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Pimavanserin

Updated: June 1, 2017.

OVERVIEW

Introduction

Pimavanserin is an atypical antipsychotic used in the treatment of hallucinations and psychosis in patients with Parkinson disease. Use of pimavanserin is associated with a low rate of serum enzyme elevations during therapy, and it has not been linked to instances of clinically apparent acute liver injury.

Background

Pimavanserin (pim" a van' ser in) is non-dopaminergic atypical antipsychotic agent that appears to act as a selective inverse agonist of the serotonin (5-HT) 2A receptor. It has little or no activity against the 5-HT2B and 2C receptors which may account for its relative lack of adverse effects. The absence of dopamine receptor activity suggested that pimavanserin would be appropriate for patients with Parkinson disease psychosis which is usually resistant to the atypical antipsychotic medications and can be worsened by inhibition of dopaminergic transmission. Clinical studies demonstrated its effectiveness in Parkinson disease psychosis and it was approved for this use in the United States in 2016. Pimavanserin is available in tablets of 17 mg under the brand name Nuplazid. The typical dose is 34 mg once daily. Common side effects include somnolence, headache, confusion, hallucinations, and peripheral edema. Rare, but potentially serious adverse events include prolongation of the QT interval and increased risk of death in elderly patients with dementia related psychosis.

Hepatotoxicity

Liver test abnormalities are uncommon (<1%) in patients taking pimavanserin, and the frequency of elevations appears to be similar to the rate that occurs with placebo therapy. No liver related serious adverse events or cases of clinically apparent liver injury were reported in the preregistration trials of pimavanserin. Pimavanserin has had limited clinical use since its approval and general availability, and it has not been implicated in published reports of clinically apparent liver injury. Thus, liver injury due to pimavanserin must be rare, if it occurs at all.

Likelihood score: E (unlikely cause of clinically apparent liver injury).

Mechanism of Injury

The potential mechanism by which pimavanserin might cause liver injury is not apparent. Pimavanserin is metabolized in the liver, primarily via CYP 3A and is susceptible to drug-drug interactions with agents that are potent inducers or inhibitors of CYP 3A activity.

Outcome and Management

Liver test abnormalities during pimavanserin therapy are uncommon and typically transient, mild and not associated with symptoms or jaundice. There have been no reports of hepatitis, acute liver failure, chronic hepatitis or vanishing bile duct syndrome attributed to pimavanserin. It is unlikely that there is cross sensitivity to liver injury between pimavanserin and other atypical antipsychotic medications.

Drug Class: Antipsychotic Agents, Atypicals

PRODUCT INFORMATION

REPRESENTATIVE TRADE NAMES

Pimavanserin – Nuplazid®

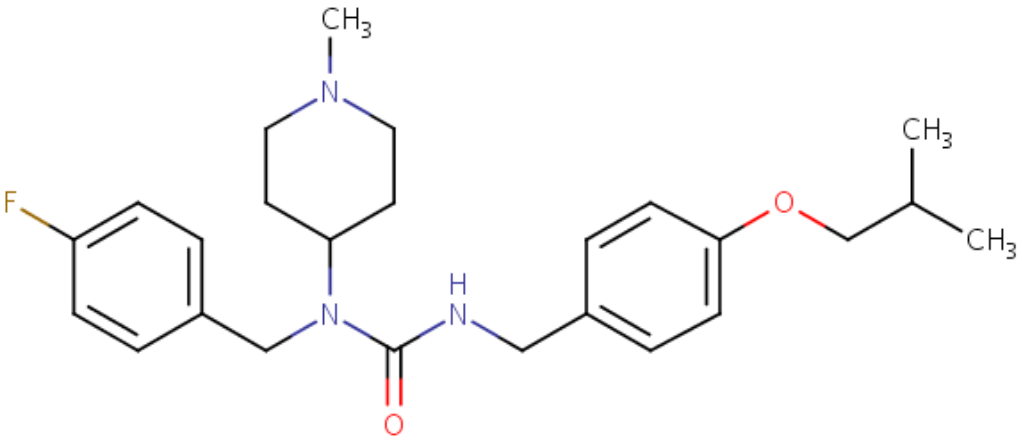
DRUG CLASS

Antipsychotic Agents

COMPLETE LABELING

Product labeling at DailyMed, National Library of Medicine, NIH

CHEMICAL FORMULA AND STRUCTURE

DRUG	CAS REGISTRY NUMBER	MOLECULAR FORMULA	STRUCTURE
Pimavanserin	706779-91-1	C25-H34-F-N3-O2	

ANNOTATED BIBLIOGRAPHY

References updated: 01 June 2017

Meyer JM. Pharmacotherapy of psychosis and mania. In, Brunton LL, Chabner BA, Knollman BC, eds. Goodman & Gilman's the pharmacological basis of therapeutics. 12th ed. New York: McGraw-Hill, 2011, pp. 417-56.

(Textbook of pharmacology and therapeutics).

Meltzer HY, Elkis H, Vanover K, Weiner DM, van Kammen DP, Peters P, Hacksell U. Pimavanserin, a selective serotonin (5-HT)2A-inverse agonist, enhances the efficacy and safety of risperidone, 2mg/day, but does not enhance efficacy of haloperidol, 2mg/day: comparison with reference dose risperidone, 6mg/day. Schizophr Res 2012; 141: 144-52. PubMed PMID: 22954754.

(Among 423 patients with an acute exacerbation of schizophrenia treated with one of five regimens combining pimavanserin or placebo with either haloperidol or risperidone for 6 weeks, combining low doses of risperidone with pimavanserin yielded better efficacy with lower rates of adverse events [including lower rates of ALT and AST elevations] compared to full doses of risperidone or haloperidol with or without pimvanserin).

Meltzer HY, Roth BL. Lorcaserin and pimavanserin: emerging selectivity of serotonin receptor subtype-targeted drugs. J Clin Invest 2013; 123: 4986-91. PubMed PMID: 24292660.

(Review of serotonin [5-HT] receptor activity and the advantages of highly selective receptor-subtype directed therapies, examples being lorcaserin, the 5-HT2C agonist [without 5-HT2B agonist activity] used for weight loss, and pimavanserin, the 5-HT2A inverse agonist [without dopaminergic activity] used for Parkinson disease psychosis).

Cummings J, Isaacson S, Mills R, Williams H, Chi-Burris K, Corbett A, Dhall R, et al. Pimavanserin for patients with Parkinson's disease psychosis: a randomised, placebo-controlled phase 3 trial. Lancet 2014; 383 (9916): 533-40. PubMed PMID: 24183563.

(Among 199 patients with Parkinson disease psychosis treated with pimavanserin [40 mg daily] or placebo for 6 weeks, symptoms improved more with pimavanserin and adverse event rates were similar; "laboratory assessments were unremarkable and no safety signals were reported").

Fox SH. Pimavanserin as treatment for Parkinson's disease psychosis. Lancet 2014; 383 (9916): 494-6. PubMed PMID: 24183566.

(Editorial in response to Cummings [2014]).

Markham A. Pimavanserin: first global approval. Drugs 2016; 76: 1053-7. PubMed PMID: 27262680.

(Review of the development of pimavanserin, its mechanism of action, pharmacodynamics, inverse agonism of 5HT-2A, clinical efficacy, and safety; no mention of ALT elevations or hepatotoxicity).

Pimavanserin (Nuplazid) for Parkinson's disease psychosis. Med Lett Drugs Ther 2016; 58 (1496): 74-5. PubMed PMID: 27249096.

(Concise review of the mechanism of action, efficacy, safety and costs of pimavanserin shortly after its approval in Parkinson psychosis in the US; no mention of ALT elevations or hepatotoxicity).

Drugs for psychotic disorders. Med Lett Drugs Ther 2016; 58 (1510): 160-4. PubMed PMID: 27960194.

(Concise review of drugs for psychiatric disorders; mentions side effects of ALT elevations and hepatotoxicity for olanzapine only).