



Pimavanserin evaluated by the FDA

The US Food and Drug Administration is conducting an evaluation of available evidence about pimavanserin. Paul Webster reports.



Jason Reed/Reuters

The US Food and Drug Administration (FDA) is conducting an evaluation of available information about pimavanserin after the publication of reports of postmarketing adverse events by the Institute for Safe Medication Practices (ISMP), a Pennsylvania-based non-profit organisation. The drug, marketed as Nuplazid by Acadia Pharmaceuticals, was approved by the agency in April, 2016, to treat hallucinations and delusions associated with psychosis experienced by some people with Parkinson's disease.

In a statement to *The Lancet* about its evaluation launched recently, the FDA cautioned that "the potential signal of a serious risk" does not mean that the agency has determined that there is "a new risk", or that patients should stop taking the medication.

Pimavanserin was given accelerated approval by the FDA despite concerns expressed by some sitting on its Psychopharmacologic Drugs Advisory Committee, notably by consumer, patient, and academic representatives and by the senior medical reviewer for the FDA, Paul Andreason. Committee member Almut Winterstein, a University of Florida pharmacy professor, told *The Lancet* she thought that "There clearly needs to be a better assessment".

The FDA granted the drug accelerated approval on the basis that it was urgently needed, that its packaging contains strong warnings (the so-called black box warning), and that its safety is being closely monitored by the FDA and Acadia.

In an April, 2016, memo, Robert Temple, FDA acting deputy director of Drug Evaluation, noted there was "disagreement within the division" as to whether the drug's benefits in treating hallucinations and delusions in Parkinson's patients outweigh the

risks of using an antipsychotic "in a relatively frail elderly population".

"The serious adverse events were more common on drug (16/202, 7.9%) than placebo (8/231, 3.5%), but had no unifying pattern and are hard to interpret as drug related, despite the numerical difference", Temple said in the memo.

The phase 3 trial in question was published online first in *The Lancet* in November, 2013. It enrolled 199 participants from 52 centres in the USA and Canada. Although the study did not provide safety data or evidence regarding durability of response beyond 6 weeks, it concluded pimavanserin was well tolerated and the drug "may benefit patients with Parkinson's disease psychosis for whom few other treatment options exist".

Reports of postmarketing adverse events—including hallucinations, confusional states, and deaths—collected by the FDA from patients using the drug were published last November by the ISMP. The institute's senior scientist for drug safety Thomas J Moore says that "the number of deaths in adverse events reports has increased very substantially since then". Moore added that "you have to be cautious about deaths in adverse events reports, so we recommended that the FDA investigate".

In its report, the ISMP suggested that "adverse event reports of hallucinations were likely showing that the drug was making some psychosis worse, or in other instances, it was not providing the expected benefit". The ISMP report also raised concerns about the use of pimavanserin in combination with other drugs.

Acadia's CEO Steve Davis told *The Lancet* that he rejects the ISMP's statements about adverse events

and deaths but welcomes the FDA's evaluation.

"We don't see any causal link to mortality and that includes when you use pimavanserin in combination with other drugs", Davis said. He added that the drug's effects on patients is being closely watched. "We feel very good about its safety profile", he said.

The ISMP's report asserts that "pimavanserin was FDA-approved on limited scientific evidence that its benefits outweighed its risks. It relied on a single clinical trial indicating a minimal treatment effect, used a measurement scale for symptoms that had not been validated, and succeeded only after three previous trials had failed to demonstrate a benefit". Davis says he "strongly disputes" these claims. "Robust efficacy" was demonstrated in the principal trial of the drug, he says, and further data supporting its efficacy was generated in three more trials.

Clive Ballard, executive dean of the University of Exeter Medical School and co-author of the pivotal trial analysed by the FDA in approving the drug, told *The Lancet* that he also rejects the ISMP's claims that the study showed a minimal treatment effect and that it used an unvalidated measurement scale. "The FDA considered the evidence to be overwhelming in that it consistently showed moderate treatment effects across all measurements" including for hallucinations, delusions, and caregiver relief, Ballard said. The measurement scale employed in the study was "well validated", he added.

"The overall decision of the FDA was correct", Ballard insisted.

Acadia told *The Lancet* that pimavanserin is currently being tested in patients with Alzheimer's disease, depression, and schizophrenia.

Paul Webster