TORONTO STAR

Star Investigation

Drug approval under the microscope as two doctors allege Health Canada received flawed evidence about blood medication

Health Canada's approval of deferiprone relied in part on data from Toronto hospital patients who received the medication before it was licensed.

By Rachel Mendleson Staff Reporter
Sat., April 15, 2023 *timer* 8 min. Read

When Health Canada approved the blood disease drug deferiprone, it relied in part on data from a University Health Network program that harmed patients and may have violated federal guidelines on the use of unlicensed medications, two doctors from the hospital allege.

Now those doctors — Nancy Olivieri and Brenda Gallie — want the federal health regulator to revisit how the drug was approved.

The UHN denies the allegations and said it properly and safely used the drug to treat patients with thalassemia. The doctor who runs the program that administered the unlicensed deferiprone said he and his colleagues have always put the interests of patients first.

From 2009 to 2015, 72 patients at UHN were treated with unlicensed deferiprone. In each case, Health Canada signed off on the use of an unapproved drug through its Special Access Program, a compassionate-use protocol intended for patients in which already licensed medications are unsuitable or don't work.

Olivieri and Gallie reviewed the medical charts of dozens of those patients and say they found no evidence to explain why so many patients were switched from approved treatments to the

unlicensed drug. Their research found many patients given deferiprone suffered "significant toxicity," and that the UHN clinic where they were treated had received funding from deferiprone's maker, Apotex.

Eight years after Health Canada licensed deferiprone, a Star investigation has confirmed that Apotex's licensing application included evidence from the UHN program, which the regulator considered in its decision to approve the drug. That acknowledgment from the regulator comes amid continued secrecy from UHN and has rekindled questions about the potential influence Big Pharma funding has inside trusted Toronto health institutions.

This story is not an attempt to settle the fraught scientific debate over the safety of deferiprone. It is about research integrity, and questions about evidence that apparently factored into the decision to approve a controversial drug.

UHN patients' experience part of Health Canada submission

Health Canada licensed deferiprone in 2015 for thalassemia patients whose current treatment is inadequate. At the time, Apotex said it was already approved with similar limitations in more than 65 other countries.

The regulator's approval of the medication — marketed as Ferriprox — was based on a large body of evidence, but primarily on data from two key studies submitted by the drug company, a spokesperson for the regulator said.

The regulator's evidence also included the experience of 46 UHN patients who were not part of any trial to test the drug's efficacy but were treated with unlicensed deferiprone, starting in 2009, as part of the UHN program run by Dr. Richard Ward, Health Canada told the Star. Ward's program was funded, in part, by drugmaker Apotex, internal documents show.

Olivieri and Gallie's 2019 study found most of the 41 UHN patients whose charts they examined suffered "significant toxicity" including liver dysfunction, diabetes and in one case, death.

Ward has presented rosier outcomes of deferiprone's use in his thalassemia program, which purports to be the largest of its kind in North America.

Health Canada said a review it conducted in 2019 of the study by Olivieri and Gallie "did not lead to a shift in the known benefit-risk profile of the drug."

But Olivieri and Gallie say the use of unlicensed deferiprone at UHN, and how Health Canada approved the drug, demands "a true forensic audit."

"Health Canada owes an obligation to the world and to patients to come and inspect all the data that was submitted to them" by Apotex alongside the patients' medical charts, Gallie said.

Apotex's licensing application to Health Canada included a summary of a report from Ward on how those patients fared from 2009 to 2012, a spokesperson for the regulator said. The contents of that report, however, are not public.

UHN has repeatedly refused to discuss Ward's role in Apotex's application, or disclose the evidence Health Canada said he provided to the drug company.

A spokesperson for Health Canada said the regulator is working on a request from the Star to release the evidence from Ward that it considered.

Concerns treatment violated federal guidelines

One reason Olivieri and Gallie want the federal regulator to take another look at how the drug was approved is that UHN's use of it may not have followed federal guidelines, they allege.

There are strict rules around testing drugs in humans. In clinical trials, scientists must typically show an ethics board that the potential benefits outweigh the possible risks, get informed consent from patients, and take steps to keep their duties as clinicians caring for patients separate from their role as investigators testing a new drug.

Unlicensed drugs obtained through special access don't undergo such ethics board scrutiny. Health Canada imposes limits on the program, which is intended to meet "emergency needs only." The program "is not a mechanism to encourage the early use of drugs nor is it a means of circumventing drug clinical development or the regulatory review of a submission for marketing," the regulator says.

All of UHN's deferiprone requests were approved by Health Canada, a spokesperson said. But Olivieri and Gallie question how such a large number of patients satisfied the requirements for approval under the special access program, and are concerned that data from these patients was apparently used to help Apotex license an experimental medication but without going the more arduous route of a clinical trial.

In a 2011 abstract in a medical journal written by Ward and other UHN colleagues and that touted the drug's benefits, the authors said they had decided to "systematically enrol" patients in the special access program.

The same year the abstract was published, Ward's program received an $80,000 unrestricted grant from ApoPharma, the division of Apotex that marketed the drug, according to documents Olivieri obtained through Freedom-of-Information (FOI) legislation. Ward told ApoPharma the money would go to "analysis and reporting of our centre's experience with deferiprone," among other activities, the documents show.

Ward agreed to share safety and efficacy data with ApoPharma, according to those documents.

Ward did not respond directly to questions for this story. In an email, he said the Star's questions raise matters that "have been thoroughly investigated by UHN and the University of Toronto on several occasions, with validation of our actions."

"As an academic clinician I take my ethical, academic, and regulatory responsibilities seriously," he said. "Myself and clinical colleagues in the (Red Blood Cell Disorders) program at UHN have acted, and will continue to act, in the best interests of patients, and to prioritize those interests over the interests of external parties, such as the pharmaceutical industry."

Unlicensed drug was part of 'standard clinical care', hospital says

UHN officials say the unlicensed drug was provided as part of "standard clinical care," which was not influenced by conflicts of interest, and that all patients who got the drug did so "following discussion regarding the risks and benefits."

"If you report that patients at UHN were given deferiprone as part of an unapproved research study, that UHN influenced Health Canada's approval of deferiprone, that patients were continued inappropriately on deferiprone without appropriate consideration, that conflicts of interest influenced the care of patients … you will be wrong," former spokesperson Gillian Howard said.

Before she retired last month, Howard told the Star that the 2011 abstract authored by Ward and colleagues reports some early findings of a retrospective review of patients' medical charts, which was approved by UHN's ethics board. Such reviews allow researchers to track impacts of various treatments, but differ significantly from clinical trials, which expose patients to drugs for the purpose of testing their efficacy and safety.

Olivieri and Gallie's 2019 study triggered a review at UHN that found the use of unlicensed deferiprone was "justified." As the Star recently reported, the hospital's review, which officials had said would include an external and independent voice, was done with the help of an expert who had received consulting fees from drugmaker Apotex and had supervised a research dissertation by Ward, the UHN program director who gave the patients the drug.

Apotex has always rejected concerns about the safety and efficacy of deferiprone.

When the Toronto-based firm sold the rights to the drug to Chiesi Group in January 2020, the companies acknowledged that no controlled trial had shown a direct treatment benefit. The companies did not directly address questions for this story

In Canada, the drug is approved to remove excess iron in patients with a severe form of thalassemia and who require frequent blood transfusions. The transfusions cause iron to build up, which can lead to organ damage or death. Thalassemia patients should take deferiprone only if their current medication is inadequate. Health Canada also has approved the drug for treatment of other blood diseases.

Some researchers and clinicians say it can be a useful thalassemia medication in limited circumstances. For others, including Olivieri, who was among the first scientists to test deferiprone on human subjects, it has no place in the doctor's tool kit.

Side effect reports 'have been omitted', doctor charges

Olivieri, a senior scientist and blood diseases expert at UHN, and Gallie, a specialist in data analysis who does pioneering research in retinoblastoma, a rare form of children's eye cancer, say there is evidence suggesting not all side effects that UHN patients experienced during their deferiprone treatments were reported to Health Canada before the drug was approved.

Health Canada requires drug companies and physicians who provide patients with unlicensed drugs through the special access program to promptly report any suspected adverse reactions, which the regulator publishes in an online database.

According to the database, just four reports of suspected adverse reactions related to deferiprone were filed from 2009 to February 2015, when the drug was licensed. Two of those reports are categorized as "non-serious," while the other two report multiple serious adverse reactions including death. It is not clear if any of the additional reports that were filed after the drug was approved relate to UHN patients.

Olivieri said the reports filed before the drug was approved do not account for "hundreds" of adverse reactions to the drug reportedly experienced by many more patients that she and Gallie documented in their paper, published in 2019 in the journal PLOS ONE, including dangerous spikes in liver-iron concentration and diabetes.

"These are facts that have been omitted," she said.

Ward, UHN and Health Canada did not directly respond to questions from the Star about this apparent discrepancy. The hospital's review found four deaths of patients treated with deferiprone from 2009 to 2015, only one of which was linked to deferiprone, and no connection between the use of the drug and diabetes.

Ward touted the benefits of deferiprone in a paper he co-authored in the European Journal of Haematology in 2019, a few months after Olivieri and Gallie's study came out. In Ward's paper, which analyzed the medical records of 71 patients who received the unlicensed drug at UHN between 2009 and 2015, he and his co-authors said serious adverse events occurred in five patients, far fewer than were reported by Olivieri and Gallie, and they did not mention diabetes.

Since 2017, roughly 1,000 prescriptions for Ferriprox have been dispensed at pharmacies across Canada each year, the regulator said. As of last May, about 30 UHN patients were taking deferiprone, a hospital official said.

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