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Allison Zayas sold the antipsychotic Seroquel for drug firm AstraZeneca. She later filed a whistleblower suit.

Drug rep says she warned of dangers

Mixing Seroquel, methadone can be fatal, lawsuit says

By Sam Roe
Chicago Tribune

Few prescription drugs were as popular as the antipsychotic Seroquel. Psychiatrists trusted it, nursing homes used it and addiction specialists prescribed it. Annual sales exceeded $3 billion.

But in the winter of 2009, one of the top pharmaceutical sales representatives selling it, Allison Zayas, began to have her doubts.

According to Zayas, one of her best clients, a doctor at a New York City outpatient clinic, told her that a patient had died while taking the drug and that the combination of Seroquel and methadone might have played a role.

Soon after, Zayas recalled, two other doctors told her as many as 10 patients at New York methadone clinics had died taking Seroquel and methadone together. Zayas said she reported the deaths to her company, drugmaker AstraZeneca, but that it continued to aggressively market the blockbuster drug, even to methadone clinics.

"Their goal was to get in there and sell Seroquel," she told the Tribune in an interview. "It was not, 'Let's draw back. Let's take a look at the information.' It was, 'Get in there and sell.' Everything is sell, sell, sell."

Alarmed at the inaction, Zayas quit AstraZeneca and filed a whistleblower lawsuit against the firm, alleg-

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Drug rep says she warned of dangers

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ing it concealed the true cardiac risks of Seroquel when taken with certain other medications.

The suit, filed in 2010, is a rare example of an employee of a major pharmaceutical company bringing a whistleblower claim over dangerous drug combinations. A filing last month in federal court in Brooklyn states the parties have reached a settlement in principle; a status report is expected by Monday. Bloomberg reported on the suit and the possible settlement last week.

Drug interactions are a serious public health problem, hospitalizing tens of thousands each year. A Tribune investigation last year exposed how health care workers often fail to recognize drug interactions, prompting widespread safety changes at U.S. pharmacy chains.

Drugmakers also have a crucial role in protecting and informing the public. Zayas' suit claims AstraZeneca failed to do either.

Her suit claims the company withheld safety information from two U.S. Food and Drug Administration advisory panels and failed to alert patients, doctors and pharmacists about Seroquel's heart risks. The FDA declined to comment for this story.

Zayas, a 46-year-old Manhattan resident, also claims AstraZeneca directed and incentivized its sales representatives to sell to doctors who it knew prescribed Seroquel with methadone and other drugs that might trigger a dangerous reaction. Methadone is a powerful opioid that treats pain as well as addiction to narcotics.

"While others saw a crisis in the opioid epidemic, AstraZeneca cynically saw a financial opportunity," Zayas' attorney James Pepper said. "While others sent help, AstraZeneca sent sales representatives. Their job? To sell Seroquel to doctors who treated this very vulnerable patient population."

A spokeswoman for United Kingdom-based AstraZeneca said the firm disputes the lawsuit's allegations but declined to comment further.

In one court document, AstraZeneca said the 313-page whistleblower suit "is long on words, paragraphs and pages, but falls far short of stating a claim."

The drugmaker wrote that Zayas cites dozens of clinical studies and articles that purportedly support her opinion about the relationship between Seroquel and a potentially dangerous heart condition "while ignoring others that do not support her opinion." As a result, the suit "provides a convoluted, often contradictory recitation of the regulatory history regarding this issue."

According to court filings, AstraZeneca in 2010 changed Seroquel's prescribing information to advise "caution" when using the drug with certain other medications; in 2011, the FDA requested the company further strengthen the label to say Seroquel "should be avoided" with those drugs.

Zayas' lawsuit says those label changes should have been made years earlier.

She is suing on behalf of the U.S. government and 27 states, including Illinois, under the federal False Claims Act and similar state and local laws. The suit alleges that had authorities in those jurisdictions known about the dangers of Seroquel in combination with other drugs, they would have not paid for the medications under Medicaid and other government-funded health programs. By bringing the suit, Zayas could receive a share of any recovered damages.

Chicago is also named as a plaintiff. Pepper said that's because Chicago has the nation's strongest false claims ordinance covering reimbursement of medications for city employees.

None of the plaintiffs named in the suit agreed to "intervene," or litigate the case themselves. A federal judge in April denied AstraZeneca's request to dismiss the suit in its entirety.

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Allison Zayas' lawsuit is a rare example of an employee of a major pharmaceutical firm bringing a whistleblower claim over dangerous drug combinations.

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Zayas said doctors told her that some patients at methadone clinics had died taking Seroquel and methadone together.

He allowed one key allegation — that the company withheld critical information about drug interactions — to move forward.

Seroquel, whose generic name is quetiapine, treats schizophrenia and other psychiatric conditions. In 2010, AstraZeneca agreed to pay $520 million to settle allegations by the U.S. government that the company marketed Seroquel for unapproved uses.

Puzzling heart condition

At the center of Zayas' allegations is a puzzling abnormality of the heart's electrical activity called QT prolongation.

The "Q" and "T" refer to the electrical waves on a patient's electrocardiogram. The time between when the heart starts squeezing to when it finishes relaxing and prepares to beat again is the QT interval. If this interval lengthens markedly, the condition is called QT prolongation, and it can trigger a potentially fatal arrhythmia.

Dozens of medications, including methadone, have been shown to cause a long QT interval and the dangerous arrhythmia, but no one knows how many people have died. Unless a person is connected to an EKG monitor at the time of death, it is difficult to prove that an abnormal heart rhythm was the culprit.

Perhaps even more difficult to determine is whether a drug combination caused the death.

According to the whistleblower suit, when Seroquel came to market in 1997, the U.S. label did not warn against taking the drug with medications known to lengthen the QT interval even though there were such warnings on Seroquel's label in the United Kingdom.

After a 2000 study by drugmaker Pfizer found evidence that Seroquel increased the QT interval, AstraZeneca laid out in an internal document a strategy to protect the Seroquel brand, the suit states. One "Key Success Factor" was to "defend against potential FDA label threats" related to QT prolongation, according to the suit.

Promoting Seroquel during this critical time was Chicago psychiatrist Dr. Michael Reinstein, a paid AstraZeneca speaker and a top company client.

In a 2001 promotional telecast, Reinstein told more than 5,000 doctors and health care workers that patients taking Seroquel with the antipsychotic ziprasidone showed no significant problems.

"These comments," Zayas' suit states, "were reckless and amounted to AstraZeneca promoting a use of Seroquel with a drug that placed patients at great risk of sudden cardiac death and other cardiac effects."

AstraZeneca paid Reinstein $490,000 between 1997 and 2007 to promote Seroquel, a joint ProPublica and Chicago Tribune investigation found in 2009. (Last year, Reinstein was sentenced to nine months in prison for taking cash, vacation trips and other kickbacks from the manufacturers of a different antipsychotic drug.)

As Reinstein promoted Seroquel in the 2000s, red flags appeared: European Union regulators reported several deaths among patients taking Seroquel and methadone together, the whistleblower suit states. And, according to the suit, Europe strengthened the Seroquel label in 2006, advising "caution" when taking the drug with QT-prolonging medications, but the U.S. label was unchanged.

By 2006, the suit states, six studies had shown that Seroquel caused clinically and statistically significant increases in the QT interval.

Zayas said that when she started working at AstraZeneca in 2006, selling Seroquel in Staten Island and parts of Brooklyn, she knew nothing about the drug's dangers.

She said she knew only what the company told her: Seroquel was safe and effective and posed no heart risk.

And that, she said, is what she communicated to physicians.

Expanding the market

Zayas said her marching orders were clear: expand the market for Seroquel.

So she didn't just call on psychiatrists but pain doctors and addiction specialists as well. She said AstraZeneca officials crafted 30-second, 2-minute and 15-minute sales pitches and bought data from pharmacies about doctors' prescribing habits to help identify sales targets.

AstraZeneca, her suit states, also wanted to expand the permitted uses of Seroquel. In 2009, the suit says, AstraZeneca submitted applications to the FDA to add several uses, including treatment for children.

But behind the scenes, the suit states, the company was increasingly concerned about the drug's heart risks and addressed the matter at an internal safety meeting.

At that meeting, in April 2009, the lawsuit states, AstraZeneca officials decided to strengthen Seroquel's "core data sheet," the company's position on a drug's safety profile that dictates changes to a label worldwide. This internal company document said that "caution" should be used when prescribing Seroquel with QT-prolonging medicines, the suit says.

Once AstraZeneca toughened Seroquel's core data sheet, the suit states, the company should have changed the prescribing information worldwide.

But Zayas alleges that AstraZeneca did not immediately change the label.

A week later, AstraZeneca officials came before an FDA advisory panel considering the firm's applications for expanded use of the drug. According to the suit, the drugmaker said there were no cardiac safety issues associated with Seroquel, and the company did not disclose it had changed the core data sheet.

Two months later, another FDA advisory panel convened to consider AstraZeneca's applications. Again, according to the suit, AstraZeneca failed to disclose that it had internally decided to toughen Seroquel's label.

"AstraZeneca had a strong financial incentive to delay notifying the FDA," the suit states, because the company had pending applications before the agency.

In December of that year, the FDA approved three of AstraZeneca's five requests to broaden the use of the drug, the suit says. Seroquel could now be used to treat large new populations, including children.

According to the suit, a month later, in January 2010, AstraZeneca amended Seroquel's warning label, advising "caution" when the drug is used with QT-prolonging medications.

Reports of deaths

That same winter, according to Zayas, a physician for one of Staten Island University Hospital's outpatient clinics gave her surprising news.

The doctor told her that a male patient taking Seroquel and methadone together had died, and the doctor thought Seroquel might have played a role. The physician told Zayas the man wasn't her patient and that she had seen him only briefly.

Zayas recalled that she had previously heard of side effects involving Seroquel but never a death. She said she followed company policy and, records cited in the lawsuit show, reported the death in an email to an AstraZeneca safety official.

She said the company never told her whether it had investigated and what it had found.

Within a few months, Zayas said, two more doctors at the hospital told her about a suspicious death.

She again wrote to her company, an excerpt of which is contained in the lawsuit. She wrote that several physicians at the hospital "have stated someone died while on the combination of Seroquel and methadone late last year. At that time, I submitted an (adverse event) report. Since then (a director at the hospital) has restated that number saying several more people and as many as 10 have died while on that combination."

Eventually, Zayas said, four doctors or officials at the hospital told her 10 methadone clinic patients had died.

That summer, Zayas contacted a lawyer and filed a whistleblower suit under seal. She then met with two of her bosses and expressed concern about the deaths, the suit states.

Zayas recalled she was told that others in the company would address the issue and that she should continue selling Seroquel as before.

"After these 10 deaths, I would have hoped there would be some sort of alert, maybe a difference in messaging, a difference in who we targeted," she said. "There was absolutely no acknowledgment of it at all. It was like swept under the rug."

She said she continued to sell Seroquel to doctors at methadone clinics for two more months, until she quit the company and became a sales representative at another drug firm. She said she regrets selling Seroquel once she learned of the dangers but thought she would be fired if she refused.

A spokesman for the Staten Island hospital said he could not corroborate Zayas' reports of 10 deaths.

"No one could recall the spate of deaths referenced in the whistleblower lawsuit," said Terence Lynam, spokesman for Northwell Health, which owns and operates the hospital and its four methadone clinics.

He did confirm that there was one patient who died around 2010 who was taking Seroquel and methadone together. That death, he said, prompted a post-erlike document to be distributed throughout the hospital's psychiatry department, warning about the potential drug interaction.

But Lynam said the department's director, who was referenced in Zayas' lawsuit, did not recall ever talking with her.

In June 2011, nearly a year after Zayas reported the possibility of 10 deaths, the FDA directed AstraZeneca to further strengthen the Seroquel label to say the drug "should be avoided" with medications known to prolong the QT interval, including methadone, the suit states.

Today, Zayas works in sales for a health care company. She said it was wrong for AstraZeneca to direct her to promote Seroquel to physicians treating at-risk populations, including those in methadone and pain clinics.

"They set me up to go in there and basically almost kill people," she said. "You don't want to know you're working for that kind of company."

sroe@chicagotribune.com