



November 1, 2017 — New data from 2017 Q1

## SAFETY SIGNALS FOR TWO NOVEL DRUGS

Hallucinations and pimavanserin (NUPLAZID), a new kind of drug for psychosis  
Hypotension with sacubitril-valsartan (ENTRESTO) for heart failure

### Executive Summary

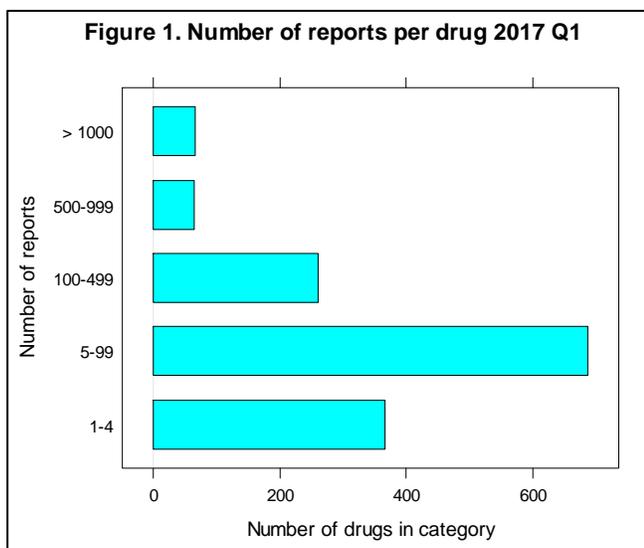
This issue of QuarterWatch focuses on early adverse event data for two new drugs with novel mechanisms of action, and intended for difficult-to-treat patient populations: Pimavanserin (NUPLAZID), approved in April 2016, provided a new biochemical approach to treating symptoms of psychosis such as hallucinations. The combination product sacubitril-valsartan (ENTRESTO), approved in July 2015, targeted a new pathway involved in the regulation of blood pressure, and was effective in patients with already damaged hearts. However, for both drugs we observed new safety signals warranting careful consideration, and likely further action.

QuarterWatch™ is an independent publication of the Institute for Safe Medication Practices (ISMP). We analyze computer excerpts from the U.S. Food and Drug Administration (FDA) Adverse Event Reporting System (FAERS). These reports (best known as MedWatch reports) are a cornerstone of the nation's system for monitoring the safety of prescription drugs after FDA marketing approval.

In 2017 Q1 the FDA received a total of 297,010 new adverse drug event reports identifying 1,445 primary suspect drugs with a median of 22 reports per drug. The report total was 8.4% higher than the previous quarter but 13.2% lower than the same quarter 1 year earlier.

Figure 1 illustrates the wide variation in the number of reports submitted for each of the 1,445 drugs with 1 or more cases. The largest group of drugs (n = 687) fell into the category of 5 to 99 reports. At the extremes, just 66 drugs had 1,000 reports or more. This small group included the two newly approved drugs examined in this report. At the other extreme, a large group of drugs (n = 367) had had so few reports (1-4 cases) that assessing a safety profile would be challenging.

Many factors—some unrelated to safety—affect the overall number of reports. These include brand name rather than generic status, overall prescription volume, manufacturer marketing and education activities,



mass tort litigation, prominent or recent FDA warnings. For a few drugs, the FDA mandates special reporting requirements that can increase reporting rates to nearly 100%.

## Pimavanserin (NUPLAZID) and Hallucinations

In April 2016, the FDA approved a new kind of antipsychotic drug, although initially for a narrowly defined initial indication for medical use—to treat hallucinations (hearing or seeing things that are not there), delusions, and other symptoms of psychosis among patients with Parkinson’s disease. This is a patient population numbering in the hundreds of thousands with a typical onset around age 65. However, pimavanserin is now being tested for use in larger patient populations, including those with psychosis in Alzheimer’s, and as adjunct therapy in schizophrenia. While most antipsychotic drugs primarily block normal signaling with the neurotransmitter dopamine, pimavanserin acts to block signaling with an important subfamily of serotonin receptors (5 HT<sub>2A</sub>) that mediate memory, cognition, learning, and numerous other body functions.

The QuarterWatch team investigated four groups of reported adverse events for pimavanserin seen in the first substantial group of adverse event reports after approval. The events defined important questions about this new drug treatment. Table 1 shows the four most frequently reported adverse event terms for the 12 months ending in March 2017.

We found 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. Further, the agency’s medical reviewer recommended against approval and was overruled. He noted that although other psychiatric drugs were often approved on limited evidence of benefit, in the case of pimavanserin treatment more than doubled the risk of death and/or serious adverse events in its pivotal trial.

Further analysis provided additional evidence 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 number of reports of hallucinations was large (n = 487), with 73% observed by health professionals, who could be expected to understand that hallucinations occur in 20-70% of Parkinson’s patients. Finally, the adverse drug event data supported the results of the pivotal clinical trial of pimavanserin where all patients were observed systematically. In that study, both hallucinations and confusional state also occurred more frequently as an adverse event in treated patients compared with those getting a placebo.

The first substantial group of pimavanserin adverse event reports disclosed an additional safety issue: We identified 318 cases where pimavanserin, which blocks serotonin signaling, 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.

We shared our preliminary results with the manufacturer, Acadia Pharmaceuticals. One reason for the large volume of adverse event reports, the company said, was because of its extensive contact with health professionals and consumers through a specialty pharmacy network that distributed the drug, and because of a company patient support program. It also said the reports of hallucinations might have occurred before the drug became fully effective approximately four weeks after treatment started.

Term	Count, (%) <sup>*</sup>
All Reports	2236
Hallucinations	487 (21.8)
Drug ineffective	333 (14.9)
Confusional state	258 (11.5)
Death <sup>**</sup>	244 (10.9)
<sup>*</sup> One report can include multiple terms	
<sup>**</sup> Includes event term and outcomes of death	

## Sacubitril-Valsartan (ENTRESTO) and Hypotension

Although the FDA has approved more than 100 drugs and combinations to treat hypertension in various forms, the new combination drug sacubitril-valsartan (ENTRESTO) still promised something new. It was the first drug to control blood pressure in part (sacubitril) through inhibiting an enzyme called neprilysin, which regulates biochemical processes in the kidneys, lungs, and brain. When sacubitril was added to valsartan, another approved hypertension drug with a different mechanism, the combination product appeared to produce better outcomes, including lower mortality, in a difficult-to-treat population: Those with chronic heart failure—patients who have insufficient cardiac output because of prior damage to the left ventricle, the main pumping chamber of the heart.

However, the signal investigated for this report suggested that many patients starting on this new drug were experiencing hypotension (low blood pressure), and the reported complications ranged from dizziness to blackouts and other consequences serious enough to require hospitalization. We identified 1,684 adverse event reports indicating a hypotension-related event, more than for any other cardiovascular drug we monitored over the 12 months ending in 2017 Q1. They occurred in older patients (median age 70 years), and although there were 69 reported deaths, in two-thirds of the cases, the health consequences were not severe.

Further investigation showed this adverse event was known, but likely underestimated in the single large clinical trial that supported the drug's FDA approval. In that study, 24.4% of carefully selected patients experienced a hypotension-related adverse event. But FDA reviewers noted this was likely an underestimate because this enriched trial was conducted only with patients already known to tolerate the study drugs without experiencing adverse events severe enough to cause discontinuation.

In this report, we analyze the signal for hypotension, explore why this and other risks were likely underestimated, and consider actions to reduce this manageable risk.

## Adverse Event Reporting System

### FDA Provides for Greater Public Access to FAERS

One of the reasons why QuarterWatch began publication in 2008 was that, while the FDA had for many years released quarterly abstracts of FAERS, using these data required substantial computer and database expertise and knowledge of drugs, drug names and adverse event terminology. In addition, there were no officially released statistics about trends in adverse event reporting, the drugs most frequently implicated, or the types of events being reported. While the FDA has steadily increased the amount and accessibility of drug safety information, including statistics about FAERS, the database itself remained difficult to use for consumers and health professionals.

That situation changed for the better last month with the FDA's release of a fully searchable "FDA Adverse Event Reporting System (FAERS) public dashboard" (<https://www.fda.gov/drugs/guidancecomplianceregulatoryinformation/surveillance/adversedrugeffects/ucm070093.htm>).

We tried out the new public dashboard using the two drugs featured in this issue of QuarterWatch. Overall, we concluded that it provides useful direct access to a globally important database of 14 million adverse drug event reports received by the FDA since 1968. However, because the underlying data are complex, new users will need a substantial investment of time to master the user interface, and an understanding of the limitations and value of these particular safety data.

Put another way, this powerful but complex web site is probably not the consumer's or health professional's first stop in seeking information about the safety profile or suspected adverse reactions for a suspect drug. However, for the thousands of people who submit Freedom of Information Act requests for

specific FAERS data, this new portal provides immediate access through a reasonably straightforward user interface.

One great advantage of software systems is that they can be readily enhanced over time. The Conclusions section outlines both some problems and some additional features that make these valuable data more accessible to a wider audience of consumers and health professionals.

## About QuarterWatch Data

Our findings should be interpreted in light of the known limitations of a reporting system that does not collect data systematically. The submission of an individual report does not in itself establish that the suspect drug caused the event described—only that an observer suspected a relationship. While the sheer numbers of case reports have scientific weight, because of variation in reporting rates, they reveal little about how frequently the events occur in the broader patient population. More complete disclaimers and descriptions of our criteria are included in the Methods Summary section of this report. A disclosure statement expands our description of this project and its staff.

## Conclusions

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 that involves learning, memory, cognition, and numerous other body functions will have substantial potential for harm. While currently approved only for a fairly narrow indication of psychosis in Parkinson's disease patients, it is now being tested for use in other larger patient populations. In addition, the physician and patient information for pimavanserin should more clearly recommend against combining treatment with quetiapine or other antipsychotic drugs.

While the new combination drug for heart failure, sacubitril-valsartan, had consistently positive results in its one large clinical trial, the adverse event data support a concern that the already known risk of hypotension was likely underestimated. Because approximately 1 in 4 patients started on the drug are likely to experience a hypotension-related event, we recommend that the FDA and manufacturer review existing safety data to see what additional warnings and precautions might help reduce the risk of this adverse drug effect.

We were pleased to see the FDA provide better and more user-friendly access to its important adverse drug event database through the FAERS public dashboard. It is an addition to an existing portfolio of important drug safety and effectiveness information that has made the FDA a world leader in transparency. We also see opportunities to enhance this portal. A) While the portal includes elaborate disclaimers and instructions about the limitations of FAERS data, it currently lacks readily accessible information about its potential uses and value. B) Product identification was a problem because users could not combine brand name drug reports with generic name reports or other synonyms. Using the FDA's drug ingredient dictionary would allow access to all the reports for a chemical entity. C) One important and simple task is to search for a particular suspected adverse reaction to a suspect drug. A basic dialog box could greatly simplify this elementary but valuable search. D) The site has a powerful feature that makes available a listing of all the adverse reaction cases identified in the search. But it is currently not possible to download the table to produce output similar to that provided in response to an FOIA request. E) The reports retrieved include many instances of multiple manufacturer revisions of the same case report, without any readily available means of eliminating this form of duplication.

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# Methods Summary

QuarterWatch monitors the safety of prescription drugs through analysis of adverse drug events reported to FDA by consumers and health professional, either directly to the agency or through drug manufacturers. The agency releases computer excerpts for research use on a quarterly basis, and these case reports are our primary data source.[1] A full description of our methodology is available on the QuarterWatch pages of the ISMP web site (<http://www.ismp.org/QuarterWatch/detailedMethods.aspx>).

The severity of the adverse event was classified as serious under FDA regulation[2] if the case report specified an outcome of death, disability, hospitalization, required intervention to prevent harm, was life threatening or had other medically serious consequences. Cases without these outcomes were classified as not serious, and all new cases were included in this analysis unless indicated otherwise. Earlier QuarterWatch issues have focused primarily on a subset of adverse events, those that are domestic and coded with serious outcomes. We continue to monitor domestic, serious reports as an important subset of the newly released case reports.

In these data, the adverse events reported are described by medical terms selected from the Medical Dictionary for Regulatory Activities (MedDRA), a terminology developed by the pharmaceutical industry to describe adverse events in clinical studies and postmarketing reports.[3] The MedDRA terminology also defines broader categories of adverse events that can include any of a list of more specific and related medical terms. We use these categories, called Standardized MedDRA Queries (SMQs), to identify possible cases of some adverse events.[4] We also group adverse event terms using a MedDRA category called High Level Terms (HLTs) that also combine several related but more specific medical terms. High Level Group Terms (HLGTs) combine several related HLTs, and System Organ Classes combine the terms into 26 categories. The QuarterWatch database was updated in November 2016 to MedDRA version 19.1.

To identify signals for various adverse events we also utilize the disproportionality method of Evans[5] to calculate a Proportional Reporting Ratio (PRR). The PRR is similar to the concept of relative risk of the specific adverse event being reported, and permits comparison among drugs with notably different total numbers of reports. In this statistical technique, we compare the fraction of a specific kind of adverse events for the suspect drug to the fraction such events occur among all other drugs in our study period. For example, if reports of hypotension occurred in 12% of all cases of the suspect drug but occurred in only 3% of the cases for all other drugs, it would produce a PRR of 4. We also calculate the Yates  $X^2$  value for the comparison and report the probability that the differences might have occurred by chance.

To provide a broader perspective on the adverse events reported, we assess the patient exposure to drugs on the basis of dispensed outpatient prescription data provided by QuintilesIMS. The data we rely on are an estimate of total non-governmental prescriptions dispensed through retail and mail channels. Our agreement with QuintilesIMS includes the following disclaimer:

“The statements, findings, conclusions, views, and opinions contained and expressed in QuarterWatch are based in part on data obtained under license from QuintilesIMS. information service called the National Prescription Audit™ for 2017 (All Rights Reserved). Such statements, findings, conclusions, views, and opinions are not necessarily those of QuintilesIMS or any of its affiliated or subsidiary entities.”

Events in QuarterWatch are attributed to the product identified as the primary suspect drug in the case report. The drug names are standardized to drug ingredient names based on the National Library of Medicine's RxNorm terminology. When cited in the text, tables, or charts, the brand name of drugs used is normally the one most frequently indicated on the case reports but may account for a small or large share of the actual reports identified. Unless specified, QuarterWatch does not distinguish dose, route of administration, or extended release and other preparations.

# Results

## Report Trends

In 2017 Q1 data, the volume of reports of adverse drug events to the FDA remained relatively stable, as it has for the preceding eight quarters. For the latest quarter the FDA received 297,010 new adverse drug event reports with 79,669 (26.8%) describing events that were fatal or serious and occurred in the U.S. Overall, 95.4% of reports were prepared and submitted by industry, with just 4.6% of cases reported directly to the FDA by consumers and health professionals. The quarterly total included 16,307 reported patient deaths in the U.S. and 11,944 death cases from abroad. In previous reports,[6] we have described the limitations of reports of patient deaths from manufacturers, who report patient deaths they learn about irrespective of whether the drug was suspected of being a contributing factor.

## Pimavanserin (NUPLAZID) and Hallucinations

Pimavanserin (NUPLAZID) was a new kind of antipsychotic drug with a novel mechanism of action. It received expedited consideration at the FDA because it targeted an important unmet medical need. While the initial target population of psychosis in Parkinson's disease was of modest size, the company is seeking expand its approved use in the future into much larger patient populations with schizophrenia and Alzheimer's. However, the FDA medical officer responsible for evaluating the company's application recommended against approval and was overruled. Additionally, in 3 out of 4 clinical trials for efficacy, the drug failed to demonstrate a benefit in reducing hallucinations and other symptoms of psychosis. And now the first substantial group of adverse drug event reports reinforces the concerns of those who warned that pimavanserin might do more harm than good.

## Hearing, Seeing Things Not There

Patients with hallucinations hear and see things that are not there. Visual hallucinations can be as subtle as a mysterious shadow glimpsed from the corner of the eye to fully-formed persons, strange objects, or animals.[7] Patients might hear sounds ranging from background crowd noise to clear voices speaking understandably. The individuals experiencing these effects may realize what they are seeing or hearing is not real. And they may not. Hallucinations are part of a broader spectrum of symptoms of psychosis,[8] which include paranoia, delusions, and other indications of a loss of touch with reality. Hallucinations commonly occur in schizophrenia. They can be induced by illegal drugs such as LSD and high doses of amphetamines, methamphetamines, or cocaine. Hallucinations are also induced by levodopa (usually given in combination with carbidopa), the initial and primary treatment for Parkinson's disease.[9]

## Hallucinations in Parkinson's

In Parkinson's disease, the dopamine-producing neurons are progressively lost. The U.S. patient population is estimated to be approximately 1 million persons, mostly over age 65.[10] The most immediate consequences of Parkinson's are movement disorders, including tremors, muscle weakness, slowed movement, and later muscle rigidity. One primary early treatment is to increase the supply of dopamine through administering levodopa, a precursor of dopamine. An additional treatment is to add dopamine agonists, drugs that bind to dopamine receptors in the brain and central nervous system. But these drug interventions do not replicate the complex signaling that occurs in the nearly instantaneous neurotransmission of dopamine, and dopamine involves many different processes in addition to movement, notably mood, impulse control, memory, and attention. The consequence of the drugs used to treat Parkinson's, combined with the progression of the disease, is that 20%-70% will develop hallucinations and other symptoms of psychosis. For years the scientific literature held that the hallucinations seen in Parkinson's were entirely drug induced[9]; later studies concluded that some cases occurred in the absence

of the dopamine drugs.[11] The standard but off-label treatment of hallucinations in Parkinson's seems a medical contradiction in terms. Customary treatment is to administer antipsychotic drugs, notably quetiapine.[12] But these drugs work by blocking the normal function of dopamine receptors (primarily a subfamily called D<sub>2</sub> receptors).[13] Not only did this make no sense in patients already losing dopaminergic function, but in addition, antipsychotic drugs independently induce movement disorders similar to those occurring in Parkinson's in approximately 35% of treated patients.[13] A significant additional drawback is that antipsychotic drugs carry a Boxed Warning that they are not recommended for use in elderly patients.[14] This is because most Parkinson's patients fall into the elderly category, and the drugs have been found to approximately double mortality.

## Enter Pimavanserin

A California pharmaceutical startup called Acadia Pharmaceuticals pursued a different path. If blocking dopamine transmission in patients with already impaired dopamine neurons did not make sense, that did not exclude the possibility of manipulating other neurotransmitters. Hallucinations are not exclusively linked to impaired dopamine function. Another contributor is an important subfamily of serotonin receptors, called type 2 or 5-HT<sub>2a</sub>. These type 2 serotonin receptors mediate many functions, and notably have a central role in learning, memory, and cognition.[15] However, the likelihood that type 2 serotonin receptors might also contribute to hallucinations was partly supported by these findings: 1) Some illegal hallucinogenic drugs also bind and stimulate type 2 serotonin receptors; 2) The antipsychotic quetiapine blocked both dopamine and serotonin type 2 receptors.[14]

The idea behind pimavanserin was that it would not block or stimulate dopamine receptors, and instead would target type 2 serotonin receptors. Not only would it prevent signal transmission with the brain's own serotonin, it had additional effects suppressing the activity of the neurons with these receptors.[16] If it worked, potential medical uses were numerous: Existing antipsychotics are poorly tolerated and marginally effective [13]; combining them with pimavanserin might increase beneficial effects, or permit lower doses of the antipsychotics, and therefore reduce drug-induced movement disorders. The Parkinson's disease population was also substantial, and even larger was the aging population with Alzheimer's. So, on one hand, here seemed to be an entirely new antipsychotic agent for a potentially large patient population where more effective and humane treatments were needed. However, on the other hand, effectively shutting down a key serotonin system central to learning, memory, and cognition could have substantial adverse effects.

## The Testing of Pimavanserin

Early testing of pimavanserin in patients began in 2004.[17] The first major trial to establish benefit and assess safety began August 2005 in 400 patients with schizophrenia. It was designed to test whether adding pimavanserin treatment to approved antipsychotic drugs would improve outcomes measured on a standard scale of psychosis. It was completed in 2007. Since no final published results are shown on the official clinical trials web site, presumably few if any benefits were found. The next year the company began testing pimavanserin in Parkinson's disease psychosis, launching a Phase 2 (or proof of concept) trial, and then two Phase 3 trials (demonstrating an effect that can be replicated in the likely treatment population). One of the Phase 3 trials was terminated early for futility; the other two trials did not provide evidence of benefit in treating hallucinations and other symptoms of psychosis in Parkinson's patients.[18]

## A Meeting at the FDA

After three trials that had failed to show a treatment benefit, the manufacturer met with the FDA seeking an agreement that the agency would approve the drug on the basis of a single new trial. Despite the previous failed trials, the agency agreed to judge the drug on a single trial (rather than the normal 2 trials) provided it could demonstrate "strong" effects. In addition to reducing the required level of evidence, the agency provided additional incentives, declaring it a "breakthrough drug" and agreeing to a faster "priority review." To grant pimavanserin "breakthrough" status was a stretch, since breakthrough status requires preliminary clinical evidence of a "substantial improvement" over available therapies.[19] At that point, pimavanserin

hadn't demonstrated improvement, although no other treatments had been approved for comparison purposes.

## A Pivotal Trial Redesigned

Seeking a better chance of demonstrating a benefit, Acadia redesigned its next trial.[18] The accepted measurement scale for measuring changes in psychotic symptoms contained 20 items. The company reduced the scale to just 9 items, a new scale subset that had not been previously validated.[20] It excluded patients with milder psychosis. It eliminated doses lower than 34 mg, twice daily. Because results had been weaker in the foreign clinical trial sites, the new trial was conducted only in North America. And all the assessments of possible benefit were conducted via video link by a single blinded, central rating team. An initial two-week period of non-pharmacological treatment was added to eliminate placebo responses.

The trial results in 199 patients provided evidence of benefit using the new psychosis rating scale. The results also showed it was not making the other Parkinson's symptoms worse (a major risk of antipsychotics). It was hard to evaluate the clinical relevance of the new scale, but the later FDA assessments suggested an improvement of about 23%.

## The FDA Medical Reviewer Objects to Approval

A hallmark of the FDA's long tradition of critical scientific evaluations is not only that it allows mid-level and senior staff dissent, but also that their reports are usually made public. The medical reviewer, a psychiatrist named Paul J. Andreason, outlined numerous concerns in a 160-page review.[20]

While noting that the results indicated a statistically significant benefit, he had other concerns. While two trials (evidence that can be replicated) were normally required, the FDA had agreed to act on a single trial. The primary measurement scale had not been used before with other drugs. The patient population was "enriched" to focus on patients most likely to respond, rather than typical patients. And 13.4% of the pimavanserin patients had protocol violations, notably use of banned antipsychotic drugs. In addition, he questioned whether the change of 3 points on a 45-point scale was clinically significant. Using one accepted assessment, a change of the effect size seen in the trial was qualitatively described as "minimal." An agency expert on clinical assessments was also consulted, and declared "We also conclude that a 3-point change (out of 45) does not clearly represent a clinically meaningful change." [21] This expert thought it would take a benefit about twice that reported to achieve a clinically meaningful change. But notably, the medical officer concluded that despite these marginal benefits he would have still recommended approval because, he said, the agency had approved numerous other psychiatric drugs with this level of evidence. His primary grounds for rejection of approval were on the other side of the drug balance: safety.

## The Safety Profile

The first concern was that despite 18 clinical trials conducted with pimavanserin, the size of the safety database was small; just 1,096 patients were exposed to the active drug (1,500 is the usual standard); and only 202 patients with Parkinson's were exposed to the recommended 34 mg dose.

What moved the medical reviewer toward rejecting the drug was that "There is a disproportionate death and serious adverse event risk in pimavanserin 34-mg daily treatment versus placebo." A drug that harms patients measured by death and serious adverse events meets an elementary definition of an unsafe drug, even if it improves some symptoms. While the numbers of patients were small, excesses of deaths or serious injuries were seen across different measures. Lumping together all the pimavanserin treated patients, 5.3% died, compared to 0.5% on placebo. Limiting the comparison to controlled trials at the recommended dose, treated patients were 2.4 times more likely to experience a serious adverse drug event (including death). Just measuring dropouts for adverse drug effects in its one pivotal trial, four times as many taking pimavanserin were discontinued for adverse effects (9.5% vs 2.1%) compared to patients on placebo.

These findings, while consistent across trials and different measures, had a limitation. The specific adverse reactions found were diverse, occurring in numerous body systems. The drug had no signature risk, such as liver toxicity or serious infections. In addition, while deaths were more numerous in the treatment group, mortality rates are substantial in the Parkinson’s disease population. On the other hand, a similar diverse but substantial increase in mortality had also occurred in antipsychotic drugs, leading to an FDA Boxed Warning against use in patients 65 years and older.[14]

The safety data for the pivotal trials at the recommended dose included one additional finding of concern, illustrated in Table 2. When hallucinations were directly reported to study investigators as an adverse event, they occurred more frequently among pimavanserin patients than among those taking a placebo. This raised further questions about the accuracy of the new psychosis rating scale and the use of assessments through video links.

**Table 2. Psychiatric adverse reactions in 6-week placebo controlled studies\***

Event Term	Pimavanserin n = 202	Placebo n=231
Hallucination	5%	3%
Confusional state	6%	3%

\* Reproduced from prescribing information

## The Approval Decision

Neither an FDA advisory committee nor senior FDA management was moved by the medical officer’s concerns. The committee voted 12-2 to recommend approval, which soon followed. In a published explanation,[22] agency officials (including the medical officer as coauthor) discounted the safety evidence. It noted that 51 deaths had occurred in open label trials, but said “no drug-related cause was apparent.” As for the clinical trials where a comparison group was present, the authors concluded “the number of events was too small to reach a firm conclusion.”

## The Adverse Event Report Data

The first substantial group of adverse event reports provides signals that support the known safety concerns, and contribute an additional one. As noted in Table 1, the leading reported adverse events were remarkably similar to the concerns raised by the medical officer’s report and the marginal benefits seen in three clinical trials, notably: numerous reports of hallucinations (n = 487) and confusional state (n = 258) as well as complaints that the drug was ineffective (n = 333) and numerous patient deaths (n = 244). It was also notable that 74% of the pimavanserin reports came from health professionals, who would be expected to be familiar with the symptoms and mortality of patients with Parkinson’s disease psychosis, and therefore less likely to report these events unless a drug role was suspected. If there was an overall message in these adverse event reports, it was that hundreds of health professionals were trying this new drug in their patients and reporting that either it didn’t work, or in some cases made the patients worse.

However, the adverse event reports revealed a new safety concern: concomitant use of antipsychotic drugs, notably quetiapine (SEROQUEL). The reports revealed 318 cases of heavily medicated Parkinson’s patients (a median of 10 drugs) where pimavanserin had been added to antipsychotic drugs (all but 7 cases were quetiapine). The health outcomes were somewhat worse comparing patients also taking antipsychotics to those who did not: deaths in 13% versus 11%, hospitalizations in 15% vs 11%. No antipsychotic drugs have been approved for use in Parkinson’s patients, and the FDA explicitly warns against their use in dementia-related psychosis in patients over 65 years age. However, it was an open secret that quetiapine and other antipsychotics were widely used anyway.\* On its face, combination therapy with quetiapine and pimavanserin appears unsound. Patients with already impaired dopamine function are given quetiapine,

\* In the FDA review article explaining the approval of pimavanserin, senior management noted that although antipsychotic use was not recommended, “the FDA, in public statements, did not suggest the use was unreasonable.” [22]

which not only blocks normal dopamine signaling, but also blocks the same type 2 serotonin receptors targeted by pimavanserin. Further, the combination therapy has never been tested. And both drugs are suspected of increasing mortality.

## Interpreting the Adverse Drug Event Reports

The adverse event reports for pimavanserin presents challenges that not only include but go beyond the normal limitations of these data. Hallucinations are the leading symptom of psychosis and so a possible adverse effect of the drug might be mistaken for a symptom of a worsening disease. However, we considered this a bona fide signal for several reasons: A) The number of reports was so large that it outnumbered similar reports for all other drugs, including antipsychotics. Sheer numbers of reports have scientific weight because it is unlikely that so many observers were uniformly wrong. B) The reports came predominantly from health professionals who apparently suspected a drug effect. C) An excess of hallucinations as an adverse drug reaction was also observed in clinical trials. On the other hand, these adverse event report totals do not support useful direct comparisons of event counts for other drugs, including antipsychotics. This is because of very large differences in patient exposure, and likely reporting rates. Drug manufacturer reports of patient deaths are challenging to interpret because if a company learns that a patient taking its drug has died, the FDA requires an early report, even if a possible drug role has not been investigated. However, the large number of reported deaths remains of concern in a setting where increased mortality was at least suspected if not proven in the clinical trials assessments at the FDA.

## The Company Response

We shared our preliminary findings with Acadia Pharmaceuticals, which provided a response. It noted that the total volume of reports was expanded because of the company's extensive direct interactions with health professionals and consumers because of its distribution of the drug through a network of specialty pharmacies rather than retail pharmacies.\* The company also said it believed that the reports of hallucinations and confusion could have occurred during early treatment "while patients were becoming accustomed to the drug." It noted that it takes 12 days to reach steady state concentrations, and benefits were not seen in the clinical trial until after 4 weeks. With regard to mortality, the company noted that in a new trial (that had been completed but not yet published) in Alzheimer's psychosis, "we observed no difference in deaths."

## Conclusions

The company's reported contacts with health professionals and patients likely did expand the number of reports, essentially because its postmarket surveillance was more extensive than for many other drugs. On the other hand, that should mean that this group of reports more accurately reflects the experience of health professionals and consumers in a real-life postmarket setting.

The numerous reports that the drug was ineffective underline the limited benefits seen in the clinical trials. Even the best trial result, a 23% decline in a sensitive measurement scale, observed only after 4 weeks of therapy, might be too small for either health professionals or consumers to observe.

We were also concerned about adverse event reports indicating off-label use in combination therapy with quetiapine, a powerful antipsychotic that was banned in the pimavanserin clinical trials. The FDA and manufacturer should consider additional warnings and other measures to deal with inappropriate combination therapy.

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\* On the other hand, the network included specialty pharmacy units of CVS and Walgreens.[23]

## Sacubitril-Valsartan (ENTRESTO) and Hypotension

The initial signal from the QuarterWatch monitoring program was hundreds of reports that included one signature adverse event term—hypotension or low blood pressure—and was linked to a newly approved suspect drug, sacubitril-valsartan (ENTRESTO). Our subsequent analysis of this new drug, manufactured by Novartis, identified many additional hypotension-related reports for this heart failure drug, and found the likely reasons why this and other risks were underestimated at the time of approval in 2015.

### Treating the Failing Heart

Chronic heart failure occurs when the heart is sufficiently damaged so that it cannot provide enough output to sustain needed organ perfusion. The condition also disrupts the interacting hormones and other signaling proteins that variously regulate blood pressure by adjusting the contractility of the heart muscle, changing the heart rate, regulating the total body volume of fluids, and closely controlling the concentrations of sodium and potassium. Heart failure also triggers a cascade of hospitalizations and rehospitalizations, more than 1 million per year, and 50% of patients will die within 5 years of a diagnosis.[24] Over many decades, numerous drugs have been developed that target one or more of the systems that regulate this central body function: Nitroglycerin causes vasodilation; beta blockers neutralize the hormone signal for an abrupt increase in cardiac output; diuretics decrease body fluid volume to reduce blood pressure; and three other families of drugs target the renin-angiotensin-aldosterone system in the kidneys. In 2015 the FDA approved a product containing sacubitril, a new kind of drug to target still another group of proteins regulating blood pressure, called natriuretic peptides. Sacubitril increased the availability of natriuretic peptides by inhibiting neprilysin, an enzyme that itself rapidly breaks down the body's available supply of these peptides. For marketing approval sacubitril was combined with valsartan, an already-approved blood pressure drug that targeted the renin-angiotensin system in the kidneys.

### A Peptide of Interest

Since 1980, researchers had been creating and testing drugs to manipulate natriuretic peptides, but with limited success. [25] In 2001 the FDA approved nesiritide, a recombinant form of the peptide, for IV administration in the most severely ill heart failure patients.[26] Its primary effect was a small decrease in one heart failure symptom, shortness of breath. Also, it required continuous IV infusions, and assessment of the drug was complicated by the use of numerous other concomitant medications. Another drug developed to target natriuretic peptides was omapatrilat, and like sacubitril it increased the availability of natriuretic peptides by blocking the enzyme neprilysin, which rapidly broke them down. However, the FDA refused to approve an omapatrilat combination product because treatment nearly doubled the risk of angioedema, a potentially life-threatening allergic reaction often triggered by blood pressure drugs that act on the kidney.[27]

### Enter Sacubitril-Valsartan

A combination of sacubitril and valsartan succeeded where previous drugs had failed or produced very small effects. The FDA approved the drug in July 2015 with evidence of efficacy from a single, large 27-month clinical trial with 8,442 patients.[28] The need for a trial this large reveals something about the likely size of the drug benefit. It means that either the drug effect is very modest, or the medical event under study occurs infrequently, or both. But in the case of sacubitril-valsartan, the results were positive across many measures.[29] In fact, the trial was stopped early for benefit. In a population at substantial risk of death from heart failure, it reduced the cardiovascular death rate from 16.5% among patients taking a comparator blood pressure drug, enalapril, to 13.3% among those taking the sacubitril-valsartan combination. It produced evidence of roughly similar benefits across other important endpoints, including total mortality, hospitalization, symptoms, and activities of daily living. The scientific weight of the trial findings was also increased because the comparison was not with placebo, but with a drug already proven to be beneficial in heart failure patients.

## FDA Review Questions

The use of a large single trial (rather than two or more) also raised questions about this novel drug combination. As a drug combination product, FDA reviewers noted, the single clinical trial did not provide the required evidence that sacubitril in fact added any benefit to the already-proven valsartan. This requirement was waived.[28] A second potential risk that could not be addressed even in this large trial was whether sacubitril's mechanism of action might increase the risk of Alzheimer's.[30] That theoretical risk occurred because the targeted enzyme neprilysin performed another function in the body: It also broke down amyloid- $\beta$  proteins. A buildup of amyloid- $\beta$  in the brain is a hallmark of Alzheimer's. Neither this study—where cognitive function was not systematically assessed—nor other kinds of studies of effects on amyloid- $\beta$  proteins—could substantiate, rule out, or otherwise measure the extent of this risk. But it was still another reminder that most drugs have many effects beyond those specifically selected as a measure of benefit.

## Underestimated Adverse Effects

The large sacubitril-valsartan trial had a design feature that limited its ability to measure accurately the drug's adverse effects. It was an "enriched" trial, meaning patients were intentionally selected as those with the best chance of benefiting from the treatment—rather than typical patients likely to be seen in clinical practice. Before patients could enter the trial, they had to pass a six-week run-in phase in which they were treated with both of the study drugs to see if they could tolerate them. In this run-in, 20% of the patients dropped out because of problems with one or both of the drugs, and the largest share of dropouts was attributed to drug adverse events. According to the FDA reviewers,[28] [30] these potentially underestimated adverse effects included hypotension, angioedema, excessive calcium levels, and kidney dysfunction.

## Hypotension Event Rates

Sacubitril-valsartan is a combination of two blood pressure-reducing drugs. Hypotension—or low blood pressure—means these patients are getting too much of what otherwise might be a good thing. How frequently this occurred provided a textbook example of how adverse effects of drugs can be understated with narrow event definitions that do not capture all the likely cases. Those reading the published journal study [29] would read that 14% of treated patients experienced "symptomatic" hypotension. Those who read the study on-line supplement would observe that the rate grew to 17.6% when all hypotension adverse events were included. When the FDA medical reviewer included the hypotension-related symptoms, the percentage total increased again to 24.4%. Finally, to get an aggregate estimate we added an additional 5.1% of patients who experienced treatment-related hypotension in the run-in period to reach a total of 29.5%. The differences are shown in Table 3. By another measure, 31.7% of patients in the trial treatment period experienced a sharp drop ( $\geq 30$  mm Hg) in systolic blood pressure.[30]

**Table 3. Hypotension definitions in clinical trial of sacubitril-valsartan\***

Definition	Percent
Symptomatic adverse event	14.0
Any hypotension adverse event	17.6
With related symptoms	24.4
With run-in period	29.5

\*Calculated from published study, FDA medical review

## The FAERS Data

In the 12 months ending March 2017, we identified 6,770 adverse drug event reports for sacubitril-valsartan, including 681 (10%) patient deaths on one extreme, but 4,131 (61%) cases that were coded as occurring but with no medically serious consequences. The reported adverse reactions included medically important adverse events also seen in the large clinical trial, including renal failure and impairment (n = 317 PRR = 3.19), angioedema (n = 152 PRR = 5.63), and hyperkalemia (n = 87; PRR = 11.51). However, the most frequently reported adverse reactions were hypotension-related events (n = 1,684 PRR = 4.8).

This large a number of hypotension-related reports over 12 months has scientific weight in its own right. In another basic comparison, it was a larger volume of hypotension-related reports than for any other cardiovascular drug in that time period. Table 4 summarizes the hypotension events that were identified.

<b>Table 4. Hypotension-related adverse drug events for sacubitril-valsartan</b>		
Total for 12 months ending 2017 Q1	1684	
Patient characteristics		
Age, (median, interquartile range)	70	(63-78)
Gender, (male %)	1063	(63.1)
Event outcomes, (%)		
Death	69	(4.1)
Disability	14	(0.8)
Other serious	493	(29.3)
Not-serious	1108	(65.8)
Hypotension-related terms*, (%)		
Hypotension**	945	(56.1)
Dizziness	603	(35.8)
Blood pressure decreased	196	(11.6)
Syncope	77	(4.6)
Loss of consciousness	69	(4.1)
Dizziness postural	37	(2.2)
Blood pressure fluctuation	26	(1.5)
Presyncope	12	(0.7)
Dizziness exertional	3	(0.2)
Depressed level of consciousness	2	(0.1)
* MedDRA terms selected from Table 62 FDA medical review		
**One case could contain multiple terms		

## Patient Exposure

Using outpatient prescription data from QuintilesIMS, we estimated that there were 40,000 patient-years of exposure in the United States for the 12 months ending 2017 Q1. However, prescriptions of this newly launched drug were growing at an average of 38% per quarter. The patient population for this drug was substantial, but modest in comparison to many drugs taken by hundreds of thousands or millions of patients.

## The Company Response

We provided our preliminary findings to Novartis. The company shared its own patient exposure, count of hypotension events, and reporting rate calculations. Although its data were worldwide and included one extra calendar quarter, its event rates and calculations were basically similar to those reported here. The company noted that while the number of hypotension reports increased every quarter, the reporting rate was stable after adjustment for the growth in prescription volume.

Novartis noted that the current prescribing information for sacubitril-valsartan contained a warning that the drug may cause hypotension. The prescribing information recommends that physicians “correct volume or salt depletion” prior to starting treatment. If hypotension occurs, it recommends considering adjusting the dosage of other medications that influence blood pressure, and finally reducing the dosage or discontinuing sacubitril-valsartan, while noting “discontinuation of therapy is usually not required.”

## Conclusions

This large volume of reports of hypotension confirms the concerns of FDA reviewers that the valsartan-sacubitril clinical trial results in carefully selected patients underestimated the risk of hypotension in normal

clinical practice. As we noted, the risk is so prominent that about 1 out of 4 patients started on this drug will experience a hypotension-related event.

We recommend that the FDA and the manufacturer more clearly communicate the full risk of hypotension, including appropriate steps for monitoring patients, and examine whether a more gradual escalation of dose to the recommended level would reduce the risk.

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