"The patients had to return all their medication," says De Rijdt. Recalling every capsule of the drug from Belgium, and freezing the work of the only two suppliers in the country, meant that people with CTX were suddenly left without any medicine.

"If you know the disease, you know you can deteriorate very quickly," says De Rijdt. This was a problem. So, he says, the hospital pharmacists, the National Institute for Health and Disability Insurance, the health minister and the pharmaceutical inspectorate hit upon a solution. For a year, the Belgian government would reimburse the costs of Leadiant's drug, allowing those patients to still be treated (normally the government only reimburses a portion of a person's health costs, with the rest being picked up by the patient or insurance). Over the course of that year, the relevant authorities would then work together to adapt the requirements a raw material must comply with—to allow versions of drugs with minor impurities, providing they pose no threat to the patient.

"We have bought time to find a solution with the compounding, because we think by compounding we can save healthcare a lot of money for the same quality of therapy," says De Rijdt. He hopes to have a solution by the end of 2019.

But in early September, things took another turn. Wouter Beke, the Belgian consumer affairs minister, used his price-regulation powers to bring down the price of CDCA Leadiant to just over €3,600 a

month—roughly a quarter of the amount Leadiant was charging. If the drug becomes more cheaply available in Belgium, says De Rijdt, then it could end up being exported and available at a lower price elsewhere.

But exactly how this will pan out remains unclear. In the meantime, Beke has urged the Belgian Competition Authority to prioritize investigating Leadiant, following the complaint lodged by Test Achats.

Debate over what constitutes a fair price for drugs isn't anything new. Nor is it limited to Europe.

Because of his willingness to play the bad guy in the press (and an odd moment when he bought a Wu-Tang Clan record), Martin Shkreli has attracted more criticism on drug pricing than perhaps anyone else. In 2015, Turing Pharmaceuticals, of which Shkreli was CEO, raised the price of its recently acquired antimalarial drug Daraprim, also used to treat AIDS-related illnesses. A pill went from $13.50 to $750 overnight—a 55-fold increase.

Shkreli's capitalist tendencies were criticized by almost everyone. This was unlike the situation with CDCA Leadiant—there was no argument that this increase was to cover Daraprim's development costs—and Shkreli himself was unrepentant: "If there was a company that was selling an Aston Martin at the price of a bicycle, and we buy that company and we ask to charge Toyota prices, I don't think that that should be a crime," he told reporters.

But the Daraprim situation was just the highest-profile example of a contest that is going on constantly between big pharmaceutical companies seeking to profit from drugs and medical staff on the frontline who worry that such profit-seeking does damage to patients needing treatment. (For what it's worth, a competitor to Turing Pharmaceuticals announced soon after that it would produce a

compound drug containing the same active ingredient in Daraprim—pyrimethamine—for $1 a pill, rather than the $750 Shkreli wanted to charge.)

One front in this battle has recently opened up in the US. In May, more than 40 states filed an antitrust lawsuit against some of the world's biggest manufacturers of generic drugs, alleging they that have colluded to fix the price of more than a hundred medicines over a number of years. When prices should go down after a drug's market exclusivity ended, the antitrust lawsuit claims that many prices have instead shot up—in some cases by more than 1,000 percent.

And back in Europe, the consumer organization Euroconsumers—of which Test Achats is part—is investigating the prices of other drugs beyond CDCA. "We've noticed a few problems with a few other drugs," says Laura Marcus of Test Achats. "It's often about drugs that are able to cure or deal with rare diseases. For sure, it's not only CDCA."

No one doubts that developing drugs costs money. A 2016 paper in the *Journal of Health Economics* estimated that the average cost of developing a prescription drug to the point of reaching the market is nearly $2.6 billion.

But the lack of hard, openly available statistics on the cost of drug development is something that many people, including Marcus and Marleen Kemper, want to change. "In most of the cases, society is willing to pay some price," says Kemper, "but now the discussion is: what is an acceptable price?"

Marcus acknowledges that Leadiant has to cover its costs, but she thinks that cannot explain the rise of CDCA to over €150,000—"the profit cannot be that high." When I ask her how much profit she thought Leadiant was making from the drug, she admits she doesn't know. "Of

course we don't have access to those numbers," she says. "That's what the Belgian Competition Authority is opening an inquiry for—to know more about the figures and the costs the company has to bear." However, when the price for CDCA has surged from €500 to over €150,000, "nothing justifies it, because there was no new research, no new nothing," she says.

Leadiant rejects this. Although CDCA had been authorized in the past, the company says that "the active pharmaceutical ingredient as well as the manufacturing of the finished product needed to be upgraded" to make sure that its version was compliant with current EU standards. These, Leadiant says, are more extensive and significantly more strict today than they were when earlier CDCA drugs were developed.

Leadiant says that its CDCA "is not a 'copy' of an old product." The very fact that it gained orphan drug status proves this, it argues. The company also says that "there was no robust evidence that CDCA was effective in CTX until Leadiant produced the data." Demonstrating this, it says, required "entirely new studies, creating new data sets"—which make up "the largest ever collection of clinical data for CTX."

"CDCA Leadiant has been developed and brought to market at substantial cost," the company says. "Our pricing is justified by our costs and investments."

But the problem is not just that Leadiant's drug is so expensive: potential alternatives have disappeared. Willemijn van der Wel, a lawyer working at European law firm AKD, has written about Leadiant's connection to competitors who previously produced CDCA. After buying the marketing authorizations for other products that contained CDCA, he says, "Leadiant began to withdraw these alternative CDCA products from the market, until only one CDCA medicinal product remained." Marcus has also queried what has happened to these products that might

have been competitors to Leadiant's. But, she says, it's not clear what is behind their CDCA monopoly.

Leadiant, though, says that it's willing to negotiate a lower price for its drug with the Dutch Ministry of Health and Dutch insurance companies. "The only reason an improvement has not been determined yet, is that the insurers have been uninterested or unwilling to enter into any substantive negotiations," it claims. (Leadiant did not respond to follow-up questions asking for more details of the negotiations, or what level of price reduction the company was offering.) It also emphasizes that it has not taken legal action against the UMC hospital for seeking to compound its own CDCA, but that it is "involved in a legal discussion with the Dutch Inspectorate about the interpretation of EU and Dutch medicines law."

Regardless of the outcome of such discussions, something needs to be done. Having pharmacies self-compound medicines is not a sustainable model—it might reduce incentives for developing drugs for rare conditions.

It also, Leadiant argues, exposes patients to risk. Pharmacies do not have to have their compounding processes checked by the European Medicines Agency or the national regulator. "There is no product control by any independent regulatory authority before or after compounding."

When it comes to market authorization and orphan drugs, Leadiant says, "it should not be about small or large scale, but safe scale."

Marleen Kemper's husband warned her that taking on Leadiant would be more difficult than she first thought. "He said, "With this initiative, don't be naive,"" she recalls. "The pharmaceutical industry is very powerful, so you really have to have back-up from the [hospital] board"—which she had. More than a year into her attempt to make her own version of the

drug, she's recognizing just how deeply dug in both sides are to their positions.

She's at pains to point out that she's not against the pharma industry. "What people forget is that the pharmaceutical industry is responsible for a lot of innovation." But if drug pricing means that patients potentially get left behind? "Then I'm getting angry," she says.

But righteous anger alone can't sustain someone over a months-long case involving lawyers and regulators, not least when they're also raising a family, running part of a pharmacy that's actively studying hundreds of drugs, and doing their job keeping patients supplied with medicine. At times Kemper has felt frustrated and worn down by the effort of taking on the price rise—but she vows to continue.

"I've said that sometimes I've thought, well, I'll stop and quit doing it because it's too much work, too emotionally draining. But due to the support, I think we'll go on. I'm patient," she says. "It has to be solved, for the patients."

Kemper's determined that she's going to provide affordable care for her patients by following the letter of the law. "I'm using the rules," she says. "I'm not cheating." Leadiant, she accepts, has used the rules and followed them to serve its own purposes. So she will too.

"I'm allowed to make medication for patients. They don't like it? So what. I'm following the rules."

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