HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use NUPLAZID safely and effectively. See full prescribing information for NUPLAZID.

NUPLAZID® (pimavanserin) capsules, for oral use
NUPLAZID® (pimavanserin) tablets, for oral use
Initial U.S. Approval: 2016

WARNING: INCREASED MORTALITY IN ELDERLY PATIENTS WITH DEMENTIA-RELATED PSYCHOSIS
See full prescribing information for complete boxed warning.
- **Elderly patients with dementia-related psychosis treated with antipsychotic drugs are at an increased risk of death.**
- **NUPLAZID is not approved for the treatment of patients with dementia-related psychosis unrelated to the hallucinations and delusions associated with Parkinson's disease psychosis. (5.1)**

----------RECENT MAJOR CHANGES----------
Dosage and Administration (2.2) 11/2020

----------INDICATIONS AND USAGE----------
NUPLAZID is an atypical antipsychotic indicated for the treatment of hallucinations and delusions associated with Parkinson's disease psychosis. (1)

----------DOSAGE AND ADMINISTRATION----------
- Recommended dose is 34 mg taken orally once daily, without titration. (2.1)
- Can be taken with or without food. (2.2)
- Capsules may be swallowed whole or opened and entire contents sprinkled over a tablespoon of certain types of soft food. (2.2)

----------DOSAGE FORMS AND STRENGTHS----------
- Capsules: 34 mg (3)
- Tablets: 10 mg (3)

----------CONTRAINDICATIONS----------
Known hypersensitivity to NUPLAZID or any of its components. (4)

----------WARNINGS AND PRECAUTIONS----------
- QT Interval Prolongation: Increases in QT interval; avoid use with drugs that also increase the QT interval and in patients with risk factors for prolonged QT interval. (5.2)

----------ADVERSE REACTIONS----------
Most common adverse reactions (≥5% and twice the rate of placebo): peripheral edema and confusional state. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Acadia Pharmaceuticals Inc. at 1-844-422-2342 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

----------DRUG INTERACTIONS----------
- Strong CYP3A4 Inhibitors (e.g., ketoconazole): Reduce NUPLAZID dose to 10 mg once daily. (2.3, 7.1)
- Strong or Moderate CYP3A4 Inducers: Avoid concomitant use of NUPLAZID. (2.3, 7.1)

See 17 for PATIENT COUNSELING INFORMATION

Revised: 11/2020

FULL PRESCRIBING INFORMATION: CONTENTS*

*Sections or subsections omitted from the full prescribing information are not listed.

FULL PRESCRIBING INFORMATION

WARNING: INCREASED MORTALITY IN ELDERLY PATIENTS WITH DEMENTIA-RELATED PSYCHOSIS

Elderly patients with dementia-related psychosis treated with antipsychotic drugs are at an increased risk of death. NUPLAZID is not approved for the treatment of patients with dementia-related psychosis unrelated to the hallucinations and delusions associated with Parkinson's disease psychosis *[see Warnings and Precautions (5.1)]*.

1 INDICATIONS AND USAGE

NUPLAZID® is indicated for the treatment of hallucinations and delusions associated with Parkinson's disease psychosis.

2 DOSAGE AND ADMINISTRATION

2.1 Recommended Dosage

The recommended dose of NUPLAZID is 34 mg taken orally once daily, without titration.

2.2 Administration Information

NUPLAZID can be taken with or without food *[see Clinical Pharmacology (12.3)]*.

NUPLAZID capsules can be taken whole, or opened and the entire contents sprinkled over a tablespoon (15 mL) of applesauce, yogurt, pudding, or a liquid nutritional supplement. Consume the drug/food mixture immediately without chewing; do not store for future use.

2.3 Dosage Modifications for Concomitant Use with CYP3A4 Inhibitors and Inducers

- Coadministration with Strong CYP3A4 Inhibitors
  The recommended dose of NUPLAZID when coadministered with strong CYP3A4 inhibitors (e.g., ketoconazole) is 10 mg, taken orally as one tablet once daily *[see Drug Interactions (7.1)]*.
- Coadministration with Strong or Moderate CYP3A4 Inducers
  Avoid concomitant use of strong or moderate CYP3A4 inducers with NUPLAZID *[see Drug Interactions (7.1)]*.

3 DOSAGE FORMS AND STRENGTHS

NUPLAZID (pimavanserin) is available as:

- 34 mg strength capsules. The capsules are opaque white and light green with "PIMA" and "34" printed in black.
- 10 mg strength tablets. The orange, round, coated tablets are debossed on one side with a "P" and "10" on the reverse side.

4 CONTRAINDICATIONS

NUPLAZID is contraindicated in patients with a history of a hypersensitivity reaction to pimavanserin or any of its components. Rash, urticaria, and reactions consistent with angioedema (e.g., tongue swelling, circumoral edema, throat tightness, and dyspnea) have been reported *[see Adverse Reactions (6.2)]*.

5 WARNINGS AND PRECAUTIONS

5.1 Increased Mortality in Elderly Patients with Dementia-Related Psychosis

Antipsychotic drugs increase the all-cause risk of death in elderly patients with dementia-related psychosis. Analyses of 17 dementia-related psychosis placebo-controlled trials (modal duration of 10 weeks and largely in patients taking atypical antipsychotic drugs) revealed a risk of death in the drug-treated patients of between 1.6- to 1.7-times that in placebo-treated patients. Over the course of a typical 10-week controlled trial, the rate of death in drug-treated patients was about 4.5%, compared to a rate of about 2.6% in placebo-treated patients.

Although the causes of death were varied, most of the deaths appeared to be either cardiovascular (e.g., heart failure, sudden death) or infectious (e.g., pneumonia) in nature. NUPLAZID is not approved for the treatment of patients with dementia-related psychosis unrelated to the hallucinations and delusions associated with Parkinson's disease psychosis *[see Boxed Warning]*.

5.2 QT Interval Prolongation

NUPLAZID prolongs the QT interval. The use of NUPLAZID should be avoided in patients with known QT prolongation or in combination with other drugs known to prolong QT interval including Class 1A antiarrhythmics (e.g., quinidine, procainamide) or Class 3 antiarrhythmics (e.g., amiodarone, sotalol), certain antipsychotic medications (e.g., ziprasidone, chlorpromazine, thioridazine), and certain antibiotics (e.g., gatifloxacin, moxifloxacin) *[see Drug Interactions (7.1)]*. NUPLAZID should also be avoided in patients with a history of cardiac arrhythmias, as well as other circumstances that may increase the risk of the occurrence of torsade de pointes and/or sudden death, including symptomatic bradycardia, hypokalemia or hypomagnesemia, and the presence of congenital prolongation of the QT interval *[see Clinical Pharmacology (12.2)]*.

6 ADVERSE REACTIONS

The following serious adverse reactions are discussed elsewhere in the labeling:

- Increased Mortality in Elderly Patients with Dementia-Related Psychosis *[see Boxed Warning and Warnings and Precautions (5.1)]*
- QT Interval Prolongation *[see Warnings and Precautions (5.2)]*

6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

The clinical trial database for NUPLAZID consists of over 1200 subjects and patients exposed to one or more doses of NUPLAZID. Of these, 616 were patients with hallucinations and delusions associated with Parkinson's disease psychosis (PDP). In the placebo-controlled setting, the majority of experience in patients comes from studies evaluating once-daily NUPLAZID doses of 34 mg (N=202) compared to placebo (N=231) for up to 6 weeks. In the controlled trial setting, the study population was approximately 64% male and 91% Caucasian, and the mean age was about 71 years at study entry. Additional clinical trial experience in patients with hallucinations and delusions associated with PDP comes from two open-label, safety extension studies (total N=497). The majority of patients receiving long-term treatment received 34 mg once-daily (N=459). Over 300 patients have been treated for more than 6 months; over 270 have been treated for at least 12 months; and over 150 have been treated for at least 24 months.

The following adverse reactions are based on the 6-week, placebo-controlled studies in which NUPLAZID was administered once daily to patients with hallucinations and delusions associated with PDP.

Common Adverse Reactions (incidence ≥5% and at least twice the rate of placebo): peripheral edema (7% NUPLAZID 34 mg vs. 2% placebo) and confusional state (6% NUPLAZID 34 mg vs. 3% placebo).

Adverse Reactions Leading to Discontinuation of Treatment

A total of 8% (16/202) of NUPLAZID 34 mg-treated patients and 4% (10/231) of placebo-treated patients discontinued because of adverse reactions. The adverse reactions that occurred in more than one patient and with an incidence at least twice that of placebo were hallucination (2% NUPLAZID vs. <1% placebo), urinary tract infection (1% NUPLAZID vs. <1% placebo), and fatigue (1% NUPLAZID vs. 0% placebo).

Adverse reactions that occurred in 6-week, placebo-controlled studies and that were reported at an incidence of ≥2% and >placebo are presented in **Table 1**.

Table 1 Adverse Reactions in Placebo-Controlled Studies of 6-Week Treatment Duration and Reported in ≥2% and >Placebo

Percentage of Patients Reporting Adverse Reaction		
	NUPLAZID 34 mg	**Placebo**
	N=202	N=231
Gastrointestinal disorders		
Nausea	7%	4%
Constipation	4%	3%
General disorders		
Peripheral edema	7%	2%
Gait disturbance	2%	<1%
Psychiatric disorders		
Hallucination	5%	3%
Confusional state	6%	3%

Adverse Reactions in Demographic Subgroups

Examination of population subgroups in the 6-week, placebo-controlled studies did not reveal any differences in safety on the basis of age (≤75 vs. >75 years) or sex. Because the study population was predominantly Caucasian (91%; consistent with reported demographics for PD/PDP), racial or ethnic differences in the safety profile of NUPLAZID could not be assessed. In addition, in the 6-week, placebo-controlled studies, no clinically relevant differences in the incidence of adverse reactions were observed among those with a Mini-Mental State Examination (MMSE) score at entry of <25 versus those with scores ≥25.

6.2 Postmarketing Experience

The following adverse reactions have been identified during postapproval use of NUPLAZID. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure. These reactions include rash, urticaria, reactions consistent with angioedema (e.g., tongue swelling, circumoral edema, throat tightness, and dyspnea), somnolence, falls, agitation, and aggression.

7 DRUG INTERACTIONS

7.1 Drugs Having Clinically Important Interactions with NUPLAZID

Table 2 Clinically Important Drug Interactions with NUPLAZID

QT Interval Prolongation	
Clinical Impact:	Concomitant use of drugs that prolong the QT interval may add to the QT effects of NUPLAZID and increase the risk of cardiac arrhythmia.
Intervention:	Avoid the use of NUPLAZID in combination with other drugs known to prolong QT interval *[see Warnings and Precautions (5.2)]*.
Examples:	Class 1A antiarrhythmics: quinidine, procainamide, disopyramide; Class 3 antiarrhythmics: amiodarone, sotalol; Antipsychotics: ziprasidone, chlorpromazine, thioridazine; Antibiotics: gatifloxacin, moxifloxacin
Strong CYP3A4 Inhibitors	
Clinical Impact:	Concomitant use of NUPLAZID with a strong CYP3A4 inhibitor increases pimavanserin exposure *[see Clinical Pharmacology (12.3)]*.
Intervention:	If NUPLAZID is used with a strong CYP3A4 inhibitor, reduce the dosage of NUPLAZID *[see Dosage and Administration (2.3)]*.
Examples:	itraconazole, ketoconazole, clarithromycin, indinavir
Strong or Moderate CYP3A4 Inducers	
Clinical Impact:	Concomitant use of NUPLAZID with strong or moderate CYP3A4 inducers reduces pimavanserin exposure *[see Clinical Pharmacology (12.3)]*.
Intervention:	Avoid concomitant use of strong or moderate CYP3A4 inducers with NUPLAZID *[see Dosage and Administration (2.3)]*.
Examples:	Strong inducers: carbamazepine, St. John's wort, phenytoin, rifampin Moderate inducers: modafinil, thioridazine, efavirenz, nafcillin

7.2 Drugs Having No Clinically Important Interactions with NUPLAZID

Based on pharmacokinetic studies, no dosage adjustment of carbidopa/levodopa is required when administered concomitantly with NUPLAZID *[see Clinical Pharmacology (12.3)]*.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

There are no data on NUPLAZID use in pregnant women that would allow assessment of the drug-associated risk of major congenital malformations or miscarriage. In animal reproduction studies, no adverse developmental effects were seen when pimavanserin was administered orally to rats or rabbits during the period of organogenesis at doses up to 10- or 12-times the maximum recommended human dose (MRHD) of 34 mg/day, respectively. Administration of pimavanserin to pregnant rats during pregnancy and lactation resulted in maternal toxicity and lower pup survival and body weight at doses which are 2-times the MRHD of 34 mg/day *[see Data]*.

The estimated background risk of major birth defects and miscarriage for the indicated population is unknown. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2-4% and 15-20%, respectively.

Data

Animal Data

Pimavanserin was not teratogenic in pregnant rats when administered during the period of organogenesis at oral doses of 0.9, 8.5, and 51 mg/kg/day, which are 0.2- and 10-times the maximum recommended human dose (MRHD) of 34 mg/day based on AUC at mid and high doses, respectively. Maternal toxicity included reduction in body weight and food consumption at the highest dose.

Administration of pimavanserin to pregnant rats during pregnancy and lactation at oral doses of 8.5, 26, and 51 mg/kg/day, which are 0.14- to 14-times the MRHD of 34 mg/day based on AUC, caused maternal toxicity, including mortality, clinical signs including dehydration, hunched posture, and rales, and decreases in body weight, and/or food consumption at doses ≥26 mg/kg/day (2-times the MRHD based on AUC). At these maternally toxic doses there was a decrease in pup survival, reduced litter size, and reduced pup weights, and food consumption. Pimavanserin had no effect on sexual maturation, neurobehavioral function including learning and memory, or reproductive function in the first generation pups up to 14-times the MRHD of 34 mg/day based on AUC.

Pimavanserin was not teratogenic in pregnant rabbits during the period of organogenesis at oral doses of 4.3, 43, and 85 mg/kg/day, which are 0.2- to 12-times the MRHD of 34 mg/day based on AUC. Maternal toxicity, including mortality, clinical signs of dyspnea and rales, decreases in body weight and/or food consumption, and abortions occurred at doses 12-times the MRHD of 34 mg/day based on AUC.

8.2 Lactation

Risk Summary

There is no information regarding the presence of pimavanserin in human milk, the effects on the breastfed infant, or the effects on milk production. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for NUPLAZID and any potential adverse effects on the breastfed infant from NUPLAZID or from the underlying maternal condition.

8.4 Pediatric Use

Safety and effectiveness of NUPLAZID have not been established in pediatric patients.

8.5 Geriatric Use

No dose adjustment is required for elderly patients.

Parkinson's disease is a disorder occurring primarily in individuals over 55 years of age. The mean age of patients enrolled in the 6-week clinical studies with NUPLAZID *[see Adverse Reactions (6.1)]* was 71 years, with 49% 65-75 years old and 31% >75 years old. In the pooled population of patients enrolled in 6-week, placebo-controlled studies (N=614), 27% had MMSE scores from 21 to 24 compared to 73% with scores ≥25. No clinically meaningful differences in safety or effectiveness were noted between these two groups.

8.6 Patients with Renal Impairment

No dosage adjustment for NUPLAZID is needed in patients with mild to severe renal impairment or end stage renal disease (ESRD); however, increased exposure (C_{max} and AUC) to NUPLAZID occurred in patients with severe renal impairment (CrCL <30 mL/min, Cockcroft-Gault) in a renal impairment study *[see Clinical Pharmacology (12.3)]*.

NUPLAZID should be used with caution in patients with severe renal impairment and end stage renal disease.

In a renal impairment study, dialysis did not appear to significantly affect the concentrations of NUPLAZID *[see Clinical Pharmacology (12.3)]*.

8.7 Patients with Hepatic Impairment
No dosage adjustment for NUPLAZID is recommended in patients with hepatic impairment based on the exposure differences observed in patients with and without hepatic impairment in a hepatic impairment study *[see Clinical Pharmacology (12.3)]*.

8.8 Other Specific Populations
No dosage adjustment is required based on patient's age, sex, ethnicity, or weight. These factors do not affect the pharmacokinetics of NUPLAZID *[see Clinical Pharmacology (12.3)]*.

9 DRUG ABUSE AND DEPENDENCE

9.1 Controlled Substance
NUPLAZID is not a controlled substance.

9.2 Abuse
NUPLAZID has not been systematically studied in humans for its potential for abuse, tolerance, or physical dependence.

While short-term, placebo-controlled and long-term, open-label clinical trials did not reveal increases in drug-seeking behavior, the limited experience from the clinical trials do not predict the extent to which a CNS-active drug will be misused, diverted, and/or abused once marketed.

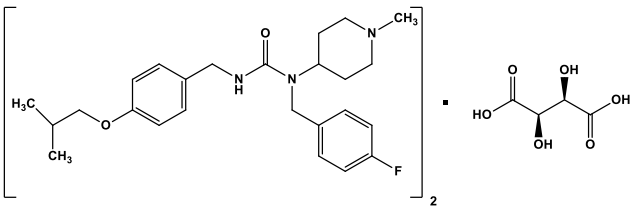
10 OVERDOSAGE

10.1 Human Experience
The pre-marketing clinical trials involving NUPLAZID in approximately 1200 subjects and patients do not provide information regarding symptoms with overdose. In healthy subject studies, dose-limiting nausea and vomiting were observed.

10.2 Management of Overdose
There are no known specific antidotes for NUPLAZID. In managing overdose, cardiovascular monitoring should commence immediately and should include continuous ECG monitoring to detect possible arrhythmias *[see Warnings and Precautions (5.2)]*. If antiarrhythmic therapy is administered, disopyramide, procainamide, and quinidine should not be used, as they have the potential for QT-prolonging effects that might be additive to those of NUPLAZID *[see Drug Interactions (7.1)]*. Consider the long plasma half-life of pimavanserin (about 57 hours) and the possibility of multiple drug involvement. Consult a Certified Poison Control Center (1-800-222-1222) for up-to-date guidance and advice.

11 DESCRIPTION

NUPLAZID contains pimavanserin, an atypical antipsychotic, which is present as pimavanserin tartrate salt with the chemical name, urea, *N*-[(4-fluorophenyl)methyl]-*N*-(1-methyl-4-piperidinyl)-*N*'-[[4-(2-methylpropoxy)phenyl]methyl]-,(2*R*,3*R*)-2,3-dihydroxybutanedioate (2:1). Pimavanserin tartrate is freely soluble in water. Its molecular formula is $(C_{25}H_{34}FN_3O_2)_2 \cdot C_4H_6O_6$ and its molecular weight is 1005.20 (tartrate salt). The chemical structure is:



The molecular formula of pimavanserin free base is $C_{25}H_{34}FN_3O_2$ and its molecular weight is 427.55.

NUPLAZID capsules are intended for oral administration only. Each capsule contains 40 mg of pimavanserin tartrate, which is equivalent to 34 mg of pimavanserin free base. Inactive ingredients include magnesium stearate and microcrystalline cellulose. Additionally, the following inactive ingredients are present as components of the capsule shell: black iron oxide, FD&C blue #1, hypromellose, titanium dioxide, and yellow iron oxide.

NUPLAZID tablets are intended for oral administration only. Each round, orange, immediate-release, film coated tablet contains 11.8 mg of pimavanserin tartrate, which is equivalent to 10 mg pimavanserin free base. Inactive ingredients include magnesium stearate, pregelatinized starch, and silicified microcrystalline cellulose. Additionally, the following inactive ingredients are present as components of the film coat: polyethylene glycol, polyvinyl alcohol, red iron oxide, talc, titanium dioxide, and yellow iron oxide.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

The mechanism of action of pimavanserin in the treatment of hallucinations and delusions associated with Parkinson's disease psychosis is unclear. However, the effect of pimavanserin could be mediated through a combination of inverse agonist and antagonist activity at serotonin 5-HT_{2A} receptors and to a lesser extent at serotonin 5-HT_{2C} receptors.

12.2 Pharmacodynamics

In vitro, pimavanserin acts as an inverse agonist and antagonist at serotonin 5-HT_{2A} receptors with high binding affinity (K_i value 0.087 nM) and at serotonin 5-HT_{2C} receptors with lower binding affinity (K_i value 0.44 nM). Pimavanserin shows low binding to sigma 1 receptors (K_i value 120 nM) and has no appreciable affinity (K_i value >300 nM), to serotonin 5-HT_{2B}, dopaminergic (including D_2), muscarinic, histaminergic, or adrenergic receptors, or to calcium channels.

Cardiac Electrophysiology

The effect of NUPLAZID on the QTc interval was evaluated in a randomized placebo- and positive-controlled double-blind, multiple-dose parallel thorough QTc study in 252 healthy subjects. A central tendency analysis of the QTc data at steady-state demonstrated that the maximum mean change from baseline (upper bound of the two-sided 90% CI) was 13.5 (16.6) msec at a dose of twice the therapeutic dose. A pharmacokinetic/ pharmacodynamic analysis with NUPLAZID suggested a concentration-dependent QTc interval prolongation in the therapeutic range.

In the 6-week, placebo-controlled effectiveness studies, mean increases in QTc interval of ~5-8 msec were observed in patients receiving once-daily doses of NUPLAZID 34 mg. These data are consistent with the profile observed in a thorough QT study in healthy subjects. Sporadic QTcF values ≥500 msec and change from baseline values ≥60 msec were observed in subjects treated with NUPLAZID 34 mg; although the incidence was generally similar for NUPLAZID and placebo groups. There were no reports of torsade de pointes or any differences from placebo in the incidence of other adverse reactions associated with delayed ventricular repolarization in studies of NUPLAZID, including those patients with hallucinations and delusions associated with PDP *[see Warnings and Precautions (5.2)]*.

12.3 Pharmacokinetics

Pimavanserin demonstrates dose-proportional pharmacokinetics after single oral doses from 17 to 255 mg (0.5- to 7.5-times the recommended dosage). The pharmacokinetics of pimavanserin are similar in both the study population and healthy subjects. The mean plasma half-lives for pimavanserin and the active metabolite (*N*-desmethylated metabolite) are approximately 57 hours and 200 hours, respectively.

Absorption

The median T_{max} of pimavanserin was 6 (range 4-24) hours and was generally unaffected by dose.
The bioavailability of pimavanserin oral tablet and pimavanserin solution was essentially identical.
The formation of the major circulating *N*-desmethylated metabolite AC-279 (active) from pimavanserin occurs with a median T_{max} of 6 hours.

Administration of one 34 mg capsule once daily results in plasma pimavanserin concentrations that are similar to exposure with two 17 mg tablets once daily.

Effect of Food

Ingestion of a high-fat meal had no significant effect on rate (C_{max}) and extent (AUC) of pimavanserin exposure. C_{max} decreased by about 9% while AUC increased by about 8% with a high-fat meal.

Distribution

Pimavanserin is highly protein bound (~95%) in human plasma. Protein binding appeared to be dose-independent and did not change significantly over dosing time from Day 1 to Day 14. Following administration of a single dose of NUPLAZID (34 mg), the mean (SD) apparent volume of distribution was 2173 (307) L.

Elimination

Metabolism

Pimavanserin is predominantly metabolized by CYP3A4 and CYP3A5 and to a lesser extent by CYP2J2, CYP2D6, and various other CYP and FMO enzymes. CYP3A4 is the major enzyme responsible for the formation of its major active metabolite (AC-279). Pimavanserin does not cause clinically significant CYP inhibition or induction of CYP3A4. Based on *in vitro* data, pimavanserin is not an irreversible inhibitor of any of the major hepatic and intestinal human CYP enzymes involved in drug metabolism (CYP1A2, 2B6, 2C8, 2C9, 2C19, 2D6, and 3A4).

Based on *in vitro* studies, transporters play no significant role in the disposition of pimavanserin.

AC-279 is neither a reversible or irreversible (metabolism-dependent) inhibitor of any of the major hepatic and intestinal human CYP enzymes involved in drug metabolism (CYP1A2, 2B6, 2C8, 2C9, 2C19, 2D6, and 3A4). AC-279 does not cause clinically significant CYP3A induction and is not predicted to cause induction of any other CYP enzymes involved in drug metabolism.

Excretion

Approximately 0.55% of the 34 mg oral dose of ^{14}C-pimavanserin was eliminated as unchanged drug in urine and 1.53% was eliminated in feces after 10 days.

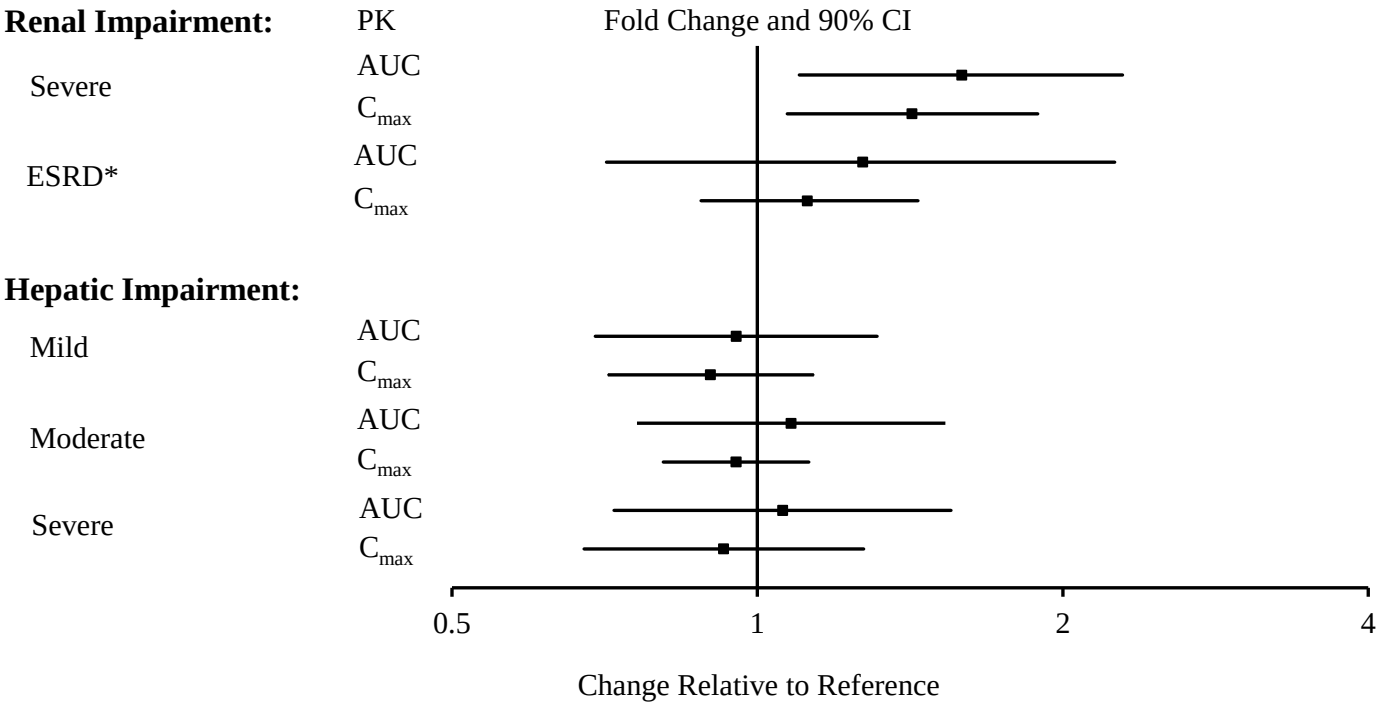
Less than 1% of the administered dose of pimavanserin and its active metabolite AC-279 were recovered in urine.

Specific Populations

Population PK analysis indicated that age, sex, ethnicity, and weight do not have clinically relevant effect on the pharmacokinetics of pimavanserin. In addition, the analysis indicated that exposure of pimavanserin in patients with mild to moderate renal impairment was similar to exposure in patients with normal renal function.

The effects of other intrinsic factors on pimavanserin pharmacokinetics is shown in **Figure 1** *[see Use in Specific Populations (8.6 and 8.7)]*.

Figure 1 Effects of Intrinsic Factors on Pimavanserin Pharmacokinetics



*Less than 10% of the administered dose of NUPLAZID was recovered in the dialysate.

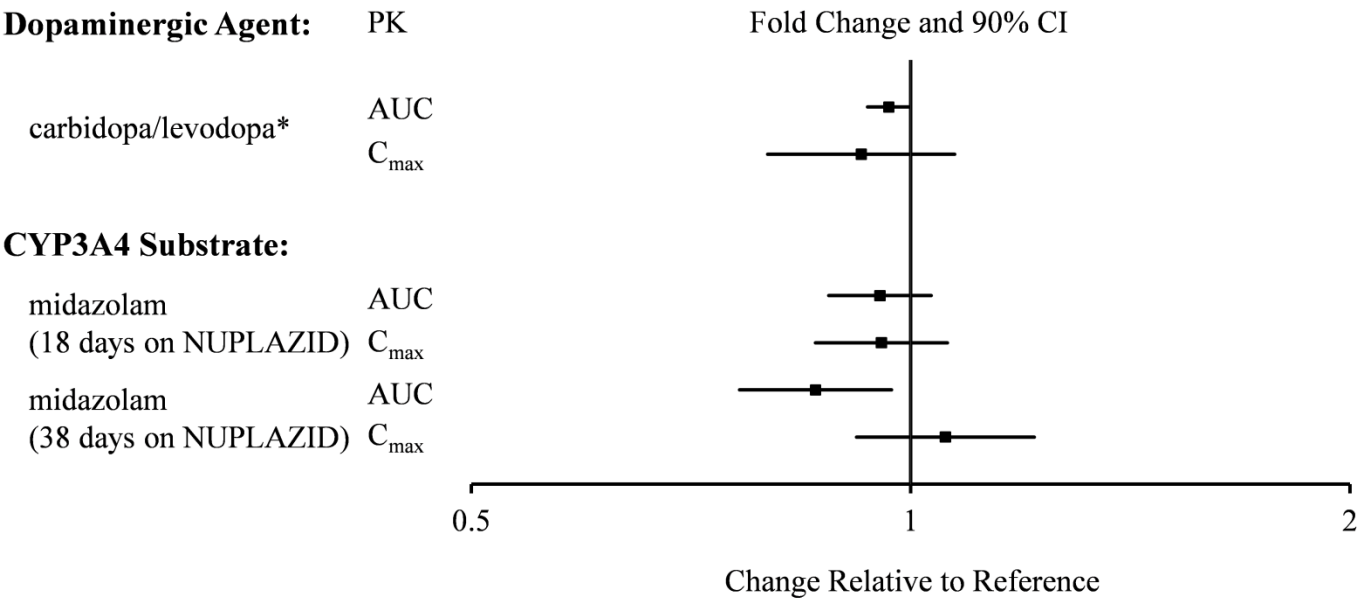
Drug Interaction Studies

CYP3A4 Inhibitor: ketoconazole, a strong inhibitor of CYP3A4, increased pimavanserin C_{max} by 1.5-fold and AUC by 3-fold. Population PK modeling and simulation show that steady-state exposure ($C_{max,ss}$ and AUC_{tau}) for 10 mg pimavanserin with ketoconazole is similar to exposure for 34 mg pimavanserin alone *[see Dosage and Administration (2.3) and Drug Interactions (7.1)]*.

CYP3A4 Inducer: In a clinical study where single doses of 34 mg pimavanserin were administered on Days 1 and 22, and 600 mg rifampin, a strong inducer of CYP3A4, was given daily on Days 15 through 21, pimavanserin C_{max} and AUC decreased by 71% and 91%, respectively, compared to pre-rifampin plasma concentrations. In a simulation with a moderate CYP3A4 inducer (efavirenz), physiologically based pharmacokinetic (PBPK) models predicted pimavanserin $C_{max,ss}$ and AUC_{tau} at steady state decreased by approximately 60% and 70%, respectively *[see Dosage and Administration (2.3) and Drug Interactions (7.1)]*.

There is no effect of pimavanserin on the pharmacokinetics of midazolam, a CYP3A4 substrate, or carbidopa/levodopa as shown in **Figure 2**.

Figure 2 Effects of Pimavanserin on the Pharmacokinetics of Other Drugs



*AUC and C_{max} depict levodopa levels.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenesis

There was no increase in the incidence of tumors following daily oral administration of pimavanserin to mice or rats for 2 years. Mice were administered pimavanserin at oral doses of 2.6, 6, and 13 (males)/8.5, 21, and 43 mg/kg/day (females) which are 0.01- to 1- (males)/0.5- to 7- (females) times the MRHD of 34 mg/day based on AUC. Rats were administered pimavanserin at oral doses of 2.6, 8.5, and 26 (males)/4.3, 13, and 43 mg/kg/day (females) which are 0.01- to 4- (males)/0.04- to 16- (females) times the MRHD of 34 mg/day based on AUC.

Mutagenesis

Pimavanserin was not mutagenic in the *in vitro* Ames reverse mutation test, or in the *in vitro* mouse lymphoma assay, and was not clastogenic in the *in vivo* mouse bone marrow micronucleus assay.

Impairment of Fertility

Pimavanserin was administered orally to male and female rats before mating, through mating, and up to Day 7 of gestation at doses of 8.5, 51, and 77 mg/kg/day, which are approximately 2-, 15-, and 22-times the maximum recommended human dose (MRHD) of 34 mg/day based on mg/m^2, respectively. Pimavanserin had no effect on fertility or reproductive performance in male and female rats at doses up to 22-times the MRHD of 34 mg based on mg/m^2. Changes in uterine parameters (decreases in the number of corpora lutea, number of implants, viable implants, and increases in pre-implantation loss, early resorptions and post-implantation loss) occurred at the highest dose which was also a maternally toxic dose. Changes in sperm parameters (decreased density and motility) and microscopic findings of cytoplasmic vacuolation in the epididymis occurred at doses approximately 15-times the MRHD of 34 mg/day based on mg/m^2.

13.2 Animal Toxicology and/or Pharmacology

Phospholipidosis (foamy macrophages and/or cytoplasmic vacuolation) was observed in multiple tissues and organs of mice, rats, and monkeys following oral daily administration of pimavanserin. The occurrence of phospholipidosis was both dose- and duration-dependent. The most severely affected organs were the lungs and kidneys. In rats, diffuse phospholipidosis was associated with increased lung and kidney weights, respiratory-related clinical signs including rales, labored breathing, and gasping, renal tubular degeneration, and, in some animals, focal/multifocal chronic inflammation in the lungs at exposures ≥10-times those at the maximum recommended human dose (MRHD) of 34 mg/day based on AUC. Phospholipidosis caused mortality in rats at exposures ≥16-times the MRHD of 34 mg/day based on AUC. The chronic inflammation in the rat lung was characterized by minimal to mild focal collagen positive fibroplasia as shown by specialized staining. Chronic inflammation of the lungs was not seen in monkeys treated for 12 months (exposures 9-times the MRHD). Based on the exposures at the estimated No Observed Effect Level (NOEL) for chronic lung inflammation in rats, there is a 5- to 9-times safety margin after 6-months of treatment and a 2- to 4-times safety margin after 24-months (lifetime) treatment compared to exposure at the MRHD. The relevance of these findings to human risk is not clear.

14 CLINICAL STUDIES

The efficacy of NUPLAZID 34 mg as a treatment of hallucinations and delusions associated with Parkinson's disease psychosis was demonstrated in a 6-week, randomized, placebo-controlled, parallel-group study. In this outpatient study, 199 patients were randomized in a 1:1 ratio to NUPLAZID 34 mg or placebo once daily. Study patients (male or female and aged 40 years or older) had a diagnosis of Parkinson's disease (PD) established at least 1 year prior to study entry and had psychotic symptoms (hallucinations and/or delusions) that started after the PD diagnosis and that were severe and frequent enough to warrant treatment with an antipsychotic. At entry, patients were required to have a Mini-Mental State Examination (MMSE) score ≥21 and to be able to self-report symptoms. The majority of patients were on PD medications at entry; these medications were required to be stable for at least 30 days prior to study start and throughout the study period.

The PD-adapted Scale for the Assessment of Positive Symptoms (SAPS-PD) was used to evaluate the efficacy of NUPLAZID 34 mg. SAPS-PD is a 9-item scale adapted for PD from the Hallucinations and Delusions domains of the SAPS. Each item is scored on a scale of 0-5, with 0 being none and 5 representing severe and frequent symptoms. Therefore, the SAPS-PD total score can range from 0 to 45 with higher scores reflecting greater severity of illness. A negative change in score indicates improvement. Primary efficacy was evaluated based on change from baseline to Week 6 in SAPS-PD total score.

As shown in **Table 3**, **Figure 3**, and **Figure 4**, NUPLAZID 34 mg (n=95) was statistically significantly superior to placebo (n=90) in decreasing the frequency and/or severity of hallucinations and delusions in patients with PDP as measured by central, independent, and blinded raters using the SAPS-PD scale. An effect was seen on both the hallucinations and delusions components of the SAPS-PD.

Table 3 Primary Efficacy Analysis Result Based on SAPS-PD (N=185)

Endpoint	Treatment Group	Mean Baseline Score (SD)	LS Mean Change from Baseline (SE)	Placebo-subtracted Difference[a] (95% CI)
SAPS-PD	NUPLAZID	15.9 (6.12)	-5.79 (0.66)	-3.06* (-4.91, -1.20)
	Placebo	14.7 (5.55)	-2.73 (0.67)	--
SAPS-PD Hallucinations[b]	NUPLAZID	11.1 (4.58)	-3.81 (0.46)	-2.01 (-3.29, -0.72)
	Placebo	10.0 (3.80)	-1.80 (0.46)	--
SAPS-PD Delusions[b]	NUPLAZID	4.8 (3.59)	-1.95 (0.32)	-0.94 (-1.83, -0.04)
	Placebo	4.8 (3.82)	-1.01 (0.32)	--

SD: standard deviation; SE: standard error; LS Mean: least-squares mean; CI: confidence interval.

[a] Difference (drug minus placebo) in least-squares mean change from baseline.

[b] Supportive analysis.

* Statistically significantly superior to placebo.

The effect of NUPLAZID on SAPS-PD improved through the six-week trial period, as shown in **Figure 3**.

Figure 3 SAPS-PD Change from Baseline through 6 Weeks Total Study Treatment

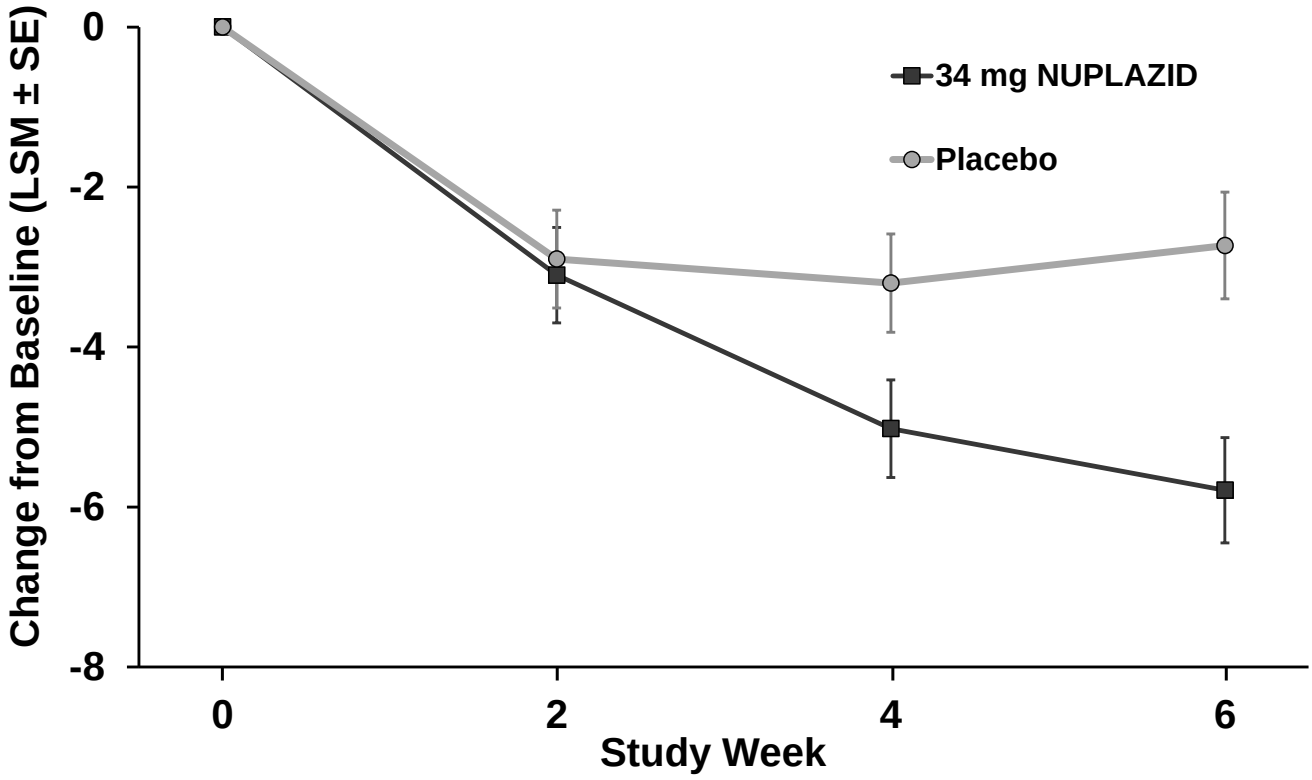
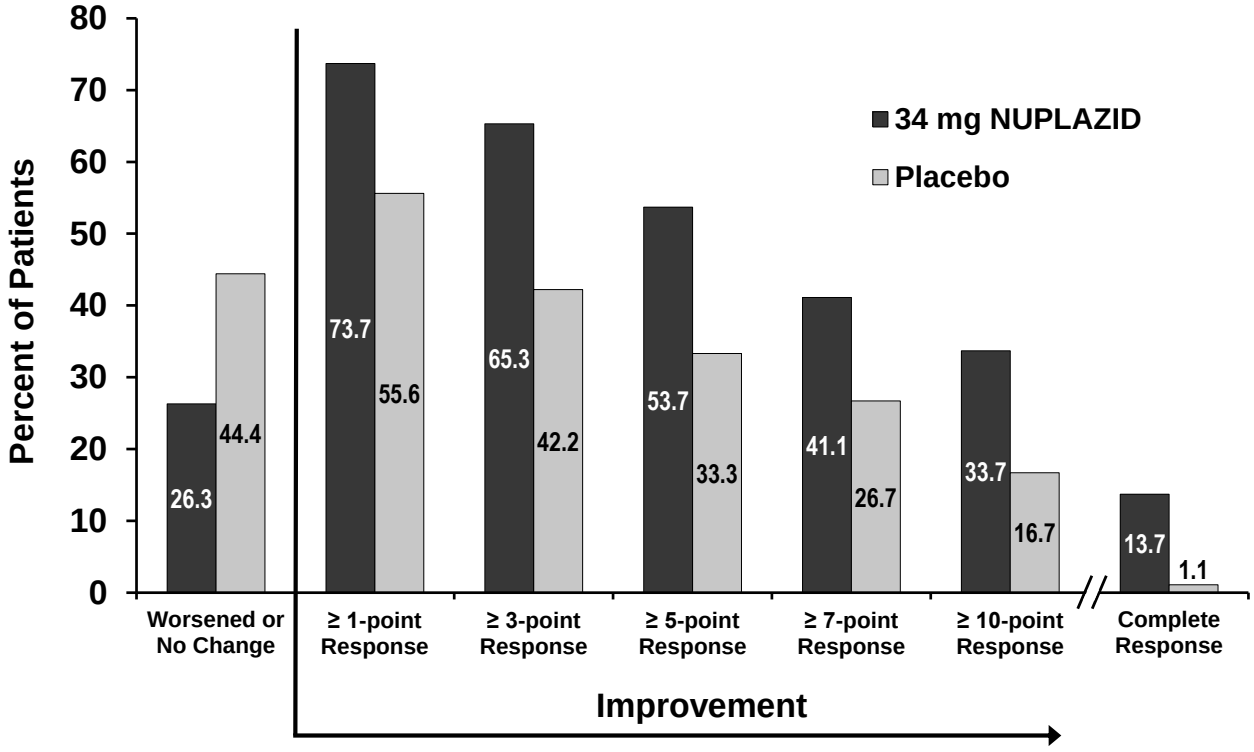


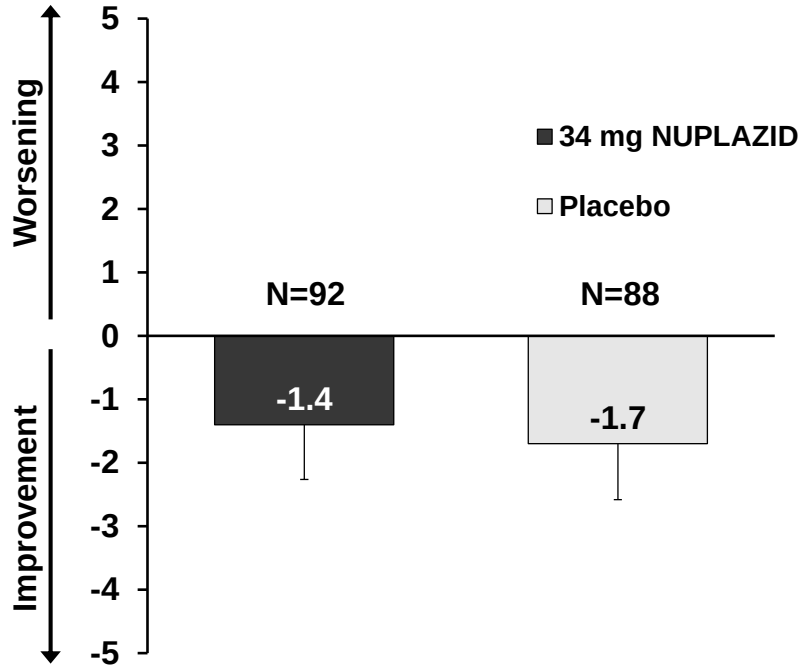
Figure 4 Proportion of Patients with SAPS-PD Score Improvement at the End of Week 6 (N=185)



Complete response = SAPS-PD score reduced to zero from baseline value.
Patients with missing values were counted as non-responders.

Motor Function in Patients with Hallucinations and Delusions Associated with Parkinson's Disease Psychosis
NUPLAZID 34 mg did not show an effect compared to placebo on motor function, as measured using the Unified Parkinson's Disease Rating Scale Parts II and III (UPDRS Parts II+III) (**Figure 5**). A negative change in score indicates improvement. The UPDRS Parts II+III was used to assess the patient's Parkinson's disease state during the 6-week double-blind treatment period. The UPDRS score was calculated as the sum of the 40 items from activities of daily living and motor examination, with a range of 0 to 160.

Figure 5 Motor Function Change from Baseline to Week 6 in UPDRS Parts II+III (LSM - SE)



LSM: least-squares mean; SE: standard error. The error bars extend one SE below the LSM.

16 HOW SUPPLIED/STORAGE AND HANDLING

NUPLAZID (pimavanserin) is available as:

34 mg Capsule:
Opaque white and light green capsule with "PIMA" and "34" printed in black.
Bottle of 30: NDC 63090-340-30

10 mg Tablet:
Orange, round, coated tablet debossed with "P" on one side and "10" on the reverse.
Bottle of 30: NDC 63090-100-30

Storage
34 mg Capsule:
Store at 20°C to 25°C (68ºF to 77°F); excursions permitted between 15°C and 30°C (59°F and 86°F) [See USP Controlled Room Temperature]. To prevent potential capsule color fading, protect from light.

10 mg Tablet:
Store at 20°C to 25°C (68°F to 77°F); excursions permitted between 15°C and 30°C (59°F and 86°F) [See USP Controlled Room Temperature].

17 PATIENT COUNSELING INFORMATION

Concomitant Medication
Advise patients to inform their healthcare providers if there are any changes to their current prescription or over-the-counter medications, since there is a potential for drug interactions *[see Warnings and Precautions (5.2), Drug Interactions (7)]*.

Administration Instructions
Advise patients to take the capsule whole or sprinkled over a tablespoon (15 mL) of applesauce, yogurt, pudding, or a liquid nutritional supplement. Advise patients to consume the drug/food mixture immediately and not to store for future use *[see Dosage and Administration (2.2)]*.

Distributed by:
Acadia Pharmaceuticals Inc.
San Diego, CA 92130 USA

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Update on the Use of Psychotropic Agents in Long-Term Care

A Focus on Selected Centers for Medicare and Medicaid Services (CMS) Regulations Impacting the Treatment of Hallucinations and Delusions Associated With Parkinson's Disease Psychosis (PDP)

Effective November 28, 2017

Why is this important?

- All long-term care team members must help ensure appropriate use of psychotropic medications
- Use of these medications must comply with all applicable clinical and regulatory guidelines
- Revisions to CMS requirements* and the State Operations Manual† provide important guidance relevant to the use of antipsychotic agents for the treatment of hallucinations and delusions associated with PDP

Note: This document is not intended to be a comprehensive review of applicable CMS regulations nor is it intended as legal advice. Please consult the full regulations for complete information.

*Centers for Medicare & Medicaid Services (CMS) Requirements for Participation under the Medicare and Medicaid Programs; Reform of Requirements for Long-Term Care Facilities (sometimes referred to as the Nursing Home Mega Rule). Accessed September 10, 2020. https://www.federalregister.gov/documents/2016/10/04/2016-23503/medicare-and-medicaid-programs-reform-of-requirements-for-long-term-care-facilities

†Centers for Medicare & Medicaid Services. State Operations Manual: Appendix PP - Guidance to Surveyors for Long Term Care Facilities. (Rev. 11-22-17). Accessed September 10, 2020. https://www.cms.gov/Medicare/Provider-Enrollment-and-Certification/GuidanceforLawsAndRegulations/Downloads/Appendix-PP-State-Operations-Manual.pdf

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F605: Chemical Restraints

Could using an antipsychotic for hallucinations and delusions associated with PDP be considered a chemical restraint?

Select Regulations	Intent of Regulations	CMS Guidance to Surveyors	For a Resident With Hallucinations and/or Delusions Related to PDP:
§483.10(e)(1) The resident has a right to be treated with respect and dignity, including: The right to be free from any physical or **chemical restraints** imposed for purposes of **discipline** or **convenience**, and not required to treat the resident's **medical symptoms**	For each person to attain and maintain his/her highest practicable well-being in an environment that prohibits the use of chemical restraints: • For discipline or convenience; and • Not required to treat a resident's medical symptoms To ensure that when a medication is used to treat a resident's symptoms: • The least restrictive alternative is used for the least amount of time • The facility re-evaluates the need for the medication on an ongoing basis • The medication is not used for discipline or convenience	A medication may be considered a chemical restraint if it restricts a resident's movement or cognition, or sedates or subdues the resident, and it is not an accepted standard of practice for the resident's medical or psychiatric condition. Facilities are responsible for knowing the effects that prescribed medications have on a resident. If a medication has a sedating or subduing effect and is not administered to treat a medical symptom, it is acting like a chemical restraint. Even if a medication was not intended to sedate the resident, but has that effect and is not the least restrictive alternative to treat the medical symptom, it can be considered a chemical restraint.	**Before initiating a medication for symptoms of PDP, prescribers should consider:** • Does this resident have a specific condition that necessitates the use of a medication? • Will adding this medication restrict the resident's movement or cognition or will it subdue or sedate the resident? • Is this medication the standard of practice for the documented indication? • Is this medication the least restrictive alternative for treating hallucinations and delusions associated with PDP? • Is this medication being prescribed for discipline or convenience or to treat a medical symptom? **When monitoring a resident with PDP, the clinical staff should ask:** • Is this resident being monitored for the effectiveness and potential adverse consequences of this medication? Is the need for this medication being re-evaluated periodically? • Is this medication helping the resident to function at the highest possible level? • If there is a continued need for this medication, is it clearly documented in the clinical record?

F757 and F758: Unnecessary Drugs and Psychotropic Drugs

How does CMS define unnecessary drugs?

Select Regulations	Intent of Regulations	CMS Guidance to Surveyors	For a Resident With Hallucinations and/or Delusions Related to PDP:
§483.45(d) Each resident's drug regimen must be free from **unnecessary drugs** **§483.45(e)(1)** Based on a comprehensive assessment of a resident, the facility must ensure that: Residents who have not used **psychotropic drugs** not receive these drugs unless the medication is necessary to treat a specific condition as diagnosed and documented in the clinical record	To ensure each resident's medication regimen is managed and monitored to promote or maintain the resident's **highest practicable mental, physical, and psychosocial well-being** To limit the use of PRN psychotropic medications and ensure they are used only when medically necessary	The IDT is responsible for evaluating if a resident's symptoms are persistent or **clinically significant** enough to warrant initiation or continuation of a medication. The IDT must also understand whether a particular medication is clinically indicated to manage the symptom or condition. For psychiatric disorders, psychotropic medications may be effective when the underlying cause of a resident's distress has been determined, non-pharmacologic approaches to care have been ineffective, or **expressions of distress** have worsened. Psychotropic medications may be appropriate in specific enduring conditions such as chronic depression, PDP, or recurrent seizures. Other potential causes of symptoms must be ruled out and symptoms must be persistent and negatively affecting the resident's quality of life. The symptoms and goals of psychotropic therapy must be documented.	**When deciding if an antipsychotic medication is necessary for a resident with PDP, clinicians should ask themselves:** • Has PDP been documented in the medical record as the cause of the resident's hallucinations or delusions? • Are the resident's PDP symptoms clinically significant, causing functional decline or resident distress? • Have the goals of antipsychotic therapy for PDP been clearly identified and documented in the medical record? • Have non-pharmacologic approaches failed to manage the resident's PDP symptoms or are non-pharmacologic approaches clinically contraindicated or declined by the resident? • Is the prescribed medication clinically indicated to treat hallucinations and delusions associated with PDP? • Is the resident being monitored for any adverse consequences, specifically increased confusion or over-sedation? • Is the prescribed medication being used on a routine basis and not as needed?

F740: Behavioral Health Services

Do hallucinations and delusions associated with PDP need to be addressed?

Select Regulations	Intent of Regulations	CMS Guidance to Surveyors	For a Resident With Hallucinations and/or Delusions Related to PDP:
§483.40 Each resident must receive and the facility must provide the necessary behavioral health care and services to attain or maintain **the highest practicable physical, mental, and psychosocial well-being**, in accordance with the comprehensive assessment and plan of care	To ensure that the facility is providing behavioral health care and services that create an environment that promotes emotional and psychosocial well-being, meets each resident's needs, and includes individualized approaches to care	Residents should receive an individualized approach to behavioral health care, directed toward understanding, preventing, relieving, and/or accommodating a resident's distress or loss of abilities. Behavioral health care and services should reflect the resident's goals for care, while maximizing his/her dignity, autonomy, privacy, socialization, independence, choice, and safety. Consider reviewing the following sections of the MDS to determine if the resident's behavioral health needs are being addressed: • Section C: Cognitive Patterns • Section D: Mood • Section E: Behavior • Section F: Activities Failing to develop individualized interventions related to the specific diagnosed conditions could result in a deficiency in F740.	**When the IDT is determining how to address a resident's hallucinations and delusions related to PDP, consider:** • Is this resident at his/her **highest practicable level of physical, mental, and psychosocial well-being?** • Have specific behavioral health care needs for this resident been identified based on a comprehensive assessment? • Does the resident have individualized interventions based on his/her specific diagnosed conditions? **When determining if an intervention for PDP is effective, ask:** • Has the resident achieved expected improvements or maintained the expected stable rate of decline based on progression of the diagnosed condition? • Is the resident receiving an intervention that is allowing him/her to maximize dignity, autonomy, privacy, socialization, independence, choice, and safety?

F757 and F758: Unnecessary Drugs and Psychotropic Drugs

Does an antipsychotic medication for PDP require a gradual dose reduction?

Select Regulations	Intent of Regulations	CMS Guidance to Surveyors	For a Resident With Hallucinations and/or Delusions Related to PDP:
§483.45(e)(2) The facility must ensure that residents who use **psychotropic drugs** receive **gradual dose reductions**, and behavioral interventions unless clinically contraindicated in an effort to discontinue these drugs	To ensure the facility implements **gradual dose reductions (GDR)** and non-pharmacologic interventions, unless contraindicated, prior to initiating or instead of continuing psychotropic medications **GDRs** seek to find an appropriate dose and duration for each psychotropic drug and minimize the risk of adverse consequences	Attempts at **GDR** may be clinically contraindicated if the resident has a documented disorder, if continued use is in accordance with relevant current standards of practice, and/or if attempts at a **GDR** resulted in a recurrence of or worsened the resident's symptoms. The physician must clearly document the clinical rationale if a **GDR** is contraindicated. Some residents with specific, enduring, progressive, or terminal conditions such as **PDP** may need specific types of psychotropic medications or other medications that affect brain activity indefinitely. Residents must be monitored for **adverse consequences** associated with antipsychotics, such as anticholinergic effects, cardiovascular adverse effects, metabolic changes, and neurologic adverse effects. If adverse events occur, the facility and prescriber, in consultation with the resident and/or family, must decide and document if the medication should continue.	**When determining if a GDR is appropriate for a resident, clinicians should ask themselves:** • Does the medical record indicate that the resident has PDP, which is an enduring condition? • Is continued use of this medication in line with the current standards of practice for the treatment of PDP? • Has a GDR been unsuccessfully attempted? • Has the prescriber indicated that reducing or stopping this medication may impair the resident's function or exacerbate his/her underlying psychiatric disorder? • Has the resident experienced any adverse consequences from the medication? If so, does the risk of continued use outweigh the benefit?

Glossary

Adverse consequence: Unwanted, uncomfortable, or dangerous effects that a drug may have, such as impairment or decline in an individual's mental or physical condition for functional or psychosocial status. It may include various types of adverse drug reactions.

Chemical restraint: Any drug that is used for discipline or staff convenience and not required to treat medical symptoms.

Clinically significant: Effects, results, or consequences that materially affect or are likely to affect an individual's mental, physical, or psychosocial well-being either positively by preventing, stabilizing, or improving a condition or reducing a risk, or negatively by exacerbating, causing, or contributing to a symptom, illness, or decline in status.

Convenience: The result of any action that has the effect of altering a resident's behavior, such that the resident requires a lesser amount of effort or care, and is not in the resident's best interest.

Discipline: Any action taken by facility staff for the purpose of punishing or penalizing residents.

Expressions or indications of distress: A person's attempt to communicate unmet needs, discomfort, or thoughts that he or she may not be able to articulate.

Gradual dose reduction (GDR): The stepwise tapering of a dose to determine if symptoms, conditions, or risks can be managed by a lower dose or if the dose or medication can be discontinued.

Highest practicable physical, mental, and psychosocial well-being: The highest possible level of functioning and well-being, limited by the individual's recognized pathology and normal aging process. Highest practicable level is determined through the comprehensive resident assessment process and by recognizing and competently and thoroughly addressing the physical, mental, or psychosocial needs of the individual.

IDT: Interdisciplinary team.

Indication for use: The identified, documented clinical rationale for administering a medication that is based upon an assessment of the resident's condition and therapeutic goals and is consistent with the manufacturer's recommendations and/or clinical practice guidelines, clinical standards of practice, medication references, clinical studies, or evidence-based review articles that are published in medical and/or pharmacy journals.

Medical symptom: An indication or characteristic of a medical, physical, or psychological condition.

Psychotropic drug: Any drug that affects brain activities associated with mental processes and behavior. These include, but are not limited to: antipsychotics, antidepressants, antianxiety medications, and hypnotics.

Unnecessary drug: Any drug when used in excessive dose (including duplicate drug therapy), for excessive duration, without adequate monitoring, without adequate indications for its use, or in the presence of adverse consequences which indicate the dose should be reduced or discontinued.

Reference: Centers for Medicare & Medicaid Services. State Operations Manual: Appendix PP - Guidance to Surveyors for Long Term Care Facilities. (Rev. 11-22-17). Accessed September 10, 2020. https://www.cms.gov/Medicare/Provider-Enrollment-and-Certification/GuidanceforLawsAndRegulations/Downloads/Appendix-PP-State-Operations-Manual.pdf

ACADIA™

FOR PROFESSIONAL CAREGIVERS

Have you seen behavior in residents with Parkinson's disease that should be reported?

During the course of their disease, about half of people living with Parkinson's may experience[1]:

Hallucinations[2-3]
Abnormal perceptions without a physical stimulus

- Seeing things
- Hearing things
- Smelling things
- Tasting things
- Sensing a presence
- Feeling things

Delusions[2,4,5]
False, fixed beliefs despite evidence to the contrary

- Thinking someone is trying to harm, steal from, or deceive them
- Believing their loved one is being unfaithful
- Thinking a song or TV show is speaking to them directly

Parkinson's disease is more than motor symptoms.[6]

- Parkinson's-related hallucinations and delusions are underrecognized and underreported nonmotor symptoms of the disease[6]
- Early signs of hallucinations and delusions associated with Parkinson's disease (PD)—also referred to as PD psychosis—should not be ignored. These symptoms can progress over time[7]
- PD psychosis also may increase the burden of care. Compared with residents with PD alone, residents with PD psychosis may exhibit more physical and verbal behavioral symptoms, experience a negative impact on participation in activities or social interactions, refuse evaluation of care necessary to achieve their goals for health and well-being, and have an increased rate of falls[8,*]

Answer the questions below to help evaluate residents for behaviors that may be signs of hallucinations or delusions.

1. Have they seen, heard, or sensed things, such as people, animals, or objects, that were unusual?	☐ Yes ☐ No
2. Have they had any beliefs or fears about someone stealing from them or trying to harm or deceive them?	☐ Yes ☐ No
3. When and how often do these symptoms occur each week?	
4. What changes to their daily life as a result of experiencing these things have you noticed? (Describe the symptoms and their impact on the resident—for example, emotionally [mood], physically [activities].)	

Routinely complete these questions for each of your residents with Parkinson's disease, and keep the nursing staff or medical director updated on the results so they can determine if further evaluation is needed.

The questions above are only examples to consider when determining if residents with PD are experiencing hallucinations and/or delusions. Healthcare professionals should exercise their clinical judgment to rule out other potential medical and psychological causes of psychosis before establishing a diagnosis of PD psychosis.

*A 2-year retrospective database analysis of US nursing facility residents (N=300,371) described the demographic, functional, and clinical characteristics of residents with PD and those with PD psychosis in a cross-sectional comparison (PD, N=6551; PD psychosis: N=2289) along with longitudinal comparison of matched cohorts (PD: N=1522; PD psychosis: N=491).

See reverse side for additional information.

DIAGNOSTIC CODES RECOGNIZED FOR PD PSYCHOSIS[9]

Coding combinations that are recognized for PD psychosis include G20 (PD) plus one of the following ICD codes:

- F06.0 Psychotic disorder with hallucinations due to known physiological condition
- F06.2 Psychotic disorder with delusions due to known physiological condition

Coding must be to the highest level of specificity, and all coding decisions are ultimately the responsibility of each prescribing healthcare professional

WHEN INITIATING ANTIPSYCHOTIC THERAPY FOR A RESIDENT WITH PD PSYCHOSIS, CONSIDER THE FOLLOWING GUIDANCE FROM THE CENTERS FOR MEDICARE AND MEDICAID SERVICES[10]:

F757 and F758 address unnecessary drugs and psychotropic drugs

- To be considered necessary, an antipsychotic should:
  - Be clinically indicated to manage the symptoms of PD psychosis
  - Be appropriate for the resident's clinical conditions, age, and underlying causes of symptoms
  - Be selected based on assessment of relative benefit and risks to, and preferences and goals of, the individual resident

F605 addresses chemical restraints

- To avoid being considered a chemical restraint, an antipsychotic for PD psychosis should:
  - Be the standard of practice for PD psychosis
  - Be the least restrictive alternative to treat the resident's hallucinations and delusions associated with PD psychosis
  - Help the resident to function at the highest possible level

References: 1. Forsaa EB, Larsen JP, Wentzel-Larsen T, et al. A 12-year population-based study of psychosis in Parkinson disease. *Arch Neurol*. 2010;67(8):996-1001. **2.** Ravina B, Marder K, Fernandez HH, et al. Diagnostic criteria for psychosis in Parkinson's disease: report of an NINDS, NIMH Work Group. *Mov Disord.* 2007;(22):1061-1068. **3**. Fénelon G, Soulas T, Zenasni F, Cleret de Langavant L. The changing face of Parkinson's disease-associated psychosis: a cross-sectional study based on the new NINDS-NIMH criteria. *Mov Disord.* 2010;25(6):755-759. **4.** Voss T, Bahr D, Cummings J, Mills R, Ravina B, Williams H. Performance of a shortened Scale for Assessment of Positive Symptoms for Parkinson's disease psychosis. *Parkinsonism Relat Disord.* 2013(19):295-299. **5.** Andreasen NC. *Scale for the Assessment of Positive Symptoms (SAPS)*. University of Iowa; 1984. **6.** Chaudhuri KR, Prieto-Jurcynska C, Naidu Y, et al. The nondeclaration of nonmotor symptoms of Parkinson's disease to health care professionals: an international study using the nonmotor symptoms questionnaire. *Mov Disord.* 2010;25(6):704-709. **7.** Goetz CG, Fan W, Leurgans S, Bernard B, Stebbins GT. The malignant course of "benign hallucinations" in Parkinson disease. *Arch Neurol*. 2006;63(5):713-716. **8.** Zarowitz B, O'Shea T, Shim A, Fredericks D, Norton JC. Clinical distinctions between US nursing home residents with Parkinson disease with and without Parkinson disease psychosis. *Ann Longterm Care*. 2019;27(10):14-21. **9.** World Health Organization. International Statistical Classification of Diseases and Related Health Problems, ICD-10 version: 2015. WHO website. Accessed June 1, 2022. http://apps.who.int/classifications/icd10/browse/2015/en. **10.** US Centers for Medicare & Medicaid Services. State Operations Manual Pub 100-07. Appendix PP-Guidance to Surveyors for Long Term Care Facilities. US Dept of Health and Human Services; 2017.

LTC Nursing Care Plan – Parkinson's Disease (PD) Psychosis

Resident Name: _____ **Room #:** _____ **Physician:** _____ **Date:** _____

Concerns & Problems	Resident/Family Nursing Goals	Assessment Date	Nonpharmacologic and/or Pharmacologic Interventions	Responsible Discipline	Reevaluation	Team Initials
Symptoms: **Hallucinations[1]:** Eg, seeing or hearing things that are not there _____ _____ **Delusions[1]:** Eg, paranoia _____ _____ **Observable behaviors:** _____ _____ _____ _____ _____	**Resident/Family:** ☐ Stabilization, reduction, or remission of symptoms/episodes ☐ Decreased intensity of symptoms/episodes ☐ Increase/preserve social interaction **Nursing:** ☐ Engage in activities of daily living (ADLs) ☐ Participate in PT/OT/ST as ordered to promote overall functioning and psychosocial well-being ☐ Maintain safe environment ☐ Monitor risk for falls ☐ Other _____ _____ _____ _____ _____		**Assessment/systematic observation[2]:** ☐ Identify problems through assessments of symptoms ☐ Assess the history and consequences of symptoms ☐ Clarify who is negatively affected **Ascertain causes for symptoms[2]:** ☐ Resident has negative view of caregiver ☐ Resident doesn't understand intent of caregiver ☐ Resident is suffering from social isolation or sensory deprivation ☐ Resident misinterprets situations **Conduct intervention matching causes of symptoms, resident's habits and preferences, and current abilities[2,3]:** ☐ Music therapy ☐ Orientation training ☐ Exercise ☐ Art-cognitive activity **Intervention addressed to[2]:** ☐ Resident ☐ Environment ☐ Staff member ☐ Family Assess and reevaluate whether symptoms and quality of life have improved post-intervention[2] **Pharmacologic Interventions[4]:** ☐ Administer medications per order ☐ Observe for effectiveness of medications ☐ Observe for adverse reactions ☐ Missed/refused medications ☐ Consult healthcare provider for any drug/dose changes		**At 30 Days:** _____ _____ _____ _____ _____ **At 60 Days:** _____ _____ _____ _____ _____ **At 90 Days:** _____ _____ _____ _____ _____ **Quarterly:** _____ _____ _____ _____ _____ **PRN:** _____ _____ _____ _____ _____	

Under CMS F657 a **comprehensive care plan** must be developed within 7 days after completion of the comprehensive assessment. This care plan should be prepared by an interdisciplinary team that includes, but is not limited to, the attending physician, a registered nurse with responsibility for the resident, a nurse aide with responsibility for the resident, a member of food and nutrition services staff, and, to the extent practicable, the resident, the resident's representatives, and other appropriate staff or professionals in disciplines determined by the resident's needs or as requested by the resident. This care plan should be reviewed and revised by the interdisciplinary team after each assessment, including the comprehensive and quarterly review assessments.[5]

Additional notes:

This planning tool is provided by ACADIA for educational purposes only. Please use your clinical judgment for establishing a full comprehensive nursing care plan for patients with Parkinson's Disease Psychosis.

This tool has been approved by:

NADONA

For additional information regarding PD psychosis, please visit www.moretoparkinsons.com.

References: 1. Ravina B, Marder K, Fernandez HH, et al. Diagnostic criteria for psychosis in Parkinson's disease: report of an NINDS, NIMH work group. *Mov Disord*. 2007;22(8):1061-1068. **2.** Cohen-Mansfield J. Nonpharmacologic interventions for psychotic symptoms in dementia. *J Geriatr Psychiatry Neurol*. 2003;16(4):219-224. **3.** Chen R, Liu C, Lin M, et al. Non-pharmacological treatment reducing not only behavioral symptoms, but also psychotic symptoms of older adults with dementia: a prospective cohort study in Taiwan. *Geriatr Gerontol Int*. 2014;14(2):440-446. **4.** Dunlop SR, Gerstenhaber M. Long-term care and nursing home issue. In: Menza M, Marsh L, eds. *Psychiatric Issues in Parkinson's Disease: A Practical Guide*. New York, NY: Informa Healthcare USA, Inc; 2009. **5.** US Centers for Medicare & Medicaid Services. *State Operations Manual Pub 100-07. Appendix PP - Guidance to Surveyors for Long Term Care Facilities*. Baltimore, MD: US Dept of Health and Human Services; 2017.