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

NUPLAZID® (pimavanserin): Proposed Mechanism of Action

This letter is provided in response to your specific request for information regarding the proposed pimavanserin mechanism of action.

Summary

- The mechanism of action (MOA) of pimavanserin in the treatment of hallucinations and delusions associated with Parkinson's disease (PD) psychosis is unclear.¹
- 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.¹

Proposed Mechanism of Action

The MOA of pimavanserin in the treatment of hallucinations and delusions associated with PD psychosis is unclear.¹ 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.

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).¹ 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 D₂), muscarinic, histaminergic, or adrenergic receptors, or to calcium channels.

The clinical relevance of the pimavanserin MOA is unknown, and healthcare providers should exercise clinical judgment when using this product.

***In Vitro* Functional Antagonist Receptor Selection and Amplification (R-SAT™) Assays**

The R-SAT platform is an assay system in which the functional activity of a wide selection of gene products or potential drug targets is evaluated through signal transduction pathways that lead to cellular growth, the signals of which are reported using marker gene technologies.² A low K_i value indicates high affinity for that receptor.³

In R-SAT assays, pimavanserin was highly selective for the 5-HT_{2A} receptor, and to a lesser extent, the 5-HT_{2C} receptor, but did not exhibit measurable affinity for dopaminergic, histaminergic, adrenergic, or muscarinic receptors.⁴ Other antipsychotics that were assessed bound to D₂ dopamine receptors and had varying activity at other receptors, including histaminergic and muscarinic receptors (**Table 1**).

Table 1. Receptor Selectivity Based on R-SAT™ Platform (K_i [nM])⁴

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 K_i values in nM derived from Receptor Selection and Amplification Technology (R-SAT™) platform.

Abbreviations: 5-HT=serotonergic; A=alpha-adrenergic; APD=antipsychotic drug; D=dopaminergic; H=histaminergic; K_i=inhibitory constant; M=muscarinic; nr=no response.

References

1. NUPLAZID® (pimavanserin) [package insert]. San Diego, CA. Acadia Pharmaceuticals Inc. [\[Link\]](#)
2. Hacksell U, Nash N, Burstein ES, Piu F, Croston G, Brann MR. Chemical genomics: massively parallel technologies for rapid lead identification and target validation. *Cytotechnology*. 2002;38(1-3):3-10. [\[PubMed\]](#)
3. Acadia Pharmaceutical Inc. NUPLAZID® Sponsor Background Information for a Meeting of the Psychopharmacologic Drugs Advisory Committee on 29 March 2016.
4. Hacksell U, Burstein ES, McFarland K, Mills RG, Williams H. On the discovery and development of pimavanserin: a novel drug candidate for Parkinson's psychosis. *Neurochem Res*. 2014;39(10):2008-2017. [\[PubMed\]](#)