The US Food and Drug Administration's Perspective on the New Antipsychotic Pimavanserin

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ABSTRACT

Objective: To summarize the US Food and Drug Administration's (FDA's) review of the safety and effectiveness for pimavanserin, an atypical antipsychotic, for the treatment of hallucinations and delusions associated with Parkinson's disease psychosis. We describe the regulatory and clinical issues important to the FDA's approval of this New Drug Application, with special focus on the risk-benefit balance. We also describe a new labeling feature that presents additional efficacy data to clinicians.

Data Sources: Data sets for all relevant clinical trials of pimavanserin and the Applicant's and FDA's analyses of these data were considered in this review. Data were available from 616 patients with Parkinson's disease with hallucinations and delusions who received at least 1 dose of pimavanserin, with a total exposure of 825 patient-years in the Parkinson's disease psychosis population.

Results: Pimavanserin 34 mg/d was effective in treating hallucinations and delusions associated with Parkinson's disease. In the Applicant's single pivotal trial, 80.5% of pimavanserin patients experienced at least some improvement in symptoms compared to 58.1% of patients taking placebo. Pimavanserin did not worsen motor function, an adverse effect commonly observed with other antipsychotics, probably because of a lack of consequential dopamine binding.

Conclusions: Pimavanserin is the only FDA-approved treatment for the hallucinations and delusions seen in patients with psychosis of Parkinson's disease. Although pimavanserin appears to have a pharmacologic mechanism that is different from other atypical antipsychotics, concern remained that the increased risk of death seen with antipsychotic use in elderly demented patients, and described in all approved antipsychotic labels, would also occur with pimavanserin. Pimavanserin bears the same boxed warning about the risk of death associated with antipsychotic use in elderly patients with dementia.

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The US Food and Drug Administration (FDA) approved pimavanserin, an inverse agonist at the serotonin 5-HT_{2A} receptor, thus, an atypical antipsychotic, for the treatment of hallucinations and delusions associated with Parkinson's disease psychosis (PDP) on April 29, 2016. This article summarizes the FDA's review of the New Drug Application (NDA) for pimavanserin, including the clinical efficacy and safety data collected from 3 clinical trials. It does not attempt to review the full literature on pimavanserin; rather, it discusses the data that were important to the FDA's approval decision, differences in the pharmacology of this drug compared to other antipsychotics, the evaluation of efficacy and safety, and the balance between benefit and risk when the drug is used to treat the hallucinations and delusions of Parkinson's disease. A novel presentation of efficacy data included in the product labeling is also discussed. The primary source documents for this article are the FDA's reviews and memoranda related to the pimavanserin NDA; these can be accessed via the FDA's website.[1] The FDA review was based on the detailed data provided by the Applicant; in instances where the controlled clinical trials have been published, we have included references to those publications.[1,2]

REGULATORY CONSIDERATIONS

Parkinson's disease is a progressive, neurodegenerative disorder characterized by abnormality of movement and coordination.[3] It affects about 1 million individuals in the United States, half of whom develop comorbid psychosis.[4] The development of PDP is associated with accelerated mortality and often leads to increased caregiver burden and the potential for placement in a nursing home.[5,6]

The recognition, by drug developers, of PDP as a potential target for drug treatment is relatively recent.[7] It was previously thought by many that this condition occurred solely as an adverse effect of treatment with antiparkinsonian drugs, given that the incidence of PDP increases substantially after the first year of therapy.[4,8,9] However, further study revealed that some patients experience PDP despite never having received antiparkinsonian drugs.[10]

Some published studies of antipsychotic use in the treatment of PDP have reported favorable effects, but with variable tolerability.[11–14] These studies[11–14] were not evaluated by the FDA (because they were not submitted in support of a labeling change) and, as a result, have not been included in drug labeling. The absence of approved therapy to treat PDP, along with the substantial impact of severe symptoms on patients, highlighted this condition as an area of significant medical need, and this need was central to the FDA's consideration of pimavanserin.

Clinical Points

- Novel treatments in vulnerable populations and areas of unmet medical need require thorough consideration of benefit versus risk.
- The pimavanserin product label provides graphical presentations of clinically important information related to treatment response for the hallucinations and delusions seen in patients with Parkinson's disease psychosis.

Pimavanserin was a new molecular entity; that is, it had not been approved for any other use before its approval for PDP. The data submitted with the application demonstrated efficacy in treating the symptoms of hallucinations and delusions associated with PDP, but there was some evidence that the drug might have an increased risk of death and serious adverse events similar to that seen with other antipsychotics when used in the frail elderly population.[1] The evidence of effectiveness of pimavanserin in PDP led the FDA, as part of its commitment to expedite novel therapies for serious illnesses in areas of unmet medical need, to grant Breakthrough Therapy Designation to pimavanserin. This designation included a commitment to work closely with the Applicant to agree on the data necessary to support approval.[15] In discussions with the Applicant, the FDA agreed that a single well-designed and robustly positive study demonstrating both improvement in PDP symptoms and no worsening of motor symptoms of Parkinson's disease could support approval. In fact, the evidence supporting approval for pimavanserin in PDP was obtained from a single, strongly positive study with supportive data from other studies.[1]

The clear benefit and significant risk concern described above presented the FDA review team with complex regulatory considerations that called for input from the Psychopharmacologic Drugs Advisory Committee (PDAC) in a public meeting. The PDAC comprised 12 clinicians and 2 patient advocates. After presentations of the data by the Applicant and the FDA, as well as comments from patients and patient-advocacy groups, the PDAC voted 12–2 in favor of a decision to approve pimavanserin for the treatment of PDP.[16]

The approval of pimavanserin for the treatment of PDP demonstrates what might be viewed as a shift in risk-benefit considerations for antipsychotics. In order to understand the reasoning behind previous regulatory decisions and the approval of pimavanserin, some historical perspective is necessary.

First, one must be clear that the FDA does not regulate the practice of medicine. Thus, the fact that no antipsychotic drug had been approved for PDP or for agitation in the demented elderly does not mean that marketed drugs could not be used for these conditions. Prior to the approval of pimavanserin, NDAs for indications involving agitation and psychosis in the frail elderly population did not gain FDA approval despite their wide use in clinical practice and observed efficacy. This lack of approval was the result of multiple factors, chief of which was the evidence of serious adverse events and death, a finding that led to the inclusion of a boxed warning in both atypical and conventional antipsychotic product labeling. Nevertheless, patient advocacy groups supported this use if it was clinically necessary after other interventions have failed, and the FDA, in public statements, did not suggest that the use was unreasonable. The formal approval of a drug to treat psychosis in a vulnerable elderly Parkinson's disease population represents a view that a clear benefit in a disease with no available therapy could outweigh, for informed caregivers and patients, possibly serious risks.

PHARMACOLOGY AND DRUG DESIGN

Pimavanserin is an atypical antipsychotic that does not have prominent dopamine antagonism as part of its binding profile, making it a logical drug to develop in a setting where dopamine augmentation therapy is a standard of care. The dopaminergic drugs used to treat Parkinson's disease are thought to exacerbate the psychotic symptoms of the disease, and treatment options prior to pimavanserin included decreasing the antiparkinsonian dopaminergic medications or adding a dopamine-blocking atypical antipsychotic (usually clozapine or quetiapine), both of which could undermine dopamine augmentation therapy in Parkinson's disease and would be expected to exacerbate parkinsonian symptoms.

It was hoped that pimavanserin's relative lack of dopamine binding would make it suitable for treating patients with Parkinson's disease who develop psychosis at some point in their disease, correcting the psychosis without worsening the motor symptoms of Parkinson's disease. This hypothesis was tested in the clinical trial submitted to support approval, and the results are presented below.[2]

Mechanism of Action

As is the case for all antipsychotics, the mechanism of pimavanserin's effect on hallucinations and delusions associated with PDP is not known with certainty. However, its mechanism of action is thought to be related to its activity as an inverse agonist and an antagonist at the serotonergic 5-HT_{2A} receptors (K_i of 0.087 nM) and, to a lesser extent, at the 5-HT_{2C} receptors (K_i of 0.44 nM) in the central nervous system,[1] similar to other atypical antipsychotics such as clozapine, olanzapine, and iloperidone. Pimavanserin's binding to dopamine receptors D_1, D_2, and D_4 is negligible, and its binding to D_3 is low (K_i of 370 nM).[1] All other marketed atypical antipsychotics have some binding at the dopamine receptors. Pimavanserin's lack of dopamine-related effects was demonstrated in animals; for example, there were no signs of ataxia, muscle incoordination, or induction of catalepsy in mice or rats.[17,18]

THE EFFICACY AND SAFETY TRIALS

Efficacy

Efficacy was established in a single trial in patients with Parkinson's disease, hallucinations, and delusions.[1] This study was a 6-week, multicenter, randomized, double-blind,

Table 1. Primary Efficacy Analysis Results: SAPS-PD Change From Baseline to Week 6[a]

End Point	Mean Baseline Score (SD)	LSM Change From Baseline (SE)	Placebo-Subtracted Difference[b] (95% CI)
SAPS-PD			
Pimavanserin	15.9 (6.12)	−5.79 (0.66)	−3.06* (−4.91 to −1.20)
Placebo	14.7 (5.55)	−2.73 (0.67)	…
SAPS-PD Hallucinations			
Pimavanserin	11.1 (4.58)	−3.81 (0.46)	−2.01 (−3.29 to −0.72)
Placebo	10.0 (3.80)	−1.80 (0.46)	…
SAPS-PD Delusions			
Pimavanserin	4.8 (3.59)	−1.95 (0.32)	−0.94 (−1.83 to −0.04)
Placebo	4.8 (3.82)	−1.01 (0.32)	…

[a]Data from New Drug Application for pimavanserin.[1]
[b]Difference (drug minus placebo) in LSM change from baseline.
*Statistically significantly superior to placebo, $P = .001$.
Abbreviations: LSM = least squares mean, SAPS-PD = Scale for the Assessment of Positive Symptoms in Parkinson's Disease.

placebo-controlled, centrally rated trial that used the Scale for the Assessment of Positive Symptoms in Parkinson's Disease (SAPS-PD) as the primary end point. The study population comprised predominantly white patients from 54 sites in North America and included 116 males and 69 females, with a mean age of 72.0 years (range, 53–90 years).[1] The SAPS-PD was derived by the Applicant from the larger SAPS scale by selecting 9 items that assessed the severity of hallucinations and delusions, the primary psychotic events in patients with Parkinson's disease that lead to treatment. The results of the primary analysis are presented in Table 1, as are supportive analyses of the hallucinations and delusions components of the SAPS-PD.

Efficacy Explorations

Although the mean effect of treatment was strongly statistically significant, it was not large, and there is value in assessing individual responses; therefore, the Applicant and the review team explored individual responses by examining the cumulative distribution of change in SAPS-PD and by using different definitions of response. Figure 1 shows a plot of the cumulative distribution function of improvement in SAPS-PD by treatment at study end point. Of note, 80.5% of pimavanserin patients experienced at least some improvement in hallucinations and delusions as compared to 58.1% of patients taking placebo. Perhaps of greater interest, over 40% of those taking pimavanserin had an 8-point improvement, a sizeable effect compared to 20% of placebo patients experiencing similar improvement.

The full range of numerical improvements can also be displayed as rates of different levels of improvement in bar graphs, as shown in Figure 2. This figure shows the range of responses at end point, and also shows the rates of complete response (no hallucinations or delusions). The visual representation of individual responses provides clinically important efficacy information from pimavanserin's pivotal study and appears to have greater relevance to clinical practice than simply reporting mean changes from baseline.

Figure 2 shows that patients taking pimavanserin had numerically greater rates of response at all levels of response, and, notably, some patients had complete response, with 13.7% of patients taking pimavanserin reporting no hallucinations or delusions at end point compared to 1.1% of placebo-treated patients. A version of this differential response graph was included in product labeling to provide clinicians with the data on individualized responses.

Time Course of Response

Change from baseline in the primary end point over time is shown in Figure 3. Although the primary end point was change from baseline to week 6 on the SAPS-PD, a nominally significant (but not a planned study end point) separation from placebo was evident at week 4 and continued until the end of the trial.

Secondary End Points

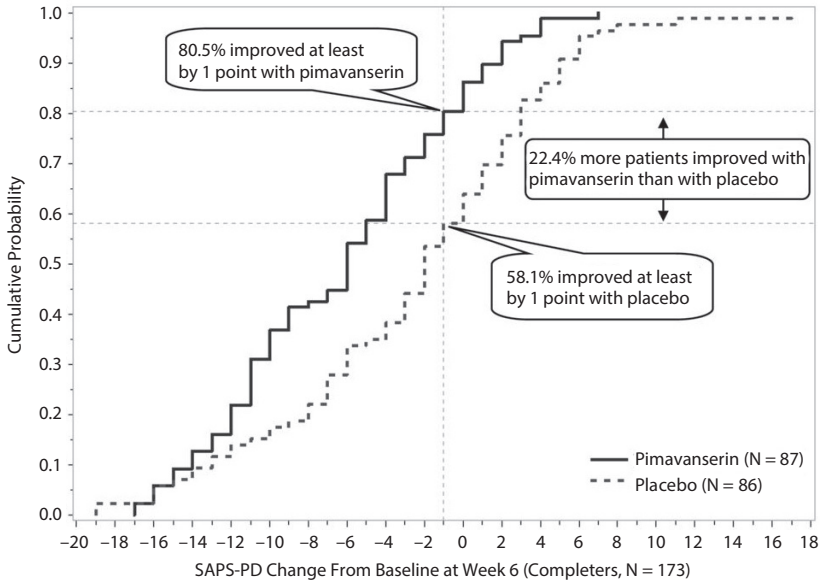
The secondary end point in the prespecified testing sequence evaluated the Applicant's hypothesis that pimavanserin would not, because of its lack of dopamine blockade, have a detrimental effect on the primary movement disorder of Parkinson's disease (ie, a demonstration of noninferiority to placebo) using the Unified Parkinson's Disease Rating Scale (UPDRS) combined Part II (activities of daily living) and Part III (motor symptom examination). A noninferiority margin of 5 points was agreed to by both the FDA and the Applicant because it was considered to be the minimal clinically important change in the UPDRS. The results of the analyses are presented in Table 2 and show that the upper limit of the 95% confidence interval did not exceed the prespecified inferiority margin, thus confirming the Applicant's hypothesis.

Pimavanserin demonstrated no worsening in motor symptoms of Parkinson's disease, as measured systematically by the UPDRS, an important finding in this disease. Although the Applicant attributes this lack of motor worsening to less dopaminergic activity, studies of clozapine have demonstrated similar results using the UPDRS,[11,19,20] implying that the true mechanism remains uncertain.

Safety

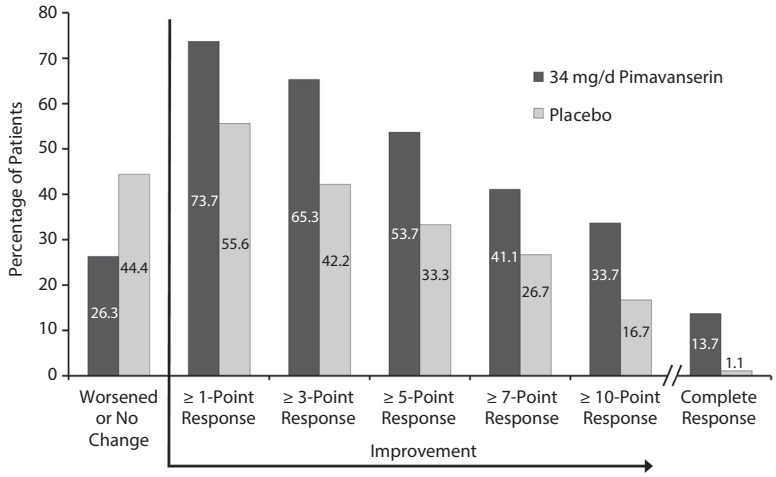
In the long-term open-label treatment population of those with PDP, there were 51 deaths among 459 treated patients with PDP (11.1%), but mortality is known to be increased in patients with PDP, and no drug-related cause was apparent.[1] An increased risk of commonly occurring adverse events, including deaths, is difficult to discern with open-label data. Therefore, the review relied primarily on the controlled trial safety data to assess the risk of drug-related mortality and morbidity. The controlled safety data showed a numerical increase in the risk of serious morbidity; but, the number of events was too small to reach a firm conclusion, and the number of individual adverse events was particularly small. Serious adverse events (SAEs) occurred in 16 of 202 patients taking pimavanserin 34 mg (7.9%) and in 8 of 231 placebo-treated patients (3.5%) in the 6-week trial population. There was no individual SAE that

Figure 1. Empirical Cumulative Distribution Function Plot by Treatment at Week 6[a]



[a]Data from the New Drug Application for pimavanserin.[1]
Abbreviation: SAPS-PD = Scale for the Assessment of Positive Symptoms in Parkinson's Disease.

Figure 2. Proportion of Patients With SAPS-PD Score Improvement at the End of Week 6 (N = 185)[a]



[a]Data from the New Drug Application for pimavanserin.[1]
Abbreviation: SAPS-PD = Scale for the Assessment of Positive Symptoms in Parkinson's Disease.

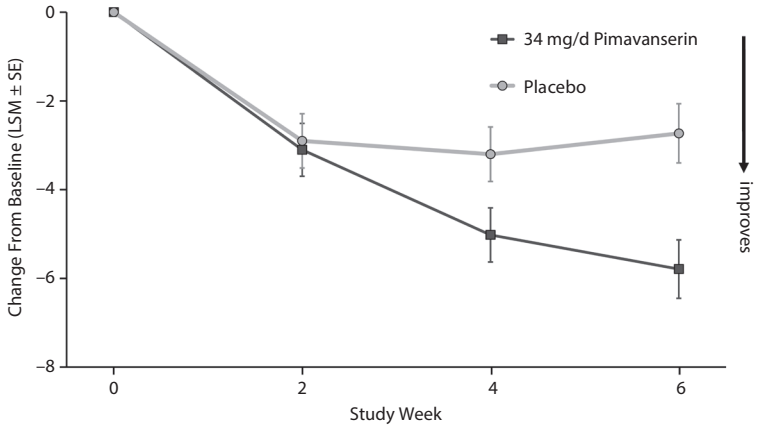
dominated this difference, with most SAEs being infections (6/202 [including 2 deaths] taking pimavanserin vs 2/231 taking placebo), mental status changes (5/202 taking pimavanserin vs 2/231 taking placebo), and cardiovascular (2/202 [including 1 death] taking pimavanserin vs 1/231 [also resulting in death] taking placebo). Thus, there appeared to be no unifying pathological mechanism.

There are, however, grounds for a general concern with the use of antipsychotics in frail, elderly, demented patients. Many studies have suggested increased mortality in elderly patients when they are treated with antipsychotics for agitation, generally without a clear and specific mechanism, and all antipsychotics bear a boxed warning stating: Elderly patients with dementia-related psychosis treated with antipsychotic drugs are at an increased risk of death. Because the safety data from pimavanserin were generally similar to those already described in antipsychotic labeling, the standard antipsychotic boxed warning was included in the approved pimavanserin labeling.[1]

Drug Toxicity Profile

Similar to other cationic amphiphilic drugs (CADs), pimavanserin causes phospholipidosis (the accumulation of lipids in cells) across multiple animal species in

Figure 3. SAPS-PD Change From Baseline Through 6 Weeks Total Study Treatment[a]



[a]Data from the New Drug Application for pimavanserin.[1]
Abbreviations: LSM = least squares mean, SAPS-PD = Scale for the Assessment of Positive Symptoms in Parkinson's Disease.

numerous tissues and organs.[1,21,22] Phospholipidosis is usually reversible after cessation of drug treatment; however, high or prolonged exposures to CADs can lead to dose-limiting functional and structural tissue damage (eg, nephrotoxicity, pulmonary toxicity, myopathy, and retinopathy).[21,23] In the case of pimavanserin, multiorgan "systemic" phospholipidosis occurred in mice, rats, and monkeys; it was both dose and duration dependent and was observed within 2 weeks of daily administration, with the lungs and kidneys being the most severely affected.[1] In rats, severe phospholipidosis correlated with chronic inflammation with or without secondary inflammatory fibrosis in the lungs and tubular degeneration in the kidneys.[1] Severe phospholipidosis in the lungs affected the general well-being of rats, caused respiratory-related clinical signs, including rales, and resulted in morbidity/mortality. There is approximately a 5-fold safety margin at the no-observed-effect level (NOEL) dose for chronic inflammation in the lungs based on the area under the curve at the maximum recommended human dose of 34 mg/d.[1]

POSTMARKETING COMMITMENTS

In an effort to enhance the established safety profile for pimavanserin, the FDA obtained commitments from the Applicant to conduct studies after approval, known as postmarketing commitments. Pimavanserin is the subject of several postmarketing commitments aimed at providing additional information about its use in the Parkinson's disease population and in frail and elderly patients. These include a commitment to conduct a drug-drug interaction study to inform dosing considerations in the presence of strong cytochrome P450 3A4 inducers and a randomized withdrawal trial after 6 weeks of treatment to determine whether an effect on the hallucinations and delusions of Parkinson's disease persists. A postmarketing commitment was also created to further explore the effects of phospholipidosis and chronic inflammation in the lungs of animals that received pimavanserin.[1]

Table 2. Primary Analysis Results of Key Secondary End Point: Parkinson's Disease Status (UPDRS II + III) Change From Baseline to Week 6[a,b]

ANCOVA (OC) LSM Estimate (SE)		Difference From Placebo in LSM Estimate (SE)	95% CI	*P* Value
Pimavanserin (N = 92)	Placebo (N = 88)			
−1.40 (0.86)	−1.69 (0.88)	0.29 (1.23)	−2.14 to 2.72	.8140

[a]Data from New Drug Application for pimavanserin.[1]
[b]Baseline UPDRS II + III combined score was approximately 52. A negative change from baseline indicates an improvement.
Abbreviations: ANCOVA = analysis of covariance, LSM = least squares mean, N = number of patients who had a baseline score and the end point score at week 6, OC = observed cases, UPDRS = Unified Parkinson's Disease Rating Scale (II = activities of daily living; III = motor symptom examination).

CONCLUSION

Pimavanserin is the first approved therapy for the treatment of hallucinations and delusions associated with PDP. Its mechanism of action is thought to be unique compared to other medications in its class due in part to its lack of consequential dopamine binding, allowing for improvement in PDP symptoms while avoiding many of the adverse events associated with activity at the dopamine receptors. Although concerns associated with the use of atypical antipsychotics in the elderly frail population are believed to also apply to pimavanserin, as described in labeling, postmarketing commitments were obtained to supplement preapproval safety information to better define other potential risks. The product labeling was also designed with a new method for conveying study data that provides useful information to inform prescribing decisions.

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