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Brexpiprazole

Updated: October 2, 2017.

OVERVIEW

Introduction

Brexpiprazole is an atypical antipsychotic used in the treatment of schizophrenia and major depressive disorders. Brexpiprazole has been associated with a low rate of serum aminotransferase elevations during therapy, but has not been linked to instances of clinically apparent acute liver injury.

Background

Brexpiprazole (brex pip' ra zole) is a second generation (atypical) antipsychotic agent that is similar in structure and mechanism of action to aripiprazole. These two agents are believed to act as partial antagonists of dopamine type 2 (D2) and serotonin (5-HT)-2A receptors and partial agonists of serotonin 5-HT-1A receptors. In several randomized controlled trials, therapy with brexpiprazole was associated with a lessening of symptoms of schizophrenia and improvement in depression symptom scores in comparison to placebo treatment. It was approved for use in the United States in 2015 as therapy for schizophrenia and as adjunctive therapy with antidepressants for major depressive disorders. Brexpiprazole is available as tablets of 0.25, 0.5, 1, 2, 3 and 4 mg under the brand name Rexulti. The standard maintenance dose for schizophrenia in adults is 2 to 4 mg daily. The dose for as an adjunctive therapy for major depression is usually less. Common side effects include restlessness (akathisia), sedation, tremor, dizziness, blurred vision, fatigue, headaches, nausea and weight gain. Rare, but potential severe adverse reactions (mentioned in most antipsychotic product labels) include tardive dyskinesia, major neurologic events, neuroleptic malignant syndrome, orthostatic hypotension, seizures and neutropenia.

Hepatotoxicity

Liver test abnormalities were reported to occur in ~1% of patients on long term therapy with brexpiprazole, but similar rates occurred in patients on placebo or with comparator agents. There have been no published reports of clinically apparent acute liver injury due to brexpiprazole and only rare instances have been reported with the much more frequently used aripiprazole. Thus, liver injury due to brexpiprazole must be rare, if it occurs at all.

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

Mechanism of Injury

Brexpiprazole is extensively metabolized by the liver via the P450 system, largely by CYP 3A4 and 2D6, and liver injury from its use might be caused by a toxic or immunogenic intermediate metabolite. Brexpiprazole, like aripiprazole, is susceptible to drug-drug interactions, strong inducers of CYP 3A4 (such as rifampin) resulting in lower drug levels and strong inhibitors (such as ketoconazole) resulting in higher levels.

Outcome and Management

The serum aminotransferase elevations that occur with brexpiprazole therapy are usually self-limited and often do not require dose modification or discontinuation. No instances of acute liver failure, chronic hepatitis or vanishing bile duct syndrome have been attributed to brexpiprazole. Cross sensitivity to liver related or other hypersensitivity reactions between brexipiprazole and other antipsychotic agents have not been demonstrated, but might be expected to occur with aripiprazole.

Drug Class: Antipsychotic Agents, Atypicals

PRODUCT INFORMATION

REPRESENTATIVE TRADE NAMES

Brexpiprazole – Rexulti®

DRUG CLASS

Antipsychotic Agents

COMPLETE LABELING

Product labeling at DailyMed, National Library of Medicine, NIH

CHEMICAL FORMULAS AND STRUCTURES

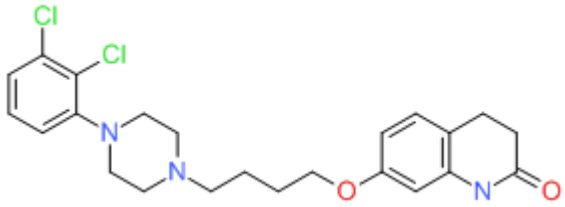
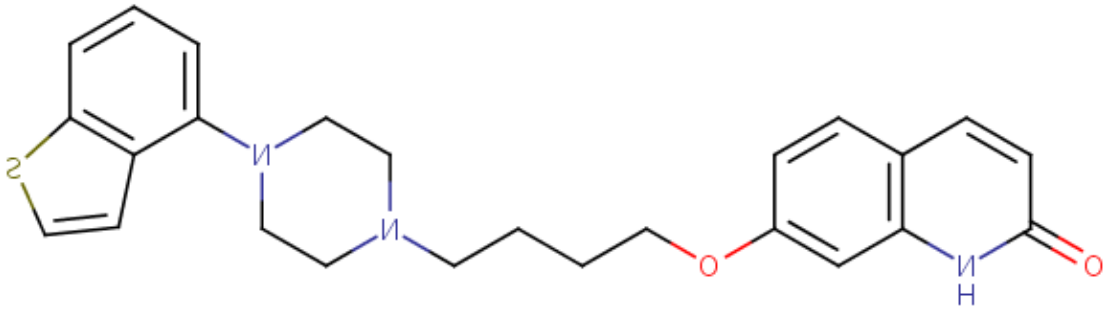
DRUG	CAS REGISTRY NUMBER	MOLECULAR FORMULA	STRUCTURE
Aripiprazole	129722-12-9	C23-H27-Cl2-N3-O2	

Table continued from previous page.

DRUG	CAS REGISTRY NUMBER	MOLECULAR FORMULA	STRUCTURE
Brexpiprazole	913611-97-9	C25-H27-N3-O2-S	

ANNOTATED BIBLIOGRAPHY

References updated: 02 October 2017

Kaplowitz 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).

Leucht S, Corves C, Arbter D, Engel RR, Li C, Davis JM. Second-generation versus first-generation antipsychotic drugs for schizophrenia: a meta-analysis. Lancet 2009; 373: 31-41.

(Systematic review of efficacy and safety of newer antipsychotic agents including aripiprazole, but not brexpiprazole; no discussion of liver related side effects or ALT elevations).

Reuben A, Koch DG, Lee WM; Acute Liver Failure Study Group. Drug-induced acute liver failure: results of a U.S. multicenter, prospective study. Hepatology 2010; 52: 2065-76. PubMed PMID: 20949552.

(Among 1198 patients with acute liver failure enrolled in a US prospective study between 1998 and 2007, 133 were attributed to drug induced liver injury including four due to psychotropic agents; one each for quetiapine, nefazodone, fluoxetine and venlafaxine, but none for aripiprazole or brexpiprazole or other second generation antipsychotic agent).

Brexpiprazole (Rexulti) for schizophrenia and depression. Med Lett Drugs Ther 2015; 57 (1475): 116-8. PubMed PMID: 26262883.

(Brief review of efficacy and safety of brexpiprazole shortly after its approval in the US; frequent side effects are anxiety, headache, nausea, constipation, insomnia, dizziness and somnolence; has little effect on weight; no mention of hepatotoxicity or effect on ALT levels).

Kane JM, Skuban A, Ouyang J, Hobart M, Pfister S, McQuade RD, Nyilas M, et al. A multicenter, randomized, double-blind, controlled phase 3 trial of fixed-dose brexpiprazole for the treatment of adults with acute schizophrenia. Schizophr Res 2015; 164: 127-35. PubMed PMID: 25682550.

(Among 674 adults with acute schizophrenia treated with brexpiprazole [1, 2 or 4 mg daily] or placebo for 6 weeks, improvements in symptom scores were greater with brexpiprazole than placebo and side effects included weight gain [1.5 vs 0.35 kg]; no mention of ALT elevations or hepatotoxicity).

Correll CU, Skuban A, Ouyang J, Hobart M, Pfister S, McQuade RD, Nyilas M, et al. Efficacy and safety of brexpiprazole for the treatment of acute schizophrenia: a 6-week randomized, double-blind, placebo-controlled trial. Am J Psychiatry 2015; 172: 870-80. PubMed PMID: 25882325.

(Among 636 adults with an acute exacerbation of schizophrenia treated with 1 or 3 doses of brexpiprazole [0.25, 2 or 4 mg daily] or placebo for 6 weeks, symptom scores improved more with brexpiprazole, and adverse events included restlessness [akathisia] and weight gain, while discontinuations due to liver test elevations occurred equally with drug and placebo [1.1%]).

Citrome L. Brexpiprazole: a new dopamine D2 receptor partial agonist for the treatment of schizophrenia and major depressive disorder. Drugs Today (Barc) 2015; 51: 397-414. PubMed PMID: 26261843.

(Systematic review of results of 4 phase III trials and subsequent extension studies of brexpiprazole in schizophrenia and major depressive disorders reported overall improvements in symptom scores with treatment, and an increase in adverse events in comparison to placebo of restlessness [5-10%], weight gain [5-30%]; no mention of ALT elevations or hepatotoxicity).

Thase ME, Youakim JM, Skuban A, Hobart M, Augustine C, Zhang P, McQuade RD, et al. Efficacy and safety of adjunctive brexpiprazole 2 mg in major depressive disorder: a phase 3, randomized, placebo-controlled study in patients with inadequate response to antidepressants. J Clin Psychiatry 2015; 76: 1224-31. PubMed PMID: 26301701.

(Among 353 patients with major depressive disorders on conventional antidepressants who were treated with brexpiprazole [2 mg daily] or placebo for 6 weeks, depression scores improved more with brexpiprazole and adverse events included restlessness [7%] and weight gain [8%]; no mention of ALT elevations or hepatotoxicity).