SICKENING:
FDA BUREAUCRACY BLOCKS
COMMON “MIRACLE DRUG”

By Mark Flatten
National Investigative Journalist
for the Goldwater Institute
How do you tell a 7-year-old child she must go back on a feeding tube?
Cassie Le is facing that terrible question.
Her daughter spent the first seven months of her life unable to eat without vomiting. The doctors ran the usual tests and tried the usual medications.
Nothing worked.
The girl was put on a feeding tube when she was 7 months old. It helped some, but she continued vomiting regularly.
“Feeding became something she feared,” Le of Texas said in a May 2016 email describing her daughter’s condition.
Finally, doctors tried domperidone, a medication widely used throughout the world to treat gastric conditions like those afflicting Le’s daughter. It worked. The feeding tube was removed about four years ago, and since then the girl has been able to eat normally.
That is coming to an end because of new rules restricting the availability of domperidone imposed by the U.S. Food and Drug Administration.
Domperidone is not approved to treat any condition in the United States. Despite that, it was relatively easy to obtain until recently through compounding pharmacies, which were able to legally get it from international suppliers and blend it into compounds to fill prescriptions from a doctor.
But in the past couple of years, the FDA has clamped down, restricting access and importation of the drug. Doctors and pharmacies risk punishment from the FDA if they prescribe or provide it to patients.
So people like Le’s daughter can no longer legally get it, except through an FDA program known as an Expanded Access Investigational New Drug (IND) protocol. The agency refuses to say how many people are receiving treatment through that program. No one younger than 12 years old can qualify, so Le’s daughter would not be eligible.
“She has been able to eat because of Domperidone,” Le wrote in an email to the FDA as part of a public comment process. “Now we are facing the inevitable reality that we will not be able to get it soon.”
– Cassie Le –

“Millions of people worldwide have regularly taken domperidone since it was first developed and marketed in 1978. It is a common treatment for a variety of gastric disorders, nausea and vomiting.
The most serious condition treated with domperidone is gastroparesis, a potentially deadly condition in which food basically sits in the stomach rather than being digested and passed normally. Patients with gastroparesis suffer from a variety of conditions, including severe and uncontrolled vomiting, bloating and abdominal pain. It can lead to other conditions such as malnutrition and dehydration.
The FDA classifies gastroparesis as a “serious or life-threatening” condition. It is the condition Le’s daughter suffers from.
The agency’s concern about domperidone is that it may cause a condition called QT prolongation. This is a pause in the electrical buildup in the heart between beats.
There are conflicting studies about how much, if any, risk of QT prolongation can be linked to domperidone in patients who are properly screened and monitored for heart
complications. Even the FDA acknowledges the connection between domperidone use and heart complications is “not well characterized.”

There are about 150 FDA-approved drugs on the market that have been linked to QT prolongation, including cardiac drugs. Only one drug is FDA-approved for treatment of gastroparesis — metoclopramide, which is sold under the brand name Reglan. However, Reglan is only effective in about 40 percent of the patients with gastroparesis, and it can cause a serious and permanent disorder characterized by uncontrollable muscle movement in the lips, tongue, eyes, face, arms and legs.

Domperidone is available in more than 100 countries, including those in the European Union, Canada and Mexico. In many of those countries, it is available over the counter. The prescription requirement was imposed only recently in the United Kingdom and some other European nations. In Canada, about 2 million prescriptions for domperidone are written annually.

In the United States, domperidone has never been approved by the FDA to treat any condition. Before any new drug can be prescribed or sold in the U.S., it must be approved by the FDA after a series of clinical trials and agency reviews to determine whether it is safe for use in humans and effective at treating the targeted condition. That process of getting FDA approval to market a single new drug normally takes more than 10 years and costs drug companies in excess of $1 billion.

Janssen Pharmaceutical conducted clinical trials and in 1985 submitted its new drug application to the FDA for approval. Those tests showed domperidone was both safe and effective. However, an FDA review panel had concerns associated with domperidone. It is a risk she is willing to take because she cannot lead anything resembling a normal life without it.

“Colleen knows about the safety concerns associated with domperidone. It is a risk she is willing to take because she cannot lead anything resembling a normal life without it. Beener, 62, of Florida, said she has taken domperidone for 15 years, and she has never had any heart problems associated with the drug. ‘I am choosing quality of life over quantity of life,’ Beener said. ‘I don’t want to spend my days in bed. And if I get 10 years less because of that, so be it. I want to enjoy my grandkids. I want to enjoy my life, and domperidone helps me do that.’

‘It certainly doesn’t make me well. But it makes me better. When I’m not taking it, I don’t get out of bed. I’m so sick I can’t do anything. But when I take it, I have days that I can go watch my grandkids swim or play soccer or whatever. As far as I am concerned, that’s the risk-reward balance that I have to take.’

Beener was a software consultant living in Florida when the symptoms of gastroparesis first surfaced about 2001. Her job required extensive travel. One day she started to vomit uncontrollably. It got so bad that she routinely carried plastic bags and paper towels on business flights, knowing she would likely vomit while in the air.

“I threw up all across this country,” Beener said. “I was in hospitals all over the country.”

Doctors tried Reglan, which worked for a while. But by 2014, the FDA was warning pharmacies they could be shut down for dispensing domperidone and doctors could face sanctions if they prescribed it, said Beener, who helped form a gastroparesis patient support group soon after she was diagnosed. Beener still gets domperidone through other sources, but doesn’t want to say what they are.

“I am going to get this drug, whatever I have to do to get it,” Beener said. “When I’m not on domperidone, I am so sick that I literally stay in bed all day. With domperidone, I can get up. ‘As long as I can get it, I don’t care. I will sacrifice and do whatever I have to do.’

– Colleen Beener
‘MIRACLE DRUG’

For 20 years, Drs. Richard McCallum and Irene Sarosiek have worked together to treat patients with severe gastrointestinal disorders with domperidone. They say the drug is for many patients the last hope for a normal life.

“We are very worried about the fact that many patients cannot get easy access to it and benefit from the medication, which we believe is like a miracle drug,” Sarosiek said. “This agent is one of the best, if not the only, drug which could help patients with gastric emptying conditions.”

McCallum is a professor and founding chair of the department of internal medicine at the Paul L. Foster School of Medicine at the Texas Tech University Health Sciences Center in El Paso, and director of its Center for Neurogastroenterology and GI Motility. Sarosiek is a professor and director of gastrointestinal motility neurostimulation research at Texas Tech.

Since 2009, McCallum and Sarosiek have run the FDA-approved expanded access program at the health center to treat patients with domperidone. They also have co-authored numerous reports advocating domperidone as the only viable treatment for many patients and a much safer alternative to other FDA-approved therapies in patients who are properly screened and monitored.

Fears about heart risks are overblown and based on academic research outside the real-world clinical setting where patients are treated on a daily basis, McCallum said. The academic studies cited by the FDA and other critics of domperidone tend to be “very, very, very poor quality studies,” he said.

Many studies were done in countries where domperidone was sold over the counter and failed to account for other factors such as complicating medical conditions and other drugs the patients were taking that also have been linked to QT prolongation and other heart problems. More controlled studies in Canada and other places showed little or no risks in properly screened and monitored patients.

Patients in the Texas Tech expanded access program are treated with much higher doses of domperidone than what are typically recommended for patients in Europe, McCallum said. Even at that, he said he has not seen evidence of any significant increase in risk, certainly not enough to outweigh the benefits to patients.

“This is a risk-benefit ratio on a population with no options,” McCallum said. “After Reglan, there is no option. So when you boil it down to that, the benefit is great and the risk is miniscule.”

At Texas Tech, patients treated with domperidone are carefully monitored with regular electrocardiograms and other tests to ensure they are not experiencing QT prolongation or other serious complications, McCallum said. No deaths of any of his patients have been linked to domperidone use, he said.

“We are living this whole thing every day,” McCallum said. “We don’t just refer to it once a year as a news release. We’re actually generating the data. We’re living it. And we just don’t see it. We don’t see it, and we have to be convinced a lot more that we’re missing something because we’re doing everything we can not to miss it.”

Sarosiek notes that every patient treated through the FDA’s expanded access program must be closely monitored and any adverse events, including deaths or other serious reactions to medication, must be reported to the agency. If there was any evidence of widespread complications from domperidone, it’s something the FDA would be aware of through those reports.

“That’s something that if the FDA had concerns, it would already be known to all of us and it would be discussed at the gastrointestinal meetings, and we would all know the drug is dangerous,” Sarosiek said. “This is not the case.”

Domperidone continues to be cited as an effective treatment for patients who cannot tolerate Reglan by the American Gastroenterological Association and the American College of Gastroenterology, though both note it is not available in the United States outside of the FDA’s expanded access program.

McCallum does not fault the FDA for restricting availability of domperidone or requiring it to be obtained only through the expanded access program. The agency is in an unenviable position. Since Janssen did not complete its new drug application, domperidone was never approved by the FDA to treat gastric disorders or any other condition in the United States. The expanded access program is a means to allow patients to be treated despite that, he said.

However, McCallum said risk aversion at the FDA does seem to be a factor in the way domperidone is treated. While there is scant evidence of harm, any possible link to heart problems is something the FDA is not likely to ignore.

“It’s really all that theoretical risk,” McCallum said. “It’s not so much a headache or tremor. It’s a cardiac event and that makes people very nervous, and that’s why there’s this paranoid approach.”

Further complicating the FDA’s attempts to regulate domperidone is that it is readily available in other countries, Sarosiek said. So rather than go through the FDA-approved process, some doctors might simply tell their patients about the benefits and risks of domperidone and inform them that it can be obtained without a prescription at a pharmacy in Mexico.

“They learn very quickly that patients can get this drug from another country across the bridge from El Paso,” Sarosiek said. “So some of those doctors, they take the risk of suggesting the drug to their patients.”

That carries risks as well — for doctors and for patients.

Someone who buys domperidone over the counter in Mexico or another country may not be told of the potential risks and safe dosage, or be sure of its quality. They might not be monitored with regular heart testing to ensure there is no QT prolongation or other complication.

Also, the fact that they are taking domperidone will not show up in their medical charts, and so their doctors will not be aware of potential interactions with other drugs.

HORRIBLE TIMES

Lexie Cox knows there are risks that come from getting domperidone outside of the FDA-approved process. But the 24-year-old who lives near Seattle is willing to take those risks.

“Domperidone is one of the only things that has helped my gastroparesis and helped improve my quality of life,” Cox said. “I’ve told many people many times I truly don’t know what I would do if I didn’t have it. The times I have had to go without, they’re miserable. It’s horrible. There’s times when I’ve wound up in the hospital because I haven’t had my domperidone and I’ve gotten so sick and I can’t maintain it on my own.”

The signs of gastroparesis started with stomach spasms when Cox was in high school. Within six months, she became extremely ill with nausea, vomiting, bloating, diarrhea and constipation. She was unable to keep any food down. Her deteriorating condition required multiple hospitalizations because of dehydration and other health concerns.

“I would throw up for days on end, anywhere from three hours to three days,” Cox said. “I would vomit continuously. I could not keep food down. I could not keep water down. I could not keep anything down.”

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Cox’s condition as gastroparesis and put her on domperidone. She regularly undergoes electrocardiograms and other monitoring. Those tests have not shown any problems with her heart.

The only side effect from domperidone has been lactation. To control that, Cox takes periodic “medication vacations” in which she stops taking it until the milk production ceases. Those are difficult times, she said.

During one of those breaks, doctors tried Reglan and she did not respond well, she said. When Cox was first put on domperidone, it was easy to obtain from a local compounding pharmacy, she said. About two years ago, when the FDA began enforcing its ban aggressively, Cox was notified domperidone was only approved as a veterinary medicine, and therefore her local pharmacy could no longer supply it.

She was forced to temporarily go without and the severe symptoms returned. Eventually she found a mail-order pharmacy in Canada to fill the prescription from her doctor. But she knows her supply could be cut off at any time.

“I would be forced to be trying other medications which I’ve already tried, which didn’t work,” she said. “I would be basically back to ground zero. Without domperidone, they don’t really know how else to get my stomach to function properly.”

Dr. Irene Sarosiek and Dr. Richard McCallum

“It’s really all that theoretical risk. It’s not so much a headache or tremor. It’s a cardiac event and that makes people very nervous, and that’s why there’s this paranoiac approach.”
– Dr. Richard McCallum

DOSING DISPUTE

There is not much dispute that domperidone is effective in treating patients with gastroparesis, nausea and vomiting. Even the FDA grudgingly acknowledges that.

There also is general acknowledgment that, like any drug, domperidone can be dangerous in very high doses for some patients. That was largely established in the 1980s when at least seven cancer patients developed serious cardiac conditions, including QT prolongation, when they were given rapid infusions of domperidone intravenously during chemotherapy. The intravenous formula was pulled from the market in 1985.
What is in dispute is whether the pill form of domperidone is dangerous at doses used to treat patients with gastroparesis, and if it is, whether those risks can be minimized with proper screening and monitoring.

Many commonly used drugs have been linked to QT prolongation, which in itself is not fatal. What is of concern is whether the connection is strong enough to prove causation, and whether the risk is severe enough that it could trigger serious events including ventricular arrhythmia — an uncontrolled irregular heartbeat — or sudden cardiac death.

The FDA’s conclusion that domperidone is too dangerous to be used outside its limited access program is based largely on two separate studies done in Canada and the Netherlands in 2010.

The Canadian study, authored by Catherine, Johannes and four other researchers, was based on electronic medical records of people receiving government-paid health care in Saskatchewan between 1990 and 2005. It identified patients with sudden ventricular arrhythmias and sudden cardiac death while using domperidone or another type of treatment, proton pump inhibitors, and compared the outcomes to those who were not taking either medication.

The Johannes study, co-authored by Charlotte van Noord and her colleagues, used a health database to track domperidone use among people who had non-fatal ventricular arrhythmias and sudden cardiac deaths. A total of 1,366 cases were identified, 1,304 of which were fatalities. Of those, the study found 10 patients who died while taking domperidone at the time of a sudden cardiac death, and none who were taking it at the time they experienced non-fatal ventricular arrhythmias.

The van Noord study concluded that the risk of a sudden ventricular arrhythmia or cardiac death among those taking domperidone was about 59 percent greater than those who were not taking the drug at the time of the event.

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The van Noord study concluded the risk for either ventricular arrhythmia or sudden cardiac death was double among patients currently taking domperidone. Among past users, there was no statistically significant risk.

For comparison, that is the same risk of sudden cardiac death that is associated with erythromycin, a commonly prescribed antibiotic that is FDA approved, has been widely used since the 1950s, and has also been linked to QT prolongation. Studies have found the risk of sudden cardiac death among people taking erythromycin who are not double those not taking it. There was no significant increase in risk among past users.

Erythromycin is sometimes prescribed by doctors to treat gastroparesis, though it is not FDA-approved for that condition. Critics in the medical and academic community dismissed those results as flawed. One common criticism is they examined elderly patients. The mean age of those in the Johannes study was 79.4 years old. In the van Noord study, the mean age was 72.5 years.

The Johannes study also lacked transparency, failing to mention the number of cases and controls in subgroups based on variables such as age, according to a separate study published in 2014 in the Canadian Journal of Hospital Pharmacy. Even at that, the data in the Johannes study indicated the number of cases in subgroups was small.

And while the Johannes study essentially merged its overall findings to show a 59 percent increase in risk, it also showed that the correlation was higher among patients more than 60 years old. However, there was no statistically significant increase in risk for patients 60 years old or younger.

The van Noord study faced similar criticism, including its reliance on elderly patients.

McCallum of Texas Tech co-authored a study published in 2015 that noted only 10 of 1,304 patients in the van Noord study were using domperidone at the time they experienced sudden cardiac death, “which translates to a statistically non-significant increased risk.”

“Domperidone has the potential for cardiac side effects based on concerns for QT prolongation and increased risk of ventricular arrhythmias, but studies do not substantiate cardiac adverse events in patients receiving oral administration of domperidone, even at very high doses,” the study concluded.

Both advocates and critics of domperidone’s safety cited other research during an October 2015 hearing by an FDA committee weighing whether access to the drug outside the expanded access program should be allowed. The FDA acknowledged an assessment done for the European Medicines Agency in 2014 that found “no clinically relevant effect of domperidone” on QT intervals when given at normal doses to healthy patients. However, FDA officials dismissed those results because doses far higher than those that would normally be used for treatment were not studied. Those “supratherapeutic” doses would better reflect “the real-world worst-case scenarios” that can occur with domperidone use, according to the FDA. They were not studied because of ethical concerns about exposing patients to very high doses of a drug with known potential dangers.

“What is in dispute is whether the pill form of domperidone had been linked to cardiac arrhythmias and sudden deaths. It warned women not to take domperidone to enhance milk production, but did not offer a specific warning against taking it to treat gastric conditions, other than to note it is not approved for any medical condition in the U.S.

The alert notified agency field personnel to watch for attempts to import domperidone so it could be “detained and refused admission into the U.S. if appropriate.”

Despite the alert, the FDA was unable to enforce the ban effectively because the law that gave it authority over compounding pharmacies was essentially in legal limbo. Compounding pharmacies were historically regulated by states with little oversight from the FDA, even though the agency had at least some regulatory authority since passage of the Food, Drug and Cosmetic Act in 1938, according to a series of reports from the Congressional Research Service.

By the mid-1990s, there were mounting concerns that some pharmacies were abusing that exception to essentially manufacture and sell drugs on a large scale under the guise of compounding. In 1997, Congress gave the FDA broader powers to define and regulate compounding pharmacies.

The revised law also specified compounded drugs could not use as ingredients any drugs that had been withdrawn or removed from the market.

Because Janssen withdrew its application, domperidone never was approved for sale in the United States by the FDA.

Officials at Janssen Pharmaceutical refused to comment.

Domperidone remained readily accessible in the United States because of the way compounding pharmacies were historically treated in the law. They were free to fill prescriptions from doctors, obtaining the domperidone from foreign suppliers and blending it into doses for individual patients.

In 2004, the FDA imposed its first import restriction, citing concerns that domperidone was improperly being used to enhance lactation in nursing mothers.

The import ban also notes that the intravenous form of domperidone had been linked to cardiac arrhythmias and sudden deaths. It was not cleared for any medical condition in the U.S., according to the FDA.

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market because they were found to be unsafe or ineffective.

Since domperidone was never approved for use in the United States, it was never removed or withdrawn from the market.

The 1997 law also included a provision that barred compounding pharmacies from advertising. That provision was challenged as a violation of free speech on First Amendment grounds. A federal judge in Nevada agreed and voided the advertising restriction, but said the balance of the law could remain intact.

The 9th U.S. Circuit Court of Appeals agreed the advertising prohibition violated the First Amendment, but said it could not be severed from the other provisions of the law. That meant the entire statute was void.

When the government appealed to the U.S. Supreme Court, it challenged only the finding dealing with the speech issue, not the law’s severability. When the high court ruled against the agency on the free speech argument, it did not resolve the issue of severability, creating a legal mess when it came to the enforceability of a nationwide import ban.

In 2012, the FDA issued another import alert, this one much more ominous than its warning eight years earlier. It declared importation of domperidone “presents a public health risk” and is against the law except in certain circumstances, including approved research or through the expanded access program. Even then, domperidone was still readily available, either through mail-order pharmacies outside the United States or as a veterinary medicine.

Then, in 2012, a meningitis outbreak linked to contaminated batches of a compounding drug was traced to unsanitary conditions at a compounding pharmacy in Massachusetts. The outbreak had nothing to do with domperidone, but it prompted Congress to renew the FDA’s authority over compounding pharmacies by passing a new law in 2013. The new law was virtually identical to the 1997 law, but without the advertising restriction. Since then, the FDA has enforced its import ban on domperidone more aggressively, and has warned compounding pharmacies of potential legal action if they continued filling prescriptions for the drug.

‘BENEFITS OUTWEIGH THE RISKS’

About that same time, European officials were scrutinizing the links between domperidone and QT prolongation, largely because of the Johannes and van Noord studies. In 2013, the European Medicines Agency reevaluated the risks and benefits of domperidone and recommended changes in the way it is used.

The FDA, in a report to the review committee that met in October 2015, characterized the EMA’s actions by saying the use of domperidone “has recently been significantly restricted because of serious safety concerns.” But what the EMA recommended was that domperidone be retained as a treatment for symptoms of nausea and vomiting, but not for other less serious conditions like heartburn and bloating. It advised the recommended dose be reduced from 20 milligrams to 10 milligrams, three times per day.

In the United Kingdom, Belgium and the Netherlands, the non-prescription status of domperidone was revoked and it was made prescription only. About 2 million people took domperidone in the United Kingdom annually.

While the FDA characterized the European reaction to safety concerns as significant, the warnings themselves were less ominous. A safety alert issued by the British Medicines and Healthcare Products Regulatory Agency (MHRA) in May, 2014, characterized it as a “small increased risk of serious cardiac side effects.”

The advisory recommended people with heart trouble or taking other drugs linked to QT prolongation not take domperidone. It also indicated domperidone was appropriate for children less than 12 years old at reduced doses. The review demonstrated the benefits outweigh the risks of using domperidone when used to treat nausea and vomiting, but that there should be restrictions on its use,” Dr. Sarah Branch, the deputy director of the MHRA’s vigilance and risk management of medicines division said at the time.

Canada also issued guidance on growing concerns about domperidone use in 2015, recommending a maximum dose of 30 milligrams per day and restricting use on patients with heart conditions or taking other drugs.

About 2 million prescriptions for domperidone were written in Canada in 2013, according to the government’s safety review. At the time of its 2015 review, Health Canada had received 18 reports of serious adverse heart events in people who took domperidone, none of which were deaths. Twelve of those cases were evaluated to determine whether domperidone was the cause of the heart event. The agency concluded that while it was a possible cause for heart problems.

“It is difficult to determine to what extent domperidone contributes to heart events because other conditions known to cause electrical heart problems were also present in many cases.”

Although Health Canada did not express confidence in the Johannes and van Noord studies or other research suggesting domperidone was the cause of serious cardiac events.

Studies in patients have shown that domperidone may increase the risk of sudden death and serious abnormal heart rhythms,” the Health Canada report says. “However, these studies had limitations, including small numbers of patients, and the possibility that factors other than domperidone could have led to the heart events.”

‘ANGRY WITH MY COUNTRY’

Roberta Stewart of Cottonwood, Ariz., is not worried about a sudden death from domperidone. She is worried she will die a slow and miserable death because she cannot get it.

Stewart, 47, was diagnosed with gastroparesis in 2010, although she had suffered from the symptoms for several years prior to that. She and her husband, Army Sgt. Patrick Stewart, led active lifestyles that included kayaking and skydiving.

Roberta Stewart worked as a paralegal and business consultant. Her husband, a Desert Storm veteran, completed his active duty and enlisted in the Nevada Army National Guard. In 2005, he was deployed to Afghanistan.

At first, Roberta Stewart was not too concerned about the queasiness she felt in her stomach, dismissing it as nerves associated with her husband’s deployment.

Her fears were realized in September 2005. Patrick was killed when the helicopter he was flying in was shot down.

Stewart became embroiled in a fight with the Department of Veterans Affairs over the placement of a religious symbol on her
husband’s tombstone. The Stewarts practiced Wicca, a religion based on the belief in the magical powers in nature.

The VA refused to recognize the Wiccan symbol of a five-pointed star in a circle. The fight gained national media attention and several elected officials intervened on Stewart’s behalf. But the controversy brought added stress, and the queasiness turned to nausea and severe vomiting.

“I was vomiting all the time and the abdominal pain was just so painful that I was calling 911 at all times and going into dehydration seizures,” Stewart said. “I’ve always been a person that can’t sit still for more than an hour. And all that changed. It took my entire life away. I can’t even go check the mail any longer.”

Stewart’s doctors spent three years trying to figure out what was wrong with her. She underwent intensive surgeries that left her esophagus and colon paralyzed. They tried Reglan, but that caused severe seizures and had to be discontinued.

Domperidone was not approved by the FDA to properly absorb even water. But because something akin to a normal life. She could eat normally and she periodically was hospitalized to control nausea and vomiting.

“I just left it to a higher power,” she said. Stewart survives now largely on nutritional drinks so she could get the nutrients her body was unable to absorb. But it was not a cure-all. But at least with domperidone, Stewart was able to start living something akin to a normal life. She could eat small bites of food without triggering excruciating pain and vomiting.

“Domperidone was the best thing for me,” she said. “I wouldn’t have to run to the bathroom and vomit after eating. So it controlled that and allowed me to live a more functional life. I did start seeing some hope.”

Stewart had to go through a pharmacy in Canada to fill the prescription. At first it was not difficult. But the FDA’s restrictions created other complications, she said. Even with the domperidone, Stewart could not eat normally and she periodically was hospitalized with complications or for hydration therapy, which was needed because her body was unable to properly absorb even water. But because domperidone was not approved by the FDA to treat her condition, she was not allowed to take it in the hospital, so that led to a cycle of stopping and starting the treatment.

As the FDA tightened its import ban, it became ever more difficult to obtain domperidone through Canada, Stewart said. With supplies dried up, and with Reglan not a viable option, the only treatments left were pain pills and a feeding tube. She wound up with renal failure and was placed in hospice care to die.

“I was very disappointed when I could no longer get (domperidone) and very angry that they had taken away the one and only drug that gave me any kind of assistance at all,” she said. “It gives us a lifestyle where we can maybe get out to lunch with our mother once a week. They are taking something away that at least allows us to get some nutrition into our body.”

“I was so angry with my country, the government, the FDA that they did this to us.”

RISK OF DEATH

For Yvanna Sherman, 42, of Philadelphia, the FDA’s rigorous enforcement of its ban on domperidone leaves her little hope of leading a somewhat normal life. With supplies dwindling and the cost shooting up, getting into the agency’s expanded access program may be her last chance to get the drug that helped save her life, she said.

Gastroparesis came on suddenly about 2004 for Sherman. She lost her appetite, was vomiting frequently and in extreme pain. Unable to keep down food or even water, she lost 80 pounds in four months.

Even after the gastroparesis was diagnosed, doctors were reluctant to try domperidone, Sherman said. They put her on a variety of gastric medications, none of which worked. When they tried Reglan, she almost immediately developed the muscle twitching that is a known side effect of the drug in some patients. It also triggered severe anxiety that required hospitalization.

The first gastroenterologist she saw refused to prescribe domperidone. That was about the time the FDA issued its first alert. He said he was concerned he might face sanctions if he sent a patient to Canada to obtain the drug.

Finally, the second doctor agreed to write a single prescription, but said he could not continue treating her.

Finally, Sherman found a third gastroenterologist who was willing to prescribe domperidone for longer-term treatment, which she obtained through a pharmacy in Canada.

“It was excellent,” she said. “I could get out of the house. I could start doing things again. I could eat. I ended up gaining weight back.”

She has been taking domperidone for about eight years. Her doctor discussed the risks before starting it, and runs tests on her heart at every visit.

“I’ve never had a problem, but I’m also willing to take that as a risk because I’m of the opinion that if I go too long without domperidone, I’m going to be at risk of death,” Sherman said.

The doctor who prescribed the domperidone also put Sherman on a gastric pacemaker, an implanted device which electrically stimulates the stomach muscle to control nausea and vomiting.

At one time, Sherman and her husband considered moving outside of the United States to obtain domperidone, but that would mean she could no longer qualify for the pacemaker, she said.

About 2014, as the FDA was more aggressively enforcing its import ban, supplies of domperidone dried up and got more expensive, Sherman said. The added restrictions and rising cost forced her to stop taking domperidone about six months after, for eight years of using it successfully.

The old symptoms quickly recurred, and have left her nearly bedridden.

Now, she is trying to qualify for an FDA-approved expanded access program in the Philadelphia area, so far without success.

As her condition deteriorates, she worries she is running out of time.

“I see my life going in a downward spiral,” Sherman said. “Since I have not been able to get it, it’s been a lot worse and I’ve gotten a lot more depressed. Just waiting is very difficult. Not knowing is very difficult.”

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WORKAROUND

The FDA’s expanded access program is supposed to be a workaround for people with gastroparesis who cannot get domperidone because of the agency’s efforts to shut down importation and compounding. There is not much evidence it is working. The FDA refuses to say how many people are being treated through the program.

Beener, the Florida woman who uses domperidone, says she has known thousands of people with gastroparesis through her work with the Gastroparesis Patient Association for
Cures and Treatments (G-PACT), a volunteer organization where she serves as operations director and a member of its board of directors. She knows only one person who is treated through the FDA's expanded access program.

McCallum, the Texas Tech doctor, said about 100 to 120 patients are getting domperidone treatment through the expanded access program in El Paso.

The FDA did say that its review of data from all retail, mail-order and long-term care pharmacies in the United States shows between 7,500 and 11,600 prescriptions for domperidone were dispensed annually between June 2009 and May 2015. Only one pharmacy is authorized to distribute domperidone through the expanded access program, and must report the information to the FDA.

Those numbers compare to the 2 million prescriptions filled annually in Canada and an estimated 2 million domperidone users in the United Kingdom as of 2013.

FDA officials acknowledged many people are getting domperidone from sources other than domestic pharmacies and outside the expanded access program.

The FDA's expanded access system is so layered with paperwork, bureaucracy and financial disincentives that it is bound to fail in most cases, the Goldwater Institute found in an investigative report published in February 2016. Doctors seeking to treat patients through expanded access, also known as “compassionate use,” had to commit to an estimated 100 hours just to fill out the agency forms. They must develop and submit treatment and monitoring plans to the FDA, report all serious incidents and patient deaths, and get approval from the drug manufacturer.

Any treatment plans also must be approved by institutional review boards (IRBs), internal panels that weigh the ethics and risks of treating an otherwise terminal patient with a drug that has not received final approval from the FDA. Doctors cannot charge for the cost of preparing the application, developing treatment protocols or securing IRB approval.

Normally, expanded access programs are available only to patients with serious or life-threatening ailments to obtain drugs undergoing clinical trials. Those are the years-long studies conducted by the drug makers to develop data they will use to show their products are safe and effective when they submit their new drug application to the FDA for authority to sell it.

‘UNWORKABLE’ COMPASSION

The domperidone program is somewhat unique, in that it treats patients with a drug that is not in clinical trials or under review for marketing approval by the FDA.

The agency has streamlined the process somewhat for the domperidone protocol by developing the model treatment plan. But its instructions for doctors seeking to treat patients through the expanded access program still list a litany of requirements, including IRB approval, extensive patient monitoring, reporting adverse events and submitting an annual report for each patient.

“It’s completely unworkable for any health care practitioner in a community setting,” said Dr. A.J. Day, a pharmacist and director of pharmacy consulting at PCCA, a drug wholesaler that supplies local pharmacies.

Day’s company nominated domperidone for inclusion on the list of drugs that could be compounded.

Day tried to navigate the process to qualify under the expanded access program to see how difficult it would be. He couldn’t get past the first step, approval from an IRB.

Day said he contacted more than 30 leading research hospitals and clinics around the country. None would agree to provide IRB reviews for doctors who are not on staff or have admitting privileges.

Day did find one independent IRB, which charged in excess of $3,000 to review the application for a single patient. When he contacted the FDA for assistance, he was told all anyone there could do was read the directions posted on the website. They could not help him find an IRB or explain anything on their website.

“Given the safety concerns, there is potential for significant harm to the public if domperidone is prescribed and used without important safeguards to ensure patient protection,” Sewell said.

Dr. Anil Rajpal, another FDA presenter, said doctors who want to treat patients through the expanded access protocol have to go through a simple process that involves filling out a two-page form.

“It’s a standardized form. So there’s just portions to complete,” Rajpal said when asked whether it is practical to expect a front-line doctor to qualify under the program. “It’s a two-page IND.”
When asked directly how many patients are being treated under the protocol, Jane Axelrad, associate director of regulatory policy at the FDA, refused to answer, saying that information was confidential. Agency officials also would not provide a figure to the Goldwater Institute.

‘HEADS IN THE SAND’

Front-line gastroenterologists and pharmacists rebutted the notion that qualifying for the FDA protocol is simple.

“The IND process is cumbersome, time-consuming,” said Dr. Alan Diamond, a gastroenterologist in Montgomery County, Md. “It takes hours to fill out those papers to get domperidone for their patients. It just isn’t going to happen. So you’re actually depriving them of that drug.”

Dr. Richard Moon, a compounding pharmacist, testified the ability of patients to get domperidone in other countries coupled with the difficulty of qualifying for the expanded access program forces many patients to get domperidone use will show up in their medical charts.

“We are not protecting the public” by prohibiting the compounding of domperidone, Moon said. “We’re just poking our heads in the sand and letting the world go on around us.”

Even committee members were skeptical of the effectiveness of the expanded access program.

“The expanded IND process is too difficult for everyone to be able to use, and probably for most people to be able to use,” said Dr. John DiGiovanna, a staff clinician at the National Cancer Institute and a member of the committee.

“To use in the equation that the expanded IND is an acceptable alternative really suggests to me that that’s coming from someone who hasn’t tried to get an expanded IND.”

Dr. Gigi Davidson, a committee member representing the U.S. Pharmacopeial Convention, said access to the drug through Canada or Mexico makes it unlikely most front-line doctors would go through the FDA’s paperwork to qualify for the expanded access program.

Davidson, a veterinary pharmacist, also noted domperidone is available in the United States as a veterinary medicine used to treat horses. Every week, she gets calls from people asking about the veterinary form of domperidone, she said.

Davidson said she struggled with the question of whether patients are best served by expected to get domperidone through the heavily regulated expanded access program “which appears to be inaccessible,” or through other sources that are less controlled.

“I’m really struggling with the gap between patient access and total, uncontrolled availability of it by going to the equine product and going across the border,” Davidson noted.

At an earlier public hearing in May 2015, the FDA took testimony from numerous patients with gastroparesis who described how domperidone had worked for them and asked that they be allowed to continue accessing it. One described domperidone as “my magic bullet” and a “godsend.” Another said she felt “blessed” when she started taking it.

“It saved my life, literally,” she said. Despite pleas from patients and their own concerns about the viability of the FDA’s expanded access program, committee members voted 8-3 to ban compounding of domperidone.

It was the first drug added to the list of products that cannot be compounded.

What happens next is unclear, said Day, the pharmacist. The 2013 law requires the Health and Human Services secretary to develop a permanent list of permitted compounds. Unless the FDA changes its view of domperidone, its status is not likely to change, he said.

There’s not much chance of a change in attitude about domperidone given the agency’s history of risk aversion, he said. Throughout the review process, FDA officials consistently discounted studies that show domperidone can be safely used in properly screened patients while overhyping those that suggest some risk, he said.

“This is beyond risk aversion,” Day said. “That lack of impartiality is just blatant. There’s not even an attempt to hide it. There is an absolute lack of impartiality when it comes to assessing the risk versus benefit equation which goes into all medications.”

FDA officials would not agree to an interview.

OUT OF OPTIONS

Beener said she has hope that Congress will do something pointy, especially in light of the Right to Try movement spearheaded by the Goldwater Institute. More than 30 states have passed Right to Try laws, which would allow patients with serious or life-threatening conditions to access drugs that have not completed clinical trials or been approved for use by the FDA.

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FDA officials would not agree to an interview.

“Countless Americans with terminal illnesses and conditions like gastroparesis face the terrible choice of spending their final days traveling abroad in search of medical care, facing prison for illegally accessing medicine through the U.S. government or dying. The FDA insists that all treatments must be approved firsthand by them, but why not consider alternative approval? Letting Americans access treatments available in Canada simply gives Americans the same opportunities as Canadians.”

Beener of G-PACT said people like her with gastroparesis fear the day when the FDA is able to fully enforce its import ban on domperidone. She also resents the federal government telling her she can no longer have access to a drug that has been safely and has changed her life, all in the name of protecting her.

“The FDA has become my parent and I don’t like that,” Beener said. “I should have the right to determine whether or not I should be able to take something that helps me. I understand that they are trying to be protective. But tell me the risks and then let me make my own decision. I don’t need a nanny.”

“If domperidone is available in Canada, for heaven’s sake, it should be available here. That’s simple.”

– Darcy Olsen

RIGHT TO TRY ACT

DOMPERIDONE

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