Pimavanserin(Nuplazid®)
FDA approved April 2016

Indication: Pimavanserin is an atypical antipsychotic indicated for the treatment of hallucinations and delusions associated with Parkinson's disease (PD) psychosis

Mechanism of Action: Unclear, thought to be mediated through a combination of inverse agonist and antagonist activity preferentially targeting serotonin 5-HT2A and to a lesser extent 5-HT2C receptors. Pimavanserin has no structural resemblance to other antipsychotic drugs

Dosage & Administration

Dosage	34 mg once daily, no titration required
Renal impairment	Mild-to-moderate: No dosage adjustment required Severe (CrCl <30 mL/min): Not evaluated
Hepatic impairment	Not recommended (not evaluated)
Administration	Can be taken with or without food

Drug Drug Interactions

Concomitant Medication	Effect
Strong CYP3A4 inhibitors	Reduce dose by one-half (17 mg)
Strong 3A4 inducers	Monitor efficacy, increased dose may be needed

Notable Adverse Effects

Most frequently (≥5%) reported & twice the rate of placebo)	Peripheral edema Confusional state
AEs (5-10%)	Nausea & peripheral edema (7%) Confusional state (6%) Hallucinations (5%)

Warnings & Precautions

Black Box Warning

- Antipsychotic drugs increase the risk of death in elderly patients with dementia-related psychosis. Not approved for the treatment of patients with dementia-related psychosis unrelated to the hallucinations and delusions associated with PD psychosis

QT prolongation

- Avoid use in clts with known QT prolongation, h/o arrhythmias, other circumstances that may increase the risk of torsade de pointes/sudden death or with other drugs that increase QT interval

Pharmacokinetics

Tmax	Median 6 (range 4-24) hours
Metabolism	primarily by CYP 3A4 & 3A5
Half-life	57 hours (pimavanserin), 200 hours (active metabolite

	N-desmethylated metabolite)
Excretion (after 10 days)	Feces (<2%); urine (~0.55 % as unchanged drug)

Discontinuation of therapy: Long half-life indicates stopping pimavanserin abruptly may be possible

Clinical trials

Efficacy: The efficacy of pimavanserin was shown in a 6 week randomized, double-blind, placebo-controlled trial. Pimavanserin was shown to be statistically significantly superior to placebo in reducing the frequency and/or severity of hallucinations and delusions

- 199 participants (mean age 72) with Parkinson's disease psychosis were randomized to pimavanserin 34 mg or placebo once daily
- The change in score on the Parkinson's disease-adapted scale for assessment of positive symptoms (SAPS-PD, scale of 0-45 with higher scores reflecting greater severity of illness) from baseline to week 6 was the primary endpoint
    - Pimavanserin group had lower score associated with an antipsychotic benefit (-5.79 with pimavanserin vs. -2.73 with placebo)
- Pimavanserin did not show to worsen the PD motor symptoms

Safety: The most common reported side effects were peripheral edema, nausea, and a confusional state

Role in Therapy

- Hallucinations and delusions occur in up to 60% of patients with PD partly because the medications used to improve motor symptoms may cause psychosis. Antipsychotics block dopamine and can worsen motor function
- Pimavanserin, the first approved medication for the treatment of PD associated psychosis, represents a medication with a unique mechanism of action. It doesn't appear to worsen PD motor symptoms since it's selective for serotonin instead of dopamine receptors
- Pimavanserin may be effective in the short-term treatment of hallucinations and delusions in patients with PD, but it seems to provide minimal benefit
- Specialty medication – supplied through Nuplazid connect
- Pimavanserin is currently studied for the treatment of psychosis related to Alzheimer's disease and as adjuvant therapy to enhance the effect of atypical antipsychotics in schizophrenia
- Long term experience in routine clinical patients, head to head comparisons with off-label treatment options, and studies powered to examine long-term symptom improvement & clinically relevant outcomes of disease progression would help define pimavanserin's benefits and risks not yet well-defined
- Treatment options for PD associated psychosis
    - Please see attached UptoDate Algorithm
    - The American Academy of Neurology guidelines for treating psychosis in PD recommends off-label use of clozapine or quetiapine
    - Consider a low dose quetiapine (a weaker dopamine blocker, usually doesn't worsen motor symptoms) or clozapine, if an antipsychotic is needed
    - Avoid other atypical or conventional antipsychotics

        - **S**tronger dopamine blockers such as haloperidol can cause severe and at times fatal reactions in PD patients
    - Consider Pimavanserin if other measures are inadequate or intolerable
        - Potential benefits of pimavanserin
            - Does not exacerbate the motor symptoms of PD
            - Not associated with sedation and metabolic AEs of quetiapine and clozapine
            - Does not require dose reduction of concomitant anti-parkinsonian dopaminergic therapy
        - Potential disadvantages of pimavanserin
            - Minimal benefit
            - AEs include peripheral edema & confusional state, can prolong QT interval
            - Drug interactions
            - Not to be used in clts with hepatic impairment or severe renal impairment
            - Specialty med, expensive

Antipsychotics (off-label use)	**Advantages**	**Disadvantages**
Clozapine (low dose ≤50 mg/d)	• Probably an effective treatment, demonstrated superior improvement in psychosis symptoms compared to placebo in at least 1 RCT • Does not seem to worsen motor Sx • Cost benefit	• May not be an optimal treatment for many clts due to AEs (agranulocytosis, somnolence, & other significant toxicity) and stringent blood monitoring • potential to worsen motor symptoms of PD
Quetiapine (low dose 12.5 mg qhs)	• Commonly used, well-tolerated • Cost benefit	• Studies do not support efficacy • potential to worsen motor symptoms of PD

Formulary recommendation/approval criteria

- Nonformulary
- Follow UptoDate treatment algorithm: https://www.uptodate.com/contents/images/NEURO/110759/Mgmt_psychosis_PD.gif
- Reduce or stop offending agents, then documentation that treatment with clozapine/quetiapine has been ineffective, intolerable or contraindicated
- Renewal - documentation of positive clinical response to Nuplazid therapy

Management of psychosis in Parkinson disease

https://www.uptodate.com/contents/images/NEURO/110759/Mgmt_psychosis_PD.gif