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For further information regarding Indication, **Boxed WARNING** and other Important Safety Information for NUPLAZID, please click here: Prescribing Information.

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NUPLAZID® (pimavanserin): Switching from Other Antipsychotics in Patients with Parkinson's Disease Psychosis

This letter is provided in response to your specific request for information regarding data on strategies for switching from other antipsychotics to pimavanserin. NUPLAZID is the only US Food and Drug Administration (FDA) approved therapy for the treatment of hallucinations and delusions associated with Parkinson's disease (PD) psychosis.

NUPLAZID prolongs the QT interval and should be avoided in patients with risk factors for QT prolongation or in combination with other drugs that also increase the QT interval.[1]

There have been no controlled studies done to assess switching from other antipsychotics to pimavanserin, and the efficacy and safety of pimavanserin in combination with other antipsychotics has not been established and approved by the FDA. The information provided herein is to inform your clinical decision making but should not be considered an endorsement from Acadia around any particular strategy.

Summary

- While **recommendations based on expert opinion** are available in the literature,[2-5] there are no controlled clinical trials that have assessed switching strategies from other antipsychotics to pimavanserin in patients with PD psychosis.
- There are several **considerations for setting up a strategy for switching antipsychotics**, such as drug half-life, time to steady state, and time for withdrawal. It is also important to identify all potential interacting medications.[6]
- Three main strategies that could be considered for switching antipsychotics are 'Abrupt Switch', 'Cross Taper' and 'Overlap and Discontinue'. Each strategy has advantages and disadvantages.[7]
- Strategies for switching to pimavanserin should be tailored to a specific patient's disease and current treatment. Expectations should be discussed with the patient and/or caregiver prior to initiating the switch to pimavanserin.

Pimavanserin Published Studies

Pimavanserin trials did not evaluate strategies of switching participants from other antipsychotics to pimavanserin because concomitant antipsychotics were discontinued prior to baseline visits. In Study 020, a randomized, double-blind, placebo-controlled, multicenter Phase 3 study of pimavanserin in 185 adult participants with PD psychosis, concomitant antipsychotics were not permitted during the study, and were discontinued no less than 5 half-lives prior to baseline visit.[8]

Considerations and Strategies for Switching Antipsychotics

There are limited controlled trials on switching antipsychotics, with no switching studies in PD psychosis and most published studies being small case reports or case series in schizophrenia or bipolar disorders.

When switching antipsychotics, there are important considerations to ensure patients attain optimal therapeutic outcomes while minimizing the risk of adverse events, including relapse.[6] It is important that patients and caregivers understand there can be challenges that arise during the transition period and that frequent dialogue with the physician/office may be warranted during this time. Similarly, it is important for the patient to continue the medication switch through to completion. Following the switch, patients and caregivers should be advised to allow enough time at a full therapeutic dose to assess the impact of the new antipsychotic. Even with close monitoring, not all patients are successfully switched to a new antipsychotic. This can occur for many reasons, including worsening of symptoms.

The pharmacokinetic (PK) and pharmacodynamic characteristics of the antipsychotics involved are important considerations, including half-life and the metabolism of the medications (**Table 1**).[2,6]

Table 1. Relevant PK Parameters for Switching Antipsychotics[2,6]

Drug	Half-life	Steady State	Major P450 Metabolic Enzymes
Pimavanserin	57 hours	2 weeks	CYP3A4 and CYP3A5
Clozapine	12 hours (range: 4–66 hours)	2.5–3 days	CYP3A4, CYP1A2, and CYP2D6
Quetiapine	7 hours; 12 hours for norquetiapine	2 days	CYP3A4

Abbreviation: PK=pharmacokinetic.

When developing the strategy for switching antipsychotics, half-life, time to steady state, and time for withdrawal should be considered.[2,6] Given that antipsychotics are mainly metabolized by the liver cytochrome P450 system, it is critical to identify all potential interacting medications. Additionally, the tolerability of switching medications for patients with PD can be influenced by the affinity of different antipsychotics for dopaminergic, muscarinic, cholinergic, histaminergic, and adrenergic receptors (**Table 2**). This can be the case especially if the withdrawal is abrupt.

Table 2. Receptor Selectivity Based on R-SAT™ Platform (K_i [nM])[9]

Receptor		Pimavanserin	Typical APD	Atypical APDs			
			Haloperidol	Clozapine	Olanzapine	Quetiapine	Risperidone
Serotonergic	5-HT_{2A}	0.4	50	7	2.5	250	0.2
	5-HT_{2B}	nr	nr	40	80	1100	12
	5-HT_{2C}	16	nr	40	80	nr	100
	5-HT_{1A}	nr	nr	nr	nr	nr	nr
Histaminergic	H1	nr	nr	0.5	4	5	60
Muscarinic	M1	nr	nr	16	60	250	nr
	M2	nr	nr	nr	nr	-	nr
	M3	nr	nr	6	nr	200	nr
	M4	nr	nr	nr	40	150	nr
	M5	nr	nr	30	60	-	nr
Dopaminergic	D1	nr	100	nr	100	-	60
	D2	nr	0.1	50	4	30	0.5
	D3	nr	0.2	nr	25	9	13
Adrenergic	A1A	nr	40	8	100	nr	3
	A1D	-	nr	nr	nr	nr	50
	A2A	nr	nr	nr	nr	nr	20
	A2B	nr	nr	50	nr	nr	50
	A2C	nr	50	40	nr	nr	13

Data are Ki values in nM derived from Receptor Selection and Amplification Technology (R-SAT™) platform.
Abbreviations: 5-HT=serotonin; A=alpha- adrenergic; APD=antipsychotic drug; D=dopamine; H=histamine; Ki=inhibitory constant; M=muscarinic acetylcholine; nM=nanomoles; nr=no response.

According to the medical literature, there are 3 main strategies that could be considered for switching antipsychotics:[7]

1. Abrupt Switch: Immediate discontinuation of the current drug and starting the new drug at full dose.
2. Cross Taper: Slow taper decreasing dose of current drug and gradual increase in dosage of new drug.
3. Overlap and Discontinue: Starting new drug at full dose with slow taper of current drug.

Each strategy has advantages and disadvantages, and the chosen strategy should be evaluated based on the efficacy-to-safety benefit and be tailored to the individual patient. These switch strategies were developed with antipsychotics that antagonize dopamine, serotonin, and a number of off target receptors.[9] Special consideration should be made for the differences in half-lives of clozapine, quetiapine, and pimavanserin (12 hours, 7 hours, and 57 hours, respectively; **Table 1**).[6]

Recommendations for Pimavanserin Initiation based on Expert Opinion

A panel of 14 experts in neurology and psychiatry created guidance for switching to pimavanserin from off-label antipsychotics (clozapine or quetiapine) with sub-optimal efficacy and/or tolerability in patients with PD psychosis by utilizing published data about switching antipsychotics in psychiatric disorders, PD psychosis-patient treatment experiences, and antipsychotic pharmacology. The consensus recommendations are derived from a brief survey completed by 12 of the 14 experts based on their own treatment experiences and preferences in

patients with PD psychosis.[2,3] These consensus recommendations form the basis of a **quick reference document** for healthcare professionals caring for patients with PD psychosis that was developed by the American Society of Consultant Pharmacists.[4]

Updated consensus recommendations have since been published using similar methodology, taking into account the treatment experience and preferences of the expert panel since their previous consensus, as well as current pathophysiology and recent clinical data. The panel of 6 experts in movement disorder neurology and psychiatry developed a consensus on first-line and subsequent treatment strategies for PD psychosis. These recommendations include an algorithm for the management of PD psychosis to reflect the rational utilization of pimavanserin, clozapine, and quetiapine based on clinical characteristics and response, with a focus on tailoring first-line therapy and identifying patients who may need to switch or combine medications.[5]

By providing this information, Acadia is not recommending or suggesting that pimavanserin, or any other drug mentioned, should be used for conditions, purposes, or uses other than the one(s) for which the drug has been approved by the FDA.

Clinical studies on evaluating the optimal strategy for switching from a prior antipsychotic to pimavanserin have not been performed. Therefore, the clinical relevance of the information provided is unknown. Strategies for switching to pimavanserin should be tailored to a specific patient's disease and current treatment. Expectations should be discussed with the patient and/or caregiver prior to initiating the switch to pimavanserin.

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