FOR YOUR PATIENTS-PARKINSON'S DISEASE

FDA Revisits Pimavanserin Amid Reports of Serious Adverse Events, Deaths in Parkinson's Patients

BY KURT SAMSON

ARTICLE IN BRIEF

Reports about adverse events associated with pimavanserin for Parkinson's disease-related psychosis have prompted the US Food and Drug Administration to re-examine the drug, which was approved for the indication in 2016.

The US Food and Drug Administration (FDA) is re-examining the antipsychotic drug pimavanserin (Nuplazid) after reports have emerged regarding rates of adverse events, including deaths, among treated Parkinson's disease patients.

Asked about the issue at an April 17 House budget hearing, FDA Commissioner Scott Gottlieb, MD, said the agency would 'take another look' at the drug, but the evaluation does not mean that it has determined that the medicine presents a new risk or that patients should stop taking it.

"The agency has a duty to investigate reports of 'adverse events' but this does not mean that the drug being investigated is the cause," Dr. Gottlieb said.

The drug was approved for Parkinson's disease (PD) psychosis in 2016 under the agency's expedited "breakthrough therapy" program. However, at that time several members of the agency's review team expressed concerns about its safety profile.

Manufactured by Acadia Pharmaceuticals pimavanserin is in a new class of medications that block a subfamily of serotonin receptors (5 HT2A). Rather than affecting dopamine like other psychosis medications, serotonin receptors help regulate a range of brain functions, including cognition, memory, and the ability to learn.

In late April, CNN reported that the FDA's Adverse Event Reporting System (FAERS) showed a total of 700 deaths, including 500 patients where the drug was the only agent likely involved.

At that time, the FDA stated, "[T]here remain limitations to the data. For example, while FAERS contains reports on adverse events associated with a particular drug or biologic, this does not mean that the drug or biologic caused the adverse event. Importantly, the FAERS data by themselves are not an indicator of the safety profile of the drug or biologic."

DR. RAJESH PAHWA: "It is unfortunate that instead of discussing scientific data from scientific journals we are more concerned about discussing biased reporting from news channels who have no idea what PD psychosis is or the risks that it involves. Such reporting would never make it in a peer-reviewed journal."

In addition to data collected from FAERS, CNN and other news reports cited a safety report released in November 2017 by the nonprofit Institute for Safe Medication Practices (ISMP). ISMP found a total of 244 deaths, or 10.9 percent of patients using the drug, in the first six months after approval. Surveillance also showed that 22.1 percent of patients suffered hallucinations while using the drug; 14.9 found the drug ineffective; and 11.5 percent experienced confusion, the ISMP reported.

The agency voted to approve the drug in March 2016, over the objections of the FDA clinical reviewer medical officer Paul J. Andreason, MD, one of only two panelists who voted against approval. He argued that the rate of serious adverse events, including death, in clinical trials were more than double than that in control group patients.

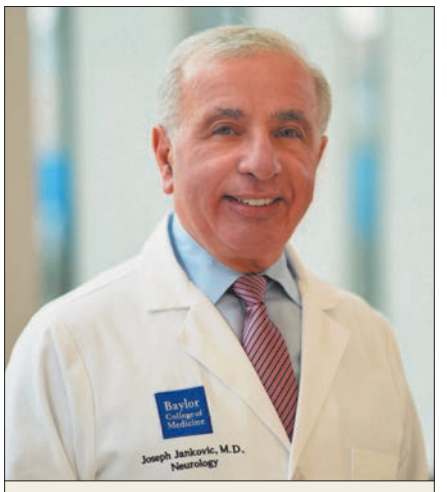
"You need to treat 91 people to get seven full responses. You'll have five serious adverse events based on these numbers, one of which will result in death," he said at that time.

The ISMP report also cited what it viewed as shortcomings in the approval.

"We share the FDA medical officer's concerns about the approval of pimavanserin in the face of weak evidence of effectiveness, on the basis of a single small trial, and with increased rates of serious adverse events including death. The early but substantial adverse event data further support these concerns."

It "makes biological sense" that suppressing a major neurotransmitter system involved in learning, memory, cognition, and many other body functions will have "substantial potential for harm," according to the report, especially when combined with other serotonin-blocking agents.

"We identified 318 cases where pimavanserin … was combined with quetiapine (Seroquel) or other antipsychotics that block dopamine signaling. These drugs are not recommended for use in the elderly and are not approved for use in Parkinson's. Also, in this subset of patients, each was taking a median of 10 different drugs," the ISMP stated.



DR. JOSEPH JANKOVIC: "I suspect that the death rates in elderly patients with advanced PD and psychosis are higher than in a control population without these problems, so it's not surprising to see deaths in such patients who are taking pimavanserin, but the cause-effect relationship has not been established."

FDA: NO LABEL CHANGES

The media reports resulted in a reported 20 percent drop in Acadia share prices, even though the data cited by CNN have not been corroborated by the FDA and the agency has said little other than it is looking into the issue.

"FDA is conducting an evaluation of available information about pimavanserin. We have nothing more to share at this time," Sandy Walsh, an agency spokesperson told *Neurology Today*. In a statement released April 25, the agency said that the evaluation does not mean that it has determined that the medicine has a new risk, nor does it suggest health care providers should not prescribe it, or that patients should stop taking the medication.

"Based on these data, the FDA has, at this time, not identified a specific safety issue that is not already adequately described in the product labelling," the agency said.

In an April 10 statement, the FDA said that it will continue to monitor adverse events submitted to FAERS. "We have noted that the cases typically involve geriatric patients with advanced-stage Parkinson's disease, as well as numerous medical conditions, who are frequently taking concomitant medications with risks for serious adverse events, including death. Based on these data, the FDA has, at this time, not identified a specific safety issue that is not already adequately described in the product labeling."

EXPERT COMMENTARY

Rajesh Pahwa, MD, FAAN, professor of neurology and chief of the Parkinson & Movement Disorders Division at the University of Kansas Medical Center in Kansas City, was critical of the news media's response to the issue.

"It is unfortunate that instead of discussing scientific data from scientific journals we are more concerned about discussing biased reporting from news channels who have no idea what PD psychosis is or the risks that it involves. Such reporting would never make it in a peer-reviewed journal," he told *Neurology Today*.

Dr. Pahwa noted that antipsychotics used for schizophrenia were and continue to be used for the treatment of PD psychosis, and all antipsychotics have black box warning about increased

Continued on page 9

Pimavanserin, Adverse Events

Continued from page 4

mortality. "Even pimavanserin has this black box warning."

To date, he noted, no clinical studies have demonstrated an increased mortality in pimavanserin patients related to the medication.

"The FDA's FAERS database is unmonitored, and there can be multiple reports of a single patient from different resources, such as a family member, physician, pharmacist, etc."

Moreover, pimavanserin is prescribed through a specialty pharmacy which has increased patient contacts even after the patient discontinues the drug, he added. "They have to report any cases of death, which is not true of medications prescribed through neighborhood pharmacies."

Mortality rates from Medicare database show mortality rates (per 100 patient years) of 7.3 for PD patients without psychosis, and 28 for PD patients with psychosis, for atypicals like quetiapine, with a rate of 18.6, and olanzapine, at 29.3, while post marketing data for pimavanserin is about 12.4, he said.

"In my personal experience with pimavanserin, it is effective in a majority of PD psychosis patients. We need to further study the reports of increased mortality, but in a scientific manner."

Joseph Jankovic, MD, FAAN, the Distinguished Chair in Movement Disorders and director of the Parkinson's Disease Center at Baylor College of

Continued on page 10

Pimavanserin, Adverse Events

Continued from page 9

Medicine in Houston, told *Neurology Today* that his patients have also responded well to treatment.

"While not all patients are completely satisfied, many of my patients have experienced marked improvement in their visual hallucinations, paranoia, and other psychotic symptoms," he said. "I suspect that the death rates in elderly patients with advanced PD and psychosis are higher than in a control population without these problems, so it's not surprising to see deaths in such patients who are taking pimavanserin, but the cause-effect relationship has not been established."

Nevertheless, he advised physicians to closely follow patients, especially if they have other medical problems or are taking concomitant medications that could increase their risk of drug-related complications.

"Long-term monitoring, and continuous and vigorous data collection, are needed before any definite conclusions can be made. For the time being, at least in my patients, I believe the benefits outweigh the risks."

DR. CYNTHIA COMELLA:
"I think it is too soon to be concerned specifically about this drug. We don't have enough data — the extent of these adverse events or how they might compare with other atypical agents."

Cynthia Comella, MD, FAAN, professor of neurology at Rush University Medical Center's Parkinson's Disease and Movement Disorders Section in Chicago, said she is not going to change how she treats her PD patients.

"I think it is too soon to be concerned specifically about this drug. We don't have enough data — the extent of these adverse events or how they might compare with other atypical agents," she told *Neurology Today*. "I feel that we need to be cautious with all of these drugs. I especially have concerns prescribing them in elderly patients because they are more fragile and usually have additional disorders and health conditions." •

DISCLOSURES

Drs. Jankovic and Comella reported no related conflicts of interest. Dr. Pahwa has received consulting fees from Abbvie, Acadia, Acorda, Adamas, Cynapsus, Global Kinetics, Ionis, Lundbeck, Neurocrine, St Jude Medical, Teva Neuroscience, UCB, and US World Meds. He has received research grants from Acorda, Adamas, Avid, Boston Scientific, Cala Health, Cynapsus, Kyowa, National Parkinson Foundation, NIH/NINDS, Parkinson Study Group, Pfizer, and US WorldMeds.

LINK UP FOR MORE INFORMATION:

- CNN Investigates: FDA worried drug was risky; now reports of deaths spark concern: **http://bit.ly/Pimavanserin**
- ISMP Report: Safety signals for two novel drugs: **http://bit.ly/ISMP-report**