REXULTI® brexpiprazole 2mg tablets

Moments Matter

Agitation Associated with Dementia Due to Alzheimer's Disease and How REXULTI is Thought to Work

The mechanism of action of REXULTI is unknown

- The activity of these compounds is based on *in vitro* data. The clinical significance of the *in vitro* data is unknown[1]

REXULTI is the first and only FDA-approved treatment of agitation associated with dementia due to Alzheimer's disease.

Limitations of Use: REXULTI is not indicated as an as needed ("prn") treatment for agitation associated with dementia due to Alzheimer's disease.

D, dopamine; N, norepinephrine; S, serotonin (5-HT).

INDICATION

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Contraindication

In patients with known hypersensitivity to brexpiprazole or any of its components. Reactions have included: rash, facial swelling, urticaria, and anaphylaxis.

IMPORTANT SAFETY INFORMATION

WARNING: INCREASED MORTALITY IN ELDERLY PATIENTS WITH DEMENTIA-RELATED PSYCHOSIS

Elderly patients with dementia-related psychosis treated with antipsychotic drugs are at increased risk of death. REXULTI is not approved for the treatment of patients with dementia-related psychosis without agitation associated with dementia due to Alzheimer's disease.

Please see FULL PRESCRIBING INFORMATION, including BOXED WARNING.

Dysfunction in neurotransmitter systems is associated with agitated behaviors in dementia due to Alzheimer's disease[2]

Imbalances in neurotransmitters norepinephrine, serotonin, and dopamine (NSD) may contribute to a separate condition called agitation associated with dementia due to Alzheimer's disease

Disrupted brain activity and dysfunctional NSD systems are believed to lead to agitated behaviors[2,3]:

NOREPINEPHRINE HYPERACTIVITY MAY CAUSE[2,4]

- Diminished executive control
- Increased emotional drive

SEROTONIN DEFICIT MAY CAUSE[2]

- Increased aggression and impulsivity

DOPAMINE DYSREGULATION MAY CAUSE[2]

- Serotonin deficits may alter dopamine release and may lead to agitation and aggressive behaviors

Agitation may present in patients with Alzheimer's dementia[5]

Agitation includes both aggressive and non-aggressive behaviors

The Cohen-Mansfield Agitation Inventory (CMAI) lists 29 behaviors across subscales. The CMAI is a clinically validated scale grouped into 3 subscales and determined by clinicians based on caregiver input.

VERBALLY AGITATED BEHAVIORS[6,7]

- Complaining
- Constant unwarranted request for attention or help
- Repetitive sentences or questions
- Negativism

PHYSICALLY NON-AGGRESSIVE BEHAVIORS[6,7]

- Pacing, aimless wandering
- General restlessness
- Inappropriate dress or disrobing
- Trying to get to a different place
- Handling things inappropriately
- Performing repetitive mannerisms

AGGRESSIVE BEHAVIORS[6,7]

- Screaming
- Biting
- Hitting
- Kicking
- Hurting self or others
- Cursing or verbal aggression
- Pushing
- Scratching
- Throwing things
- Spitting
- Tearing things/ destroying property
- Grabbing onto people

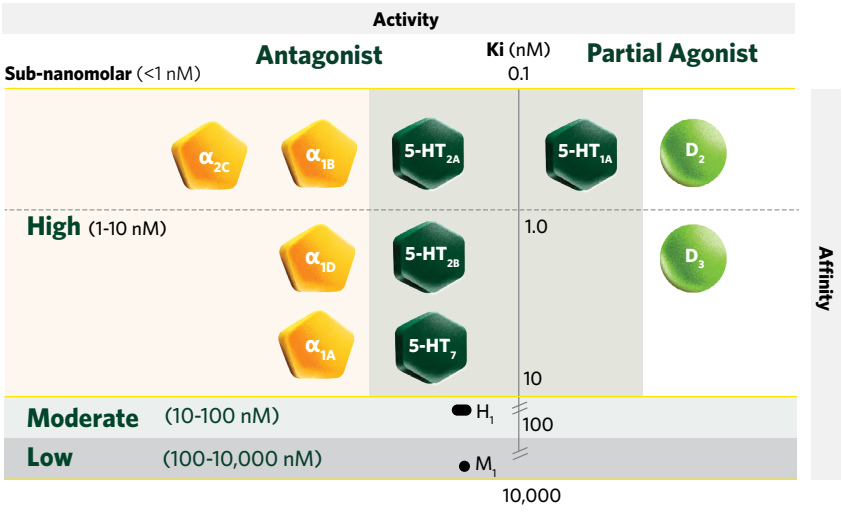
Additional behaviors that often have low rates of occurrence include making physical sexual advances, intentional falling, eating/drinking inappropriate substances, hiding things, hoarding things, making verbal sexual advances, and strange noises (weird laughter or crying).[6,7]

REXULTI® (brexpiprazole) interacts with 3 key neurotransmitter systems[8,9]

REXULTI has high binding affinity[a] to norepinephrine, serotonin, and dopamine[8,9]:

Pharmacodynamic profile—binding affinities across neurotransmitter systems

RECEPTOR BINDING AFFINITY	
Norepinephrine	
α_{1B}-adrenergic	0.17 nM
α_{2C}-adrenergic	0.59 nM
α_{1D}-adrenergic	2.60 nM
α_{1A}-adrenergic	3.80 nM
Serotonin	
5-HT$_{1A}$	0.12 nM
5-HT$_{2A}$	0.47 nM
5-HT$_{2B}$	1.9 nM
5-HT$_{7}$	3.7 nM
Dopamine	
D_2	0.30 nM
D_3	1.1 nM
Histamine	
H_1	19 nM
Muscarinic	
M_1	10,000 nM



Norepinephrine, serotonin, and dopamine modulate each other's activity[9]

The mechanism of action of REXULTI is unknown. However, the efficacy of REXULTI may be mediated through a combination of partial agonist activity at serotonin 5-HT$_{1A}$ and dopamine D_2 receptors, and antagonist activity at serotonin 5-HT$_{2A}$ receptors.

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[a]The binding affinity of brexpiprazole was determined *in vitro* in cells overexpressing human receptors and is expressed as an nM concentration with lower value representing higher affinity. High binding affinity Ki <1 nM.[7]

D, dopamine; H, histamine; Ki, binding affinity; M, muscarinic; N, norepinephrine; nM, nanomolar; S, serotonin (5-HT).

IMPORTANT SAFETY INFORMATION (CONT'D)

Contraindication: In patients with known hypersensitivity to brexpiprazole or any of its components. Reactions have included: rash, facial swelling, urticaria, and anaphylaxis.

Cerebrovascular Adverse Events, Including Stroke: In clinical trials, elderly patients with dementia randomized to risperidone, aripiprazole, and olanzapine had a higher incidence of stroke and transient ischemic attack, including fatal stroke. REXULTI is not approved for the treatment of patients with dementia-related psychosis without agitation associated with dementia due to Alzheimer's disease.

IMPORTANT SAFETY INFORMATION for REXULTI® (brexpiprazole)

IMPORTANT SAFETY INFORMATION (CONT'D)

Neuroleptic Malignant Syndrome (NMS): NMS is a potentially fatal symptom complex reported in association with administration of antipsychotic drugs, including REXULTI. Clinical signs of NMS are hyperpyrexia, muscle rigidity, altered mental status, and evidence of autonomic instability (irregular pulse or blood pressure, tachycardia, diaphoresis, and cardiac dysrhythmia). Additional signs may include elevated creatinine phosphokinase, myoglobinuria (rhabdomyolysis), and acute renal failure. Manage NMS with immediate discontinuation of REXULTI, intensive symptomatic treatment, and monitoring.

Tardive Dyskinesia (TD): Risk of TD, and the potential to become irreversible, appear to increase with duration of treatment and total cumulative dose of antipsychotic drugs. TD can develop after relatively brief treatment periods, at low doses, or after discontinuation of treatment. For chronic treatment, use the lowest dose and shortest duration of REXULTI needed to produce a clinical response. If signs and symptoms of TD appear, drug discontinuation should be considered.

Metabolic Changes: Atypical antipsychotic drugs, including REXULTI, have caused metabolic changes including:

- **Hyperglycemia/Diabetes Mellitus:** Hyperglycemia and diabetes mellitus, in some cases extreme and associated with diabetic ketoacidosis, hyperosmolar coma, or death, have been reported in patients treated with atypical antipsychotics. Assess fasting plasma glucose before or soon after initiation of antipsychotic medication and monitor periodically during long-term treatment.
- **Dyslipidemia:** Atypical antipsychotics cause adverse alterations in lipids. Before or soon after initiation of antipsychotic medication, obtain a fasting lipid profile at baseline and monitor periodically during treatment.
- **Weight Gain:** Weight gain has been observed in patients treated with REXULTI. Monitor weight at baseline and frequently thereafter.

Pathological Gambling and Other Compulsive Behaviors: Intense urges, particularly for gambling, and the inability to control these urges have been reported while taking REXULTI. Other compulsive urges have been reported less frequently. Prescribers should ask patients or their caregivers about the development of new or intense compulsive urges. Consider dose reduction or stopping REXULTI if such urges develop.

Leukopenia, Neutropenia, and Agranulocytosis: Leukopenia and neutropenia have been reported with antipsychotics. Agranulocytosis (including fatal cases) has been reported with other agents in this class. Monitor complete blood count in patients with pre-existing low white blood cell count (WBC)/absolute neutrophil count or history of drug-induced leukopenia/neutropenia. Discontinue REXULTI at the first sign of a clinically significant decline in WBC and in patients with severe neutropenia.

Orthostatic Hypotension and Syncope: Atypical antipsychotics cause orthostatic hypotension and syncope. Generally, the risk is greatest during initial dose titration and when increasing the dose. Monitor in patients vulnerable to hypotension and those with cardiovascular and cerebrovascular diseases.

Falls: Antipsychotics may cause somnolence, postural hypotension, and motor and sensory instability, which may lead to falls causing fractures or other injuries. For patients with diseases, conditions, or medications that could exacerbate these effects, complete fall risk assessments when initiating treatment and recurrently during treatment.

Seizures: REXULTI may cause seizures and should be used with caution in patients with a history of seizures or with conditions that lower the seizure threshold.

Body Temperature Dysregulation: Use REXULTI with caution in patients who may experience conditions that increase body temperature (eg, strenuous exercise, extreme heat, dehydration, or concomitant use with anticholinergics).

Dysphagia: Esophageal dysmotility and aspiration have been associated with antipsychotics, including REXULTI, and should be used with caution in patients at risk for aspiration.

Potential for Cognitive and Motor Impairment: REXULTI may cause somnolence and has the potential to impair judgment, thinking, or motor skills. Patients should be cautioned about operating hazardous machinery, including operating motor vehicles, until they are reasonably certain REXULTI does not affect them adversely.

Concomitant Medication: Dosage adjustments are recommended in patients who are known cytochrome P450 (CYP) 2D6 poor metabolizers and in patients taking concomitant CYP3A4 inhibitors or CYP2D6 inhibitors or strong CYP3A4 inducers.

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The first and only FDA-approved treatment of agitation associated with dementia due to Alzheimer's disease

Agitation associated with dementia due to Alzheimer's disease may be caused by dysfunction in 3 neurotransmitter systems—NSD[2]

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The mechanism of action of REXULTI is unknown. The activity of these compounds is based on *in vitro* data. The clinical significance of the *in vitro* data is unknown.[1]

Scan to see the efficacy data from the clinical trials

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References: 1. Ross EM, Kenakin TP. Pharmacodynamics: mechanisms of drug action and the relationship between drug concentration and effect. In: Hardman JG, Limbird LE, eds. *Goodman & Gilman's The Pharmacological Basis of Therapeutics*. 10th ed. New York, NY: McGraw-Hill; 2001:31-43. **2.** Cummings JL, Brubaker M, Selzler KJ, Gonzalez ST, Patel M, Stahl SM. An overview of the pathophysiology of agitation in Alzheimer's dementia with a focus on neurotransmitters and circuits. *CNS Spectr*. 2024;29(5):316-325. **3.** Azizi SA. Monoamines: dopamine, norepinephrine, and serotonin, beyond modulation, "switches" that alter the state of target networks. *The Neuroscientist*. 2022;28:121-143. **4.** Arnsten AF, Raskind MA, Taylor FB, et al. The effects of stress exposure on prefrontal cortex: translating basic research into successful treatments for post-traumatic stress disorder. *Neurobiol Stress*. 2015;1:89-99. **5.** Halpern R, Seare J, Tong J, et al. Using electronic health records to estimate the prevalence of agitation in Alzheimer disease/dementia. *Int J Geriatr Psychiatry*. 2019;34:420-431. **6.** Cohen-Mansfield J. Agitated behavior in persons with dementia: the relationship between type of behavior, its frequency, and its disruptiveness. *J Psychiatr Res*. 2008;43:64-69. **7.** Rabinowitz J, Davidson M, De Deyn PP, et al. Factor analysis of the Cohen-Mansfield Agitation Inventory in three large samples of nursing home patients with dementia and behavioral disturbance. *Am J Geriatr Psychiatry*. 2005;13(11):991-998. **8.** Maeda K, Sugino H, Akazawa H, et al. Brexpiprazole I: in vitro and in vivo characterization of a novel serotonin-dopamine activity modulator. *J Pharmacol Exp Ther*. 2014;350:589-604. **9.** El Mansari M, Guiard BP, Chernoloz O, et al. Relevance of norepinephrine-dopamine interactions in the treatment of major depressive disorder. *CNS Neurosci Ther*. 2010;16:e1-e17.

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IMPORTANT SAFETY INFORMATION (CONT'D)

Most commonly observed adverse reactions: In clinical trials of adults, the most common adverse reactions were:

- **Agitation associated with dementia due to Alzheimer's disease** (≥4% incidence and at least twice the rate of placebo for REXULTI vs placebo): nasopharyngitis and dizziness.

Dystonia: Symptoms of dystonia may occur in susceptible individuals during the first days of treatment and at low doses.

Pregnancy: Adequate and well-controlled studies to assess the risks of REXULTI during pregnancy have not been conducted. REXULTI should be used during pregnancy only if the benefit justifies the risk to the fetus.

Lactation: It is not known if REXULTI is excreted in human breast milk. A decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

To report SUSPECTED ADVERSE REACTIONS, contact Otsuka America Pharmaceutical, Inc. at 1-800-438-9927 or FDA at 1-800-FDA-1088 (www.fda.gov/medwatch).

Otsuka Lundbeck

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