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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 D_2), 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 D_2 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			Typical APD	Atypical APDs			
		Pimavanserin	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=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]**