The First and Only FDA-Approved Treatment of Agitation Associated With Dementia due to Alzheimer's Disease

REXULTI® brexpiprazole 2mg tablets

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

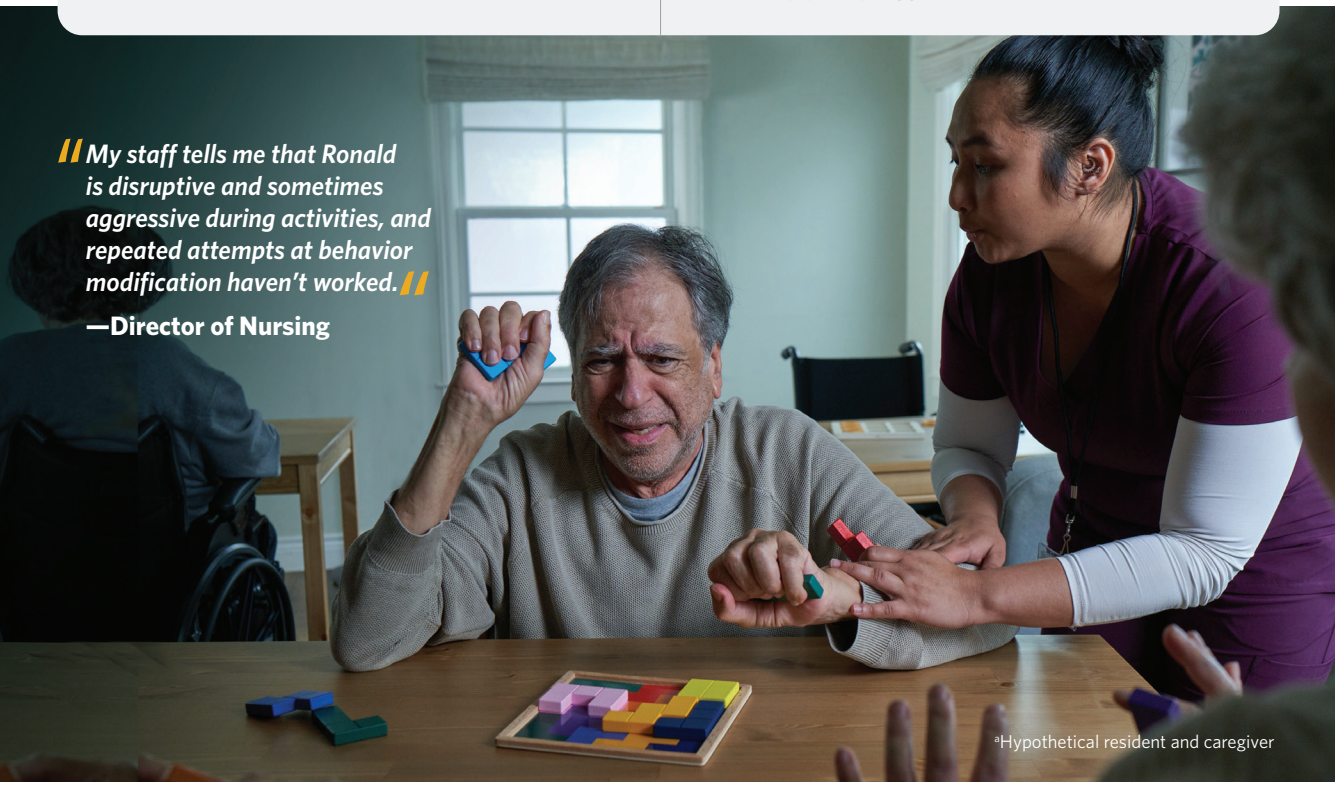
Meet Ronald, 82, a long-term resident in a nursing home facility struggling with agitation associated with dementia due to Alzheimer's disease[a]

CURRENT PRESENTATION

- Alzheimer's dementia (diagnosed 5 years ago); receiving cholinesterase inhibitor and NMDA antagonist
- Previous exam showed no history of UTI

CAREGIVER REPORTED RECENT AGITATION SYMPTOMS

- Constant requests for attention **(verbally agitated)**
- Repetitive mannerisms **(physically non-aggressive)**
- Screaming/yelling **(aggressive)**



NMDA, N-methyl-D-aspartate; UTI, urinary tract infection.

INDICATION

REXULTI is indicated for 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.

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 IMPORTANT SAFETY INFORMATION.

Agitation associated with dementia due to Alzheimer's disease is highly prevalent and identified by an array of symptoms[1]

Prevalence data

~1 in 2 people living with dementia due to Alzheimer's disease suffer from agitation[1]

Agitated behaviors as defined by CMAI[2]

The Cohen-Mansfield Agitation Inventory (CMAI) is a clinically validated scale measuring the frequency of 29 agitated behaviors.

- Grouped into 3 subscales
- Scored by clinicians based on caregiver input

Verbally Agitated

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

Physically Non-aggressive

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

Aggressive

- 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 assessed by CMAI total score 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).[2,3]

Contraindication

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

Please see IMPORTANT SAFETY INFORMATION.

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REXULTI® (brexpiprazole) pivotal studies

Two Phase III, 12-week, randomized, double-blind, placebo-controlled fixed-dose studies evaluated frequency (CMAI total score) of agitation symptoms in patients with dementia due to Alzheimer's disease[4,5]

Study 6: Evaluated REXULTI 1 mg/day (n=134) or 2 mg/day (n=138), or placebo (n=131). Titration began at 0.25 mg/day for Days 1–3, then increased to 0.5 mg/day at Days 4–14, 1 mg/day at Days 15–28, and maintained at either 1 or 2 mg/day from Day 29 onward depending on assigned dose.[4]

Study 7: Evaluated REXULTI 2 mg/day or 3 mg/day (n=228), or placebo (n=117). Titration began at 0.5 mg/day for Days 1–7, then increased to 1 mg/day at Days 8–14, 2 mg/day at Days 15–28, and either maintained at 2 mg/day or increased to 3 mg/day from Day 29 onward.[5]

Key Inclusion Criteria[4,5]

- Probable Alzheimer's disease diagnosis per NINCDS-ADRDA Criteria
- Agitation as determined by NPI-NH A/A score ≥4
- MMSE: ≥5 and ≤22
- Exhibited sufficient agitation behaviors at time of entry to warrant use of pharmacotherapy, after excluding other factors

Additional inclusion criteria in Study 7

- Met criteria for agitation as defined by the IPA provisional definition
- Aggressive agitation at baseline (≥1 CMAI Factor 1 behavior)

Concomitant medications

- Cholinesterase inhibitors, memantine, and other cognitive enhancers, as well as antidepressants (like SSRI or SNRI), were permitted for the duration of the studies

EFFICACY ASSESSMENTS

PRIMARY ENDPOINT
Primary endpoint was change in agitation symptom frequency (CMAI total score) from baseline at Week 12 in both studies.

Baseline Characteristics[4,5]

		Age (mean in years)	Gender (% female)	CMAI total score (mean)	MMSE score (% of patients) Mild (>18)	Moderate (13-18)	Severe (≤12)
Study 6	**REXULTI 1 mg/day** (n=137)	**74**	**57%**	**70.7**	**5.1%**	**55.5%**	**39.4%**
	REXULTI 2 mg/day (n=140)	**74**	**56%**	**71.0**	**7.9%**	**62.1%**	**30.0%**
	Placebo (n=136)	74	52%	72.0	14.0%	54.4%	31.6%
Study 7	**REXULTI 2 and 3 mg/day** (n=228)	**75**	**59%**	**80.4**	**23.2%**	**55.7%**	**21.1%**
	Placebo (n=117)	73	51%	79.4	23.9%	56.4%	19.7%

CMAI, Cohen-Mansfield Agitation Inventory; IPA, International Psychogeriatric Association; MMSE, Mini-Mental State Examination; NINCDS-ADRDA, National Institute of Neurological and Communicative Diseases and Stroke/Alzheimer's Disease and Related Disorders Association; NPI-NH A/A, Neuropsychiatric Inventory – Nursing Home version, Agitation/aggression domain; SNRI, serotonin and norepinephrine reuptake inhibitor; SSRI, selective serotonin reuptake inhibitor.

Important Warning and Precaution for 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.

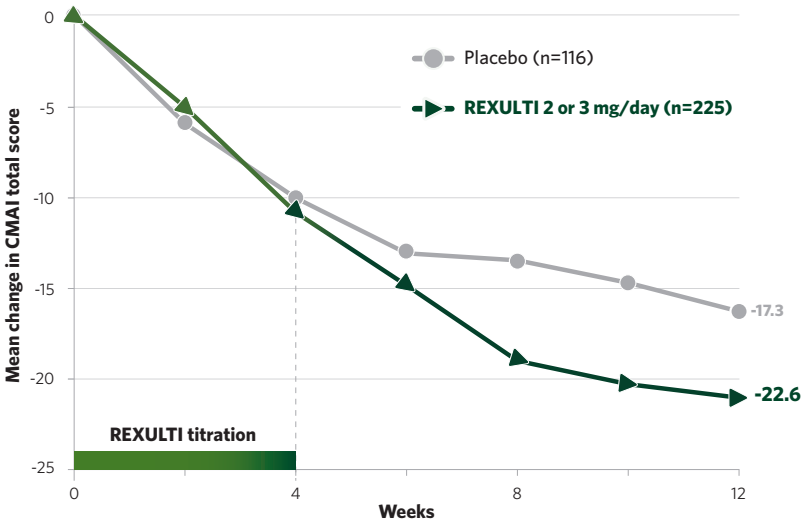
Please see IMPORTANT SAFETY INFORMATION.

REXULTI® brexpiprazole 2mg tablets

REXULTI® (brexpiprazole): Proven to reduce the FREQUENCY of agitation symptoms

Study 6 and 7: REXULTI 2 or 3 mg/day arm was statistically significantly superior to placebo in mean change from baseline in the CMAI total score at week 12

Study 7 Results



STATISTICALLY SIGNIFICANTLY SUPERIOR to placebo

Study 6 and 7 design and efficacy summary

REXULTI was studied in 2 Phase III, 12-week, randomized, double-blind, placebo-controlled, fixed-dose pivotal trials evaluating frequency of agitation symptoms and safety profile in patients with dementia due to Alzheimer's disease. After a screening phase of 6 weeks, patients titrated for 2 to 4 weeks to their assigned dose.[4,5]

Primary endpoint was change in agitation symptom frequency (CMAI total score) from baseline at Week 12 in both studies.

Study 6 and 7 Results[4,5]:

	Treatment Group	Mean Baseline Score	Mean Change	Treatment Difference	*P*-Value
Study 6	**REXULTI 1 mg/day** (n=134)	**70.5**	**-17.6**	**0.2**	*P*=0.90[4]
	REXULTI 2 mg/day[a] (n=138)	**71.0**	**-21.6**	**-3.8**	***P*=0.040**[4]
	Placebo (n=131)	72.2	-17.8	—	—
Study 7	**REXULTI 2 or 3 mg/day**[a] (n=225)	**80.6**	**-22.6**	**-5.3**	***P*=0.003**[5]
	Placebo (n=116)	79.2	-17.3	—	—

[a]Dosages statistically significantly superior to placebo.
CMAI, Cohen-Mansfield Agitation Inventory.

Important Warning and Precaution for 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.

Please see IMPORTANT SAFETY INFORMATION.

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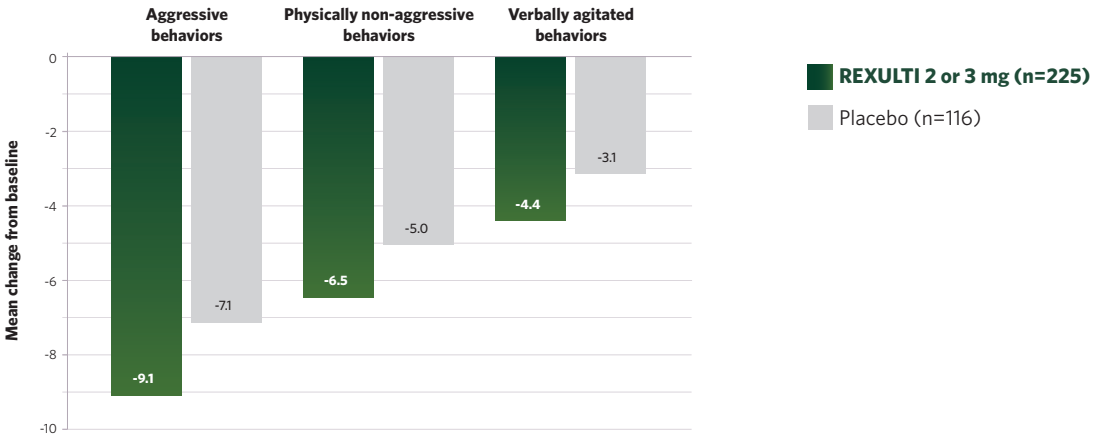
REXULTI® (brexpiprazole): Change in frequency across subscales of agitation symptoms

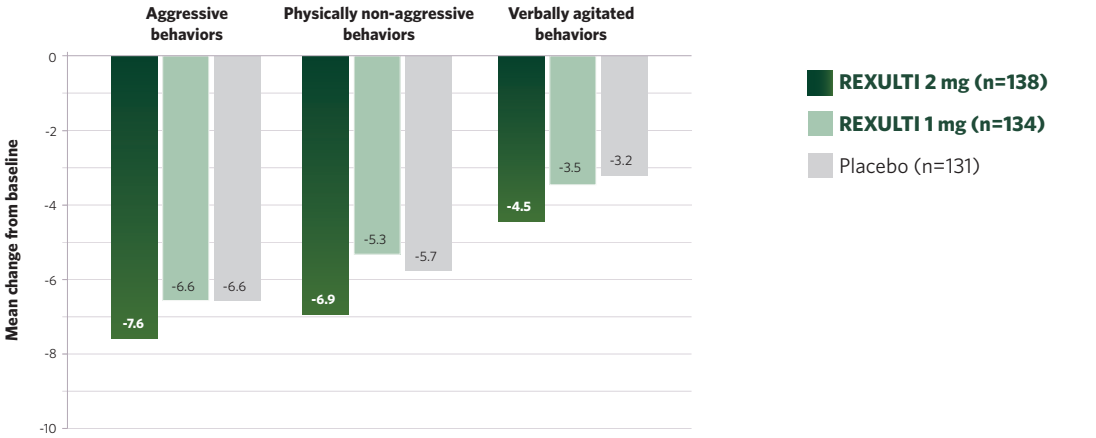
REXULTI was approved for the treatment of agitation associated with dementia due to Alzheimer's disease based on the primary endpoint, change in CMAI total score from baseline at Week 12.

A secondary endpoint was the change from baseline at Week 12 in CMAI subscale scores.

Study 7: Mean change in CMAI subscales[5,a]



Study 6: Mean change in CMAI subscales[6,a]



[a]In a supplementary analysis to examine the magnitude and direction of CMAI subscale response, Factor 1 (aggressive behavior), Factor 2 (physically non-aggressive behavior), and Factor 3 (verbal agitation) scores trended in the same direction with no single factor overly influencing the CMAI total score.

CMAI, Cohen-Mansfield Agitation Inventory.

Important Warning and Precaution for 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.

Please see IMPORTANT SAFETY INFORMATION.

REXULTI® brexpiprazole 2mg tablets

REXULTI® (brexpiprazole): Demonstrated safety profile

Adverse reactions in ≥2% of patients treated with REXULTI and greater than placebo from two 12-week pivotal trials across all doses

	REXULTI 1 mg/day[a] (n=137)	REXULTI 2 mg/day (n=213)	REXULTI 3 mg/day (n=153)	ALL REXULTI (n=503)	Placebo (n=251)
Infections and infestations					
Nasopharyngitis	**4%**	**2%**	**3%**	**3%**	**2%**
Urinary Tract Infection	**2%**	**3%**	**3%**	**3%**	**1%**
Nervous system disorders					
Dizziness[b]	**1%**	**5%**	**3%**	**3%**	**2%**
Headache	**9%**	**9%**	**7%**	**8%**	**8%**
Somnolence[c]	**2%**	**3%**	**4%**	**3%**	**1%**
Psychiatric disorder					
Insomnia[d]	**5%**	**5%**	**2%**	**4%**	**3%**

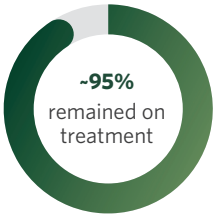
[a]1 mg once a day REXULTI dosage is not a recommended dosage for the treatment of agitation associated with dementia due to Alzheimer's disease.
[b]Dizziness and vertigo are grouped to dizziness.
[c]Sedation and somnolence are grouped to somnolence.
[d]Initial insomnia and insomnia are grouped to insomnia.

Most common adverse reactions occurring in ≥4% of patients and at least twice the rate of placebo were nasopharyngitis and dizziness.

At a dose 4 times the MRHD for the treatment of agitation associated with dementia due to Alzheimer's disease, REXULTI does not prolong the **QTc interval** to any clinically relevant extent.

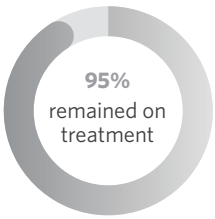
REXULTI vs placebo: Similar discontinuation rates due to adverse reactions from two 12-week pivotal trials across all doses

REXULTI
5.6%
discontinued due to adverse reactions (n=28/503)



VS

PLACEBO
4.8%
discontinued due to adverse reactions (n=12/251)



Approximately 95% of patients remained on treatment without discontinuation, whether treated with REXULTI or placebo

MRHD, Maximum Recommended Human Dose.

Important Warning and Precaution for 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.

Please see IMPORTANT SAFETY INFORMATION.

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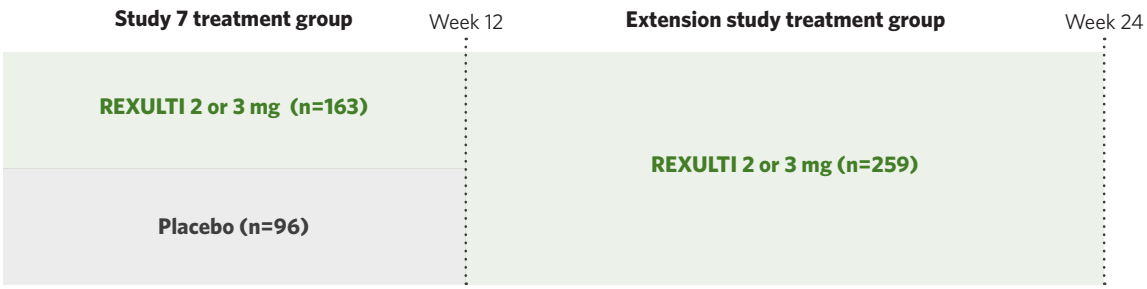
REXULTI® (brexpiprazole): Long-term extension study design[7]

Study design



- **All patients were initiated on REXULTI at Week 12; there was no placebo treatment arm during the extension study period**

Baseline characteristics*

	Extension study REXULTI 2 or 3 mg		
Demographic characteristics	**Total** (N=259)	**Placebo to REXULTI** (n=96)	**Continued REXULTI** (n=163)
Age, mean in years (SD)	**74.3 (7.6)**	**73.4 (6.8)**	**74.8 (7.9)**
Gender, % female	**56.0**	**47.9**	**60.7**
BMI, mean kg/m^2 (SD)	**26.6 (4.7)**	**26.9 (4.8)**	**26.4 (4.6)**
Race, % Caucasian	**95.8**	**97.9**	**94.5**
Clinical characteristics			
CMAI total score, mean (SD)	**59.6 (17.8)**	**63.3 (18.3)**	**57.3 (17.2)**
MMSE score, mean (SD)	**16.7 (4.5)**	**16.4 (4.3)**	**16.9 (4.7)**

*Baseline is the Week 12 visit of the placebo-controlled trial.

BMI, body mass index; CMAI, Cohen-Mansfield Agitation Inventory; MMSE, Mini-Mental State Examination; SD, standard deviation.

Important Warning and Precaution for 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.

Please see IMPORTANT SAFETY INFORMATION.

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REXULTI® (brexpiprazole): Extension study primary objective assessed the long-term safety and tolerability[7]

Study Details[7]

This extension trial studied REXULTI 2 or 3 mg in a Phase III, 12-week, multicenter, non-pivotal, single-arm trial

- Patients previously randomized to REXULTI continued their previous dose
- Patients previously randomized to placebo were initiated on REXULTI
- Dosing was concealed to maintain blinding of the placebo-controlled trial; dose adjustments were permitted

Study Limitations[7-9]

- The extension study did not include a control group and was a nonrandomized, single-group assignment
- Sample size was not based on statistical power considerations
- The trial population was derived from eligible patients who rolled over from Study 7

Adverse reactions in ≥2% of patients treated with REXULTI[7]

	Total (N=259)	**Placebo to REXULTI** (n=96)	**Continued REXULTI** (n=163)
Infections and infestations			
Nasopharyngitis	**2%**	**5%**	**0%**
Nervous system disorders			
Dizziness	**2%**	**1%**	**3%**
Headache	**4%**	**3%**	**4%**
Somnolence	**2%**	**1%**	**3%**
Psychiatric disorder			
Agitation	**2%**	**3%**	**1%**
EPS-related adverse reactions			
Any EPS-related adverse reaction, excluding akathisia	**1%**	**1%**	**1%**
Akathisia	**0%**	**0%**	**0%**
Other			
Hypotension	**1%**	**2%**	**0%**
Falls	**2%**	**1%**	**3%**

The incidence of reported EPS-related adverse reactions, excluding akathisia, from the 12-week extension study across all doses was 1% for patients being treated with REXULTI.

EPS, extrapyramidal symptoms.

Important Warning and Precaution for 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).

Please see IMPORTANT SAFETY INFORMATION.

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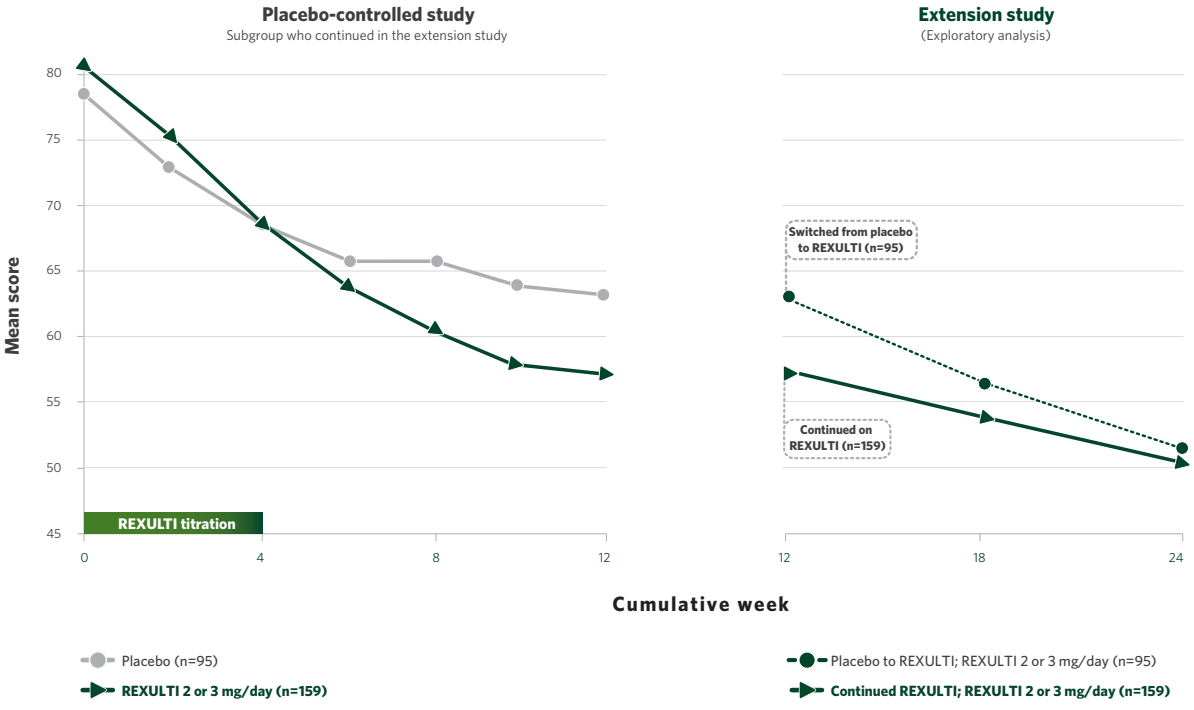
REXULTI® (brexpiprazole): Exploratory analysis of CMAI total score[7]

Efficacy of REXULTI in the extension study was an exploratory endpoint



CMAI, Cohen-Mansfield Agitation Inventory.

- An exploratory analysis examined the change from Week 12 to Week 24 in CMAI total score

Important Warning and Precaution for 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.

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.

Please see IMPORTANT SAFETY INFORMATION.

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REXULTI® (brexpiprazole): Low starting dose and 2- to 4-week titration schedule

Once-daily dosing

Pills not actual size.

- After at least 14 days on 2 mg/day (target dose), dosage can be increased to 3 mg/day (maximum dose), based on clinical response and tolerability
- With or without food

Dose adjustments for REXULTI

- Dose adjustments may be needed in patients with hepatic or renal impairment
- Administer half the dose of REXULTI when taken with strong CYP3A4 inhibitors or in patients who are known CYP2D6 poor metabolizers
- Administer a quarter of the dose with the concurrent use of both strong/moderate CYP2D6 inhibitors and strong/moderate CYP3A4 inhibitors. Likewise, administer a quarter of the dose in patients who are known CYP2D6 poor metabolizers taking strong/moderate CYP3A4 inhibitors
- Double the dose over 1 to 2 weeks when administering with strong CYP3A4 inducers

Important Warning and Precaution for 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.

References: 1. 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(3):420-431. **2.** 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(1):64-69. **3.** 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. **4.** Grossberg GT, Kohegyi E, Mergel V, et al. Efficacy and safety of brexpiprazole for the treatment of agitation in Alzheimer's dementia: two 12-week, randomized, double-blind, placebo-controlled trials. *Am J Geriatr Psychiatry*. 2020;28(4):383-400. **5.** Lee D, Slomkowski M, Hefting N, et al. Brexpiprazole for the treatment of agitation in Alzheimer dementia: a randomized clinical trial. *JAMA Neurol*. 2023;80(12):1307-1316. **6.** Data on file (REX-283). **7.** Grossberg GT, Lee D, Slomkowski M, et al. Efficacy, safety and tolerability of brexpiprazole for the treatment of agitation associated with dementia due to Alzheimer's disease: a 12-week, randomized, double-blind, placebo-controlled trial and a 12-week extension study. Poster presented at: American Society of Clinical Psychopharmacology; May 30-June 2, 2023; Miami Beach, FL. **8.** A 12-week extension trial to evaluate the safety and tolerability of brexpiprazole in the treatment of subjects with agitation associated with dementia of the Alzheimer's type. ClinicalTrials.gov identifier: NCT03594123. Updated November 14, 2023. Accessed May 15, 2024. https://clinicaltrials.gov/study/NCT03594123?tab=table **9.** ClinicalTrials.gov. Accessed February 26, 2024. https://storage.googleapis.com/ctgov2-large-docs/23/NCT03594123/Prot_000.pdf **10.** IMS NPA Data. 2023. **11.** Data on file Otsuka (REX-31048).

Please see IMPORTANT SAFETY INFORMATION.

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IMPORTANT SAFETY INFORMATION for REXULTI® (brexpiprazole)

IMPORTANT SAFETY INFORMATION

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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.

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.

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- **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.

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).

Please see FULL PRESCRIBING INFORMATION, including BOXED WARNING.

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


Hypothetical resident and caregiver

PROVEN TO REDUCE THE FREQUENCY OF AGITATION SYMPTOMS

The primary endpoint was change in agitation symptom frequency (CMAI total score) from baseline at Week 12 in both studies.[4,5]

REXULTI® (brexpiprazole) was studied in 2 Phase III, 12-week, randomized, double-blind, placebo-controlled, fixed-dose pivotal studies evaluating frequency of agitation symptoms and safety profile in patients with dementia due to Alzheimer's disease.

- Study 6 and 7: REXULTI 2 or 3 mg/day were **statistically significantly superior** to placebo at week 12

DEMONSTRATED SAFETY PROFILE

- Adverse reactions ≥2% than placebo: nasopharyngitis, urinary tract infection, dizziness, headache, somnolence, insomnia
- Discontinuation rates due to adverse reactions were 5.6% (n=28/503) with REXULTI and 4.8% (n=12/251) with placebo
  - ~95% of patients remained on treatment with REXULTI without discontinuation, whether treated with REXULTI or placebo

ONCE-DAILY TREATMENT

- **Low starting dose** and a **2- to 4-week titration schedule** with a recommended **target dose of 2 mg/day**
- If clinically warranted, titration can extend to a recommended maximum dose of 3 mg/day

REXULTI has been **prescribed 6 million times since initial FDA approval** in 2015.[10] **100% of patients on Medicare Part D** and **96% of patients nationally** have coverage for REXULTI.[11,a]

[a]Across all channels: Commercial, Medicare Part D, and Medicaid.
CMAI, Cohen-Mansfield Agitation Inventory.

Start REXULTI today for your appropriate patients

For more information on Medicare, Medicaid, coverage, and how to access REXULTI, scan this QR code or visit **REXULTI.com/savings-cost**

INDICATION

REXULTI is indicated for 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.

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 IMPORTANT SAFETY INFORMATION.

Otsuka Lundbeck

REXULTI® brexpiprazole 2mg tablets

 July 2024 11US24EBP0245