HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use REXULTI safely and effectively. See full prescribing information for REXULTI.

REXULTI® (brexpiprazole) tablets, for oral use
Initial U.S. Approval: 2015

WARNING: INCREASED MORTALITY IN ELDERLY PATIENTS WITH DEMENTIA-RELATED PSYCHOSIS and SUICIDAL THOUGHTS AND BEHAVIORS
See full prescribing information for complete boxed warning.

- **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. (5.1)**
- **Antidepressants increased the risk of suicidal thoughts and behaviors in patients aged 24 years and younger. Monitor for clinical worsening and emergence of suicidal thoughts and behaviors. Safety and effectiveness of REXULTI have not been established in pediatric patients with MDD. (5.2, 8.4)**

----------RECENT MAJOR CHANGES ----------

Boxed Warning	12/2021
Indications and Usage (1)	12/2021
Dosage and Administration (2.2)	12/2021
Warnings and Precautions (5.6)	12/2021

---------- INDICATIONS AND USAGE ----------

REXULTI is an atypical antipsychotic indicated for:

- Use as an adjunctive therapy to antidepressants for the treatment of major depressive disorder (MDD) in adults (1, 14.1)
- Treatment of schizophrenia in adults and pediatric patients ages 13 years and older (1, 14.2)

---------- DOSAGE AND ADMINISTRATION ----------

Administer REXULTI once daily with or without food. (2.1, 2.2, 12.3)

Indication	Starting Dose	Recommended Dose	Maximum Dose
MDD Adults (2.1)	0.5 mg/day or 1 mg/day	2 mg/day	3 mg/day
Schizophrenia Adults (2.2)	1 mg/day	2 to 4 mg/day	4 mg/day
Schizophrenia Pediatric (13 - 17 years) (2.2)	0.5 mg/day	2 to 4 mg/day	4 mg/day

- *Moderate to Severe Hepatic Impairment (Child-Pugh score ≥7):* Maximum recommended dosage is 2 mg once daily for patients with MDD and 3 mg once daily for patients with schizophrenia. (2.3)
- *Moderate, Severe or End-Stage Renal Impairment (CrCl<60 mL/minute):* Maximum recommended dosage is 2 mg once daily for patients with MDD and 3 mg once daily for patients with schizophrenia. (2.4)
- *Known CYP2D6 Poor Metabolizers:* Reduce the usual dosage by half. (2.5)

---------- DOSAGE FORMS AND STRENGTHS ----------

Tablets: 0.25 mg, 0.5 mg, 1 mg, 2 mg, 3 mg, and 4 mg (3)

----------CONTRAINDICATIONS ----------

Known hypersensitivity to REXULTI or any of its components (4)

---------- WARNINGS AND PRECAUTIONS ----------

- *Cerebrovascular Adverse Reactions in Elderly Patients with Dementia-Related Psychosis:* Increased incidence of cerebrovascular adverse reactions (e.g., stroke, transient ischemic attack) (5.3)
- *Neuroleptic Malignant Syndrome:* Manage with immediate discontinuation and close monitoring. (5.4)
- *Tardive Dyskinesia:* Discontinue if clinically appropriate. (5.5)
- *Metabolic Changes:* Monitor for hyperglycemia/diabetes mellitus, dyslipidemia, and weight gain. (5.6)
- *Pathological Gambling and Other Compulsive Behaviors:* Consider dose reduction or discontinuation. (5.7)
- *Leukopenia, Neutropenia, and Agranulocytosis:* Perform complete blood counts (CBC) in patients with pre-existing low white blood cell count (WBC) or history of leukopenia or neutropenia. Consider discontinuing REXULTI if a clinically significant decline in WBC occurs in absence of other causative factors. (5.8)
- *Orthostatic Hypotension and Syncope:* Monitor heart rate and blood pressure and warn patients with known cardiovascular or cerebrovascular disease, and risk of dehydration or syncope. (5.9)
- *Seizures:* Use cautiously in patients with a history of seizures or with conditions that lower the seizure threshold. (5.11)

---------- ADVERSE REACTIONS ----------

Most common adverse reactions in adults were (6.1):

- **MDD:** Weight increased and akathisia (≥5% and at least twice the rate for placebo)
- **Schizophrenia:** Weight increased (≥4% and at least twice the rate for placebo)

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

----------DRUG INTERACTIONS ----------

Factors	Dosage Adjustments for REXULTI (2.5)
Strong CYP2D6* or CYP3A4 inhibitors	Administer half of usual dose.
Strong/moderate CYP2D6 with Strong/moderate CYP3A4 inhibitors	Administer a quarter of usual dose.
Known CYP2D6 poor metabolizers taking strong/moderate CYP3A4 inhibitors	Administer a quarter of usual dose.
Strong CYP3A4 inducers	Double the usual dose and further adjust based on clinical response.

** REXULTI may be administered without dosage adjustment in patients with MDD when administered with strong CYP2D6 inhibitors (e.g., paroxetine, fluoxetine).*

---------- USE IN SPECIFIC POPULATIONS ----------

Pregnancy: May cause extrapyramidal and/or withdrawal symptoms in neonates with third trimester exposure (8.1)

See 17 for PATIENT COUNSELING INFORMATION and Medication Guide.

Revised: 12/2021

FULL PRESCRIBING INFORMATION: CONTENTS*

*Sections or subsections omitted from the full prescribing information are not listed.

FULL PRESCRIBING INFORMATION

WARNING: INCREASED MORTALITY IN ELDERLY PATIENTS WITH DEMENTIA-RELATED PSYCHOSIS and SUICIDAL THOUGHTS AND BEHAVIORS

Increased Mortality in Elderly Patients with Dementia-Related Psychosis

Elderly patients with dementia-related psychosis treated with antipsychotic drugs are at an increased risk of death. REXULTI is not approved for the treatment of patients with dementia-related psychosis *[see Warnings and Precautions (5.1)]*.

Suicidal Thoughts and Behaviors

Antidepressants increased the risk of suicidal thoughts and behaviors in patients aged 24 years and younger in short-term studies. Monitor closely for clinical worsening and for emergence of suicidal thoughts and behaviors. The safety and effectiveness of REXULTI have not been established in pediatric patients with MDD *[see Warnings and Precautions (5.2), Use in Specific Populations (8.4)]*.

1 INDICATIONS AND USAGE

REXULTI is indicated for:

- Adjunctive treatment of major depressive disorder (MDD) in adults.
- Treatment of schizophrenia in adults and pediatric patients ages 13 years and older

2 DOSAGE AND ADMINISTRATION

2.1 Adjunctive Treatment of Major Depressive Disorder (Adults)

The recommended starting dosage for REXULTI as adjunctive treatment of MDD in adults is 0.5 mg or 1 mg once daily, taken orally with or without food *[see Clinical Pharmacology (12.3)]*.

Titrate to 1 mg once daily, then up to the target dosage of 2 mg once daily. Dosage increases should occur at weekly intervals based on the patient's clinical response and tolerability. The maximum recommended daily dosage is 3 mg. Periodically reassess to determine the continued need and appropriate dosage for treatment.

2.2 Treatment of Schizophrenia (Adults and Pediatric Patients 13 to 17 Years)

Adults

The recommended starting dosage for REXULTI for the treatment of schizophrenia in adults is 1 mg once daily on Days 1 to 4, taken orally with or without food *[see Clinical Pharmacology (12.3)]*. Titrate to 2 mg once daily on Day 5 through Day 7, then to 4 mg on Day 8 based on the patient's clinical response and tolerability. The recommended target REXULTI dosage is 2 mg to 4 mg once daily. The maximum recommended daily dosage is 4 mg.

Pediatric Patients (13 to 17 years of age)

The recommended starting dosage for REXULTI for the treatment of schizophrenia in pediatric patients 13 to 17 years of age is 0.5 mg once daily on Days 1 to 4, taken orally with or without food *[see Clinical Pharmacology (12.3)]*. Titrate to 1 mg once daily on Day 5 through Day 7, then to 2 mg on Day 8 based on the patient's clinical response and tolerability. Weekly dose increases can be made in 1 mg increments. The recommended target REXULTI dosage is 2 mg to 4 mg once daily. The maximum recommended daily dosage is 4 mg.

2.3 Dosage Adjustments for Hepatic Impairment

For patients with moderate to severe hepatic impairment (Child-Pugh score ≥7), the maximum recommended dosage is 2 mg once daily for patients with MDD, and 3 mg once daily for patients with schizophrenia *[see Use in Specific Populations (8.7), Clinical Pharmacology (12.3)]*.

2.4 Dosage Adjustments for Renal Impairment

For patients with moderate, severe, or end-stage renal impairment (creatinine clearance CrCl<60 mL/minute), the maximum recommended dosage is 2 mg once daily for patients with MDD and 3 mg once daily for patients with schizophrenia *[see Use in Specific Populations (8.8), Clinical Pharmacology (12.3)]*.

2.5 Dosage Modifications for CYP2D6 Poor Metabolizers and for Concomitant Use with CYP Inhibitors or Inducers

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 (see Table 1). If the coadministered drug is discontinued, adjust the REXULTI dosage to its original level. If the coadministered CYP3A4 inducer is discontinued, reduce the REXULTI dosage to the original level over 1 to 2 weeks *[see Drug Interactions (7.1), Clinical Pharmacology (12.3)]*.

Table 1 Dosage Adjustments of REXULTI for CYP2D6 Poor Metabolizers and for Concomitant Use with CYP3A4 and CYP2D6 Inhibitors and/or CYP3A4 Inducers

Factors	Adjusted REXULTI Dosage
CYP2D6 Poor Metabolizers	
CYP2D6 poor metabolizers	Administer half of the usual dose.
Known CYP2D6 poor metabolizers taking strong/moderate CYP3A4 inhibitors	Administer a quarter of the usual dose.
Patients Taking CYP2D6 Inhibitors and/or CYP3A4 Inhibitors	
Strong CYP2D6 inhibitors*	Administer half of the usual dose.
Strong CYP3A4 inhibitors	Administer half of the usual dose.
Strong/moderate CYP2D6 inhibitors with strong/moderate CYP3A4 inhibitors	Administer a quarter of the usual dose.
Patients Taking CYP3A4 Inducers	
Strong CYP3A4 inducers	Double usual dose over 1 to 2 weeks.

*In the clinical trials examining the adjunctive use of REXULTI in the treatment of MDD, dosage was not adjusted for strong CYP2D6 inhibitors (e.g., paroxetine, fluoxetine). Thus, CYP considerations are already factored into general dosing recommendations, and REXULTI may be administered without dosage adjustment in patients with MDD.

3 DOSAGE FORMS AND STRENGTHS

REXULTI tablets are available in 6 strengths:

- 0.25 mg tablets are light brown, round, shallow convex, bevel-edged body with “BRX” and “0.25” imprinted on one side
- 0.5 mg tablets: are light orange, round, shallow convex, bevel-edged body with “BRX” and “0.5” imprinted on one side
- 1 mg tablets are light yellow, round, shallow convex, bevel-edged body with “BRX” and “1” imprinted on one side

- 2 mg tablets are light green, round, shallow convex, bevel-edged body with “BRX” and “2” imprinted on one side
- 3 mg tablets are light purple, round, shallow convex, bevel-edged body with “BRX” and “3” imprinted on one side
- 4 mg tablets are white, round, shallow convex, bevel-edged body with “BRX” and “4” imprinted on one side

4 CONTRAINDICATIONS

REXULTI is contraindicated in patients with a known hypersensitivity to brexpiprazole or any of its components. Reactions have included rash, facial swelling, urticaria, and anaphylaxis.

5 WARNINGS AND PRECAUTIONS

5.1 Increased Mortality in Elderly Patients with Dementia-Related Psychosis

Elderly patients with dementia-related psychosis treated with antipsychotic drugs are at an increased risk of death. Analyses of 17 placebo-controlled trials (modal duration of 10 weeks), largely in patients taking atypical antipsychotic drugs, revealed a risk of death in drug-treated patients of between 1.6 to 1.7 times the risk of death in placebo-treated patients. Over the course of a typical 10-week controlled trial, the rate of death in drug-treated patients was about 4.5%, compared to a rate of about 2.6% in the placebo group.

Although the causes of death were varied, most of the deaths appeared to be either cardiovascular (e.g., heart failure, sudden death) or infectious (e.g., pneumonia) in nature. REXULTI is not approved for the treatment of patients with dementia-related psychosis *[see Boxed Warning, Warnings and Precautions (5.3)]*.

5.2 Suicidal Thoughts and Behaviors in Children, Adolescents, and Young Adults

In pooled analyses of placebo-controlled trials of antidepressant drugs (SSRIs and other antidepressant classes) that included approximately 77,000 adult patients and over 4400 pediatric patients, the incidence of suicidal thoughts and behaviors in patients age 24 years and younger was greater in antidepressant-treated patients than in placebo-treated patients. The drug-placebo differences in the number of cases of suicidal thoughts and behaviors per 1000 patients treated are provided in Table2.

No suicides occurred in any of the pediatric studies. There were suicides in the adult studies, but the number was not sufficient to reach any conclusion about antidepressant drug effect on suicide.

Table 2 Risk Differences of the Number of Patients with Suicidal Thoughts or Behaviors in the Pooled Placebo-Controlled Trials of Antidepressants in Pediatric* and Adult Patients

Age Range (years)	Drug-Placebo Difference in Number of Patients with Suicidal Thoughts or Behaviors per 1000 Patients Treated
	Increases Compared to Placebo
<18	14 additional patients
18 to 24	5 additional patients
	Decreases Compared to Placebo
25 to 64	1 fewer patient
≥65	6 fewer patients

*REXULTI is not approved in pediatric patients with MDD.

It is unknown whether the risk of suicidal thoughts and behaviors in children, adolescents, and young adults extends to longer-term use, i.e., beyond four months. However, there is substantial evidence from placebo-controlled maintenance studies in adults with MDD that antidepressants delay the recurrence of depression.

Monitor all antidepressant-treated patients for clinical worsening and emergence of suicidal thoughts and behaviors, especially during the initial few months of drug therapy and at times of dosage changes. Counsel family members or caregivers of patients to monitor for changes in behavior and to alert the healthcare provider. Consider changing the therapeutic regimen, including possibly discontinuing REXULTI, in patients whose depression is persistently worse or who are experiencing emergent suicidal thoughts or behaviors.

5.3 Cerebrovascular Adverse Reactions Including Stroke in Elderly Patients with Dementia-Related Psychosis

In placebo-controlled trials in elderly patients with dementia, patients 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 *[see Boxed Warning, Warnings and Precautions (5.1)]*.

5.4 Neuroleptic Malignant Syndrome (NMS)

A potentially fatal symptom complex, sometimes referred to as neuroleptic malignant syndrome (NMS), has been reported in association with administration of antipsychotic drugs, including REXULTI. Clinical manifestations of NMS are hyperpyrexia, muscle rigidity, altered mental status, and evidence of autonomic instability. Additional signs may include elevated creatinine phosphokinase, myoglobinuria (rhabdomyolysis), and acute renal failure.

If NMS is suspected, immediately discontinue REXULTI and provide intensive symptomatic treatment and monitoring.

5.5 Tardive Dyskinesia

Tardive dyskinesia, a syndrome consisting of potentially irreversible, involuntary, dyskinetic movements, may develop in patients treated with antipsychotic drugs. The risk appears to be highest among the elderly, especially elderly women, but it is not possible to predict which patients are likely to develop the syndrome. Whether antipsychotic drugs differ in their potential to cause tardive dyskinesia is unknown.

The risk of tardive dyskinesia and the likelihood that it will become irreversible increase with the duration of treatment and the cumulative dose. The syndrome can develop after a relatively brief treatment period, even at low doses. It may also occur after discontinuation of treatment.

Tardive dyskinesia may remit, partially or completely, if antipsychotic treatment is discontinued. Antipsychotic treatment itself, however, may suppress (or partially suppress) the signs and symptoms of the syndrome, possibly masking the underlying process. The effect that symptomatic suppression has upon the long-term course of tardive dyskinesia is unknown.

Given these considerations, REXULTI should be prescribed in a manner most likely to reduce the risk of tardive dyskinesia. Chronic antipsychotic treatment should generally be reserved for patients: (1) who suffer from a chronic illness that is known to respond to antipsychotic drugs; and (2) for whom alternative, effective, but potentially less harmful treatments are not available or appropriate. In patients who do require chronic treatment, use the lowest dose and the shortest duration of treatment needed to produce a satisfactory clinical response. Periodically reassess the need for continued treatment.

If signs and symptoms of tardive dyskinesia appear in a patient on REXULTI, drug discontinuation should be considered. However, some patients may require treatment with REXULTI despite the presence of the syndrome.

5.6 Metabolic Changes

Atypical antipsychotic drugs, including REXULTI, have caused metabolic changes, including hyperglycemia, diabetes mellitus, dyslipidemia, and body weight gain. Although all of the drugs in the class to date have been shown to produce some metabolic changes, each drug has its own specific risk profile.

Hyperglycemia and Diabetes Mellitus

Hyperglycemia, in some cases extreme and associated with ketoacidosis or hyperosmolar coma or death, has been reported in patients treated with atypical antipsychotics. There have been reports of hyperglycemia in patients treated with REXULTI. Assess fasting plasma glucose before or soon after initiation of antipsychotic medication and monitor periodically during long-term treatment.

Major Depressive Disorder

In the 6-week placebo-controlled, fixed-dose clinical trials in adult patients with MDD, the proportions of patients with shifts in fasting glucose from normal (<100 mg/dL) to high (≥126 mg/dL) and borderline (≥100 and <126 mg/dL) to high were similar in patients treated with REXULTI and placebo.

In the long-term, open-label depression studies, 5% of adult patients with normal baseline fasting glucose experienced a shift to high while taking REXULTI plus an antidepressant (ADT); 25% of patients with borderline fasting glucose experienced shifts to high. Combined, 9% of patients with normal or borderline fasting glucose experienced shifts to high fasting glucose during the long-term depression studies.

Schizophrenia

Adults

In the 6-week placebo-controlled, fixed-dose clinical trials in adult patients with schizophrenia, the proportions of patients with shifts in fasting glucose from normal (<100 mg/dL) to high (≥126 mg/dL) or borderline (≥100 and <126 mg/dL) to high were similar in patients treated with REXULTI and placebo.

In the long-term, open-label schizophrenia studies, 8% of adult patients with normal baseline fasting glucose experienced a shift from normal to high while taking REXULTI; 17% of patients with borderline fasting glucose experienced shifts from borderline to high. Combined, 10% of patients with normal or borderline fasting glucose experienced shifts to high fasting glucose during the long-term schizophrenia studies.

Pediatric Patients (13 to 17 years of age)

In the long-term, open-label study in pediatric patients with schizophrenia, 2.7% of pediatric patients with normal baseline fasting glucose experienced a shift from normal (<100 mg/dL) to high (≥126 mg/dL) while taking REXULTI.

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.

Major Depressive Disorder

In the 6-week placebo-controlled, fixed-dose clinical trials in adult patients with MDD, changes in fasting total cholesterol, LDL cholesterol, and HDL cholesterol were similar in REXULTI- and placebo-treated patients. Table 3 shows the proportions of patients with changes in fasting triglycerides.

Table 3 Change in Fasting Triglycerides in the 6-Week Placebo-Controlled, Fixed-Dose MDD Trials

Proportion of Patients with Shifts Baseline to Post-Baseline				
Triglycerides	**Placebo**	**1 mg/day**	**2 mg/day**	**3 mg/day**
Normal to High (<150 mg/dL to ≥200 and <500 mg/dL)	6% (15/257)*	5% (7/145)*	13% (15/115)*	9% (13/150)*
Normal/Borderline to Very High (<200 mg/dL to ≥500 mg/dL)	0% (0/309)*	0% (0/177)*	0.7% (1/143)*	0% (0/179)*

*denotes n/N where N=the total number of patients who had a measurement at baseline and at least one post-baseline result
n=the number of patients with shift

In the long-term, open-label depression studies, shifts in baseline fasting cholesterol from normal to high were reported in 9% (total cholesterol), 3% (LDL cholesterol), and shifts in baseline from normal to low were reported in 14% (HDL cholesterol) of patients taking REXULTI. Of patients with normal baseline triglycerides, 17% experienced shifts to high, and 0.2% experienced shifts to very high. Combined, 0.6% of patients with normal or borderline fasting triglycerides experienced shifts to very high fasting triglycerides during the long-term depression studies.

Schizophrenia

Adults

In the 6-week placebo-controlled, fixed-dose clinical trials in adult patients with schizophrenia, changes in fasting total cholesterol, LDL cholesterol, and HDL cholesterol were similar in REXULTI- and placebo-treated patients. Table 4 shows the proportions of patients with changes in fasting triglycerides.

Table 4 Change in Fasting Triglycerides in the 6-Week Placebo-Controlled, Fixed-Dose Schizophrenia Trials in Adult Patients

Proportion of Patients with Shifts Baseline to Post-Baseline				
Triglycerides	**Placebo**	**1 mg/day**	**2 mg/day**	**4 mg/day**
Normal to High (<150 mg/dL to ≥200 and <500 mg/dL)	6% (15/253)*	10% (7/72)*	8% (19/232)*	10% (22/226)*
Normal/Borderline to Very High (<200 mg/dL to ≥500 mg/dL)	0% (0/303)*	0% (0/94)*	0% (0/283)*	0.4% (1/283)*

*denotes n/N where N=the total number of patients who had a measurement at baseline and at least one post-baseline result
n=the number of patients with shift

In the long-term, open-label schizophrenia studies in adult patients, shifts in baseline fasting cholesterol from normal to high were reported in 6% (total cholesterol), 2% (LDL cholesterol), and shifts in baseline from normal to low were reported in 17% (HDL cholesterol) of patients taking REXULTI. Of patients with normal baseline triglycerides, 13% experienced shifts to high, and 0.4% experienced shifts to very high triglycerides. Combined, 0.6% of patients with normal or borderline fasting triglycerides experienced shifts to very high fasting triglycerides during the long-term schizophrenia studies.

Pediatric Patients (13 to 17 years of age)

In the long-term, open-label study in pediatric patients with schizophrenia, shifts in baseline fasting total cholesterol from normal to high (<170 to ≥200 mg/dL) were reported in 7% of patients taking REXULTI, and shifts in baseline HDL cholesterol from normal to low (≥40 to <40 mg/dL) were reported in 12.9% of patients taking REXULTI. Of patients with normal baseline triglycerides, 8.5% experienced shifts from normal to high (<150 to ≥200 mg/dL).

Weight Gain

Weight gain has been observed in patients treated with atypical antipsychotics, including REXULTI. Monitor weight at baseline and frequently thereafter.

Major Depressive Disorder

Table 5 shows weight gain data at last visit and percentage of adult patients with ≥7% increase in body weight at endpoint from the 6-week placebo-controlled, fixed-dose clinical studies in patients with MDD.

Table 5 Increases in Body Weight in the 6-Week Placebo-Controlled, Fixed-Dose MDD Trials

	Placebo	**1 mg/day**	**2 mg/day**	**3 mg/day**
	n=407	**n=225**	**n=187**	**n=228**
Mean Change from Baseline (kg) at Last Visit				
All Patients	+0.3	+1.3	+1.6	+1.6
Proportion of Patients with a ≥7% Increase in Body Weight (kg) at Any Visit (*n/N)				
	2%	5%	5%	2%
	(8/407)*	(11/225)*	(9/187)*	(5/228)*

*N=the total number of patients who had a measurement at baseline and at least one post-baseline result
n=the number of patients with a shift ≥7%

In the long-term, open-label depression studies, 4% of patients discontinued due to weight increase. REXULTI was associated with mean change from baseline in weight of 2.9 kg at Week 26 and 3.1 kg at Week 52. In the long-term, open-label depression studies, 30% of patients demonstrated a ≥7% increase in body weight, and 4% demonstrated a ≥7% decrease in body weight.

Schizophrenia

Adults

Table 6 shows weight gain data at last visit and percentage of adult patients with ≥7% increase in body weight at endpoint from the 6-week placebo-controlled, fixed-dose clinical studies in adult patients with schizophrenia.

Table 6 Increases in Body Weight in the 6-Week Placebo-Controlled, Fixed-Dose Schizophrenia Trials in Adult Patients

	Placebo	**1 mg/day**	**2 mg/day**	**4 mg/day**
	n=362	**n=120**	**n=362**	**n=362**
Mean Change from Baseline (kg) at Last Visit				
All Patients	+0.2	+1.0	+1.2	+1.2
Proportion of Patients with a ≥7% Increase in Body Weight (kg) at Any Visit (*n/N)				
	4%	10%	11%	10%
	(15/362)*	(12/120)*	(38/362)*	(37/362)*

*denotes n/N where N=the total number of patients who had a measurement at baseline and at least one post-baseline result

n=the number of patients with a shift ≥7%

In the long-term, open-label schizophrenia studies in adult patients, 0.6% of patients discontinued due to weight increase. REXULTI was associated with mean change from baseline in weight of 1.3 kg at Week 26 and 2.0 kg at Week 52. In the long-term, open label schizophrenia studies, 20% of patients demonstrated a ≥7% increase in body weight, and 10% demonstrated a ≥7% decrease in body weight.

Pediatric Patients (13 to 17 years of age)

In the long-term, open label study in pediatric patients with schizophrenia, 0.5% of patients discontinued due to weight increase. The mean increase in weight from the open-label study baseline to last visit was 3.8 kg. To adjust for normal growth, z-scores were derived (measured in standard deviations [SD]), which normalize for natural growth of children and adolescents by comparisons to age- and gender- matched population standards. A z-score change <0.5 SD is considered not clinically significant. In this trial, the mean change in z-score from open-label baseline to last visit was 0.10 SD for body weight, while 20% of patients had an increase in age-and-gender-adjusted body weight z-score of at least 0.5 SD from baseline. When treating pediatric, weight gain should be monitored and assessed against that expected for normal growth.

5.7 Pathological Gambling and Other Compulsive Behaviors

Post-marketing case reports suggest that patients can experience intense urges, particularly for gambling, and the inability to control these urges while taking REXULTI. Other compulsive urges, reported less frequently, include sexual urges, shopping, eating, or binge eating, and other impulsive or compulsive behaviors. Because patients may not recognize these behaviors as abnormal, it is important for prescribers to ask patients or their caregivers specifically about the development of new or intense gambling urges, compulsive sexual urges, compulsive shopping, binge or compulsive eating, or other urges while being treated with REXULTI. In some cases, although not all, urges were reported to have stopped when the dose was reduced, or the medication was discontinued. Compulsive behaviors may result in harm to the patient and others if not recognized. Consider dose reduction or stopping the medication if a patient develops such urges.

5.8 Leukopenia, Neutropenia, and Agranulocytosis

Leukopenia and neutropenia have been reported during treatment with antipsychotic agents. Agranulocytosis (including fatal cases) has been reported with other agents in this class.

Possible risk factors for leukopenia and neutropenia include pre-existing low white blood cell count (WBC) or absolute neutrophil count (ANC) and history of drug-induced leukopenia or neutropenia. In patients with a pre-existing low WBC or ANC or a history of drug-induced leukopenia or neutropenia, perform a complete blood count (CBC) frequently during the first few months of therapy. In such patients, consider discontinuation of REXULTI at the first sign of a clinically significant decline in WBC in the absence of other causative factors.

Monitor patients with clinically significant neutropenia for fever or other symptoms or signs of infection and treat promptly if such symptoms or signs occur. Discontinue REXULTI in patients with absolute neutrophil count <1000/mm^3 and follow their WBC until recovery.

5.9 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. In the short-term, placebo-controlled clinical studies of REXULTI plus ADT in adult patients with MDD, the incidence of orthostatic hypotension-related adverse reactions in REXULTI plus ADT-treated patients compared to placebo plus ADT-treated patients included:

dizziness (2% versus 2%) and orthostatic hypotension (0.1% versus 0%). In the short-term, placebo-controlled clinical studies of REXULTI in adult patients with schizophrenia, the incidence of orthostatic hypotension-related adverse reactions in REXULTI-treated patients compared to placebo patients included: dizziness (2% versus 2%), orthostatic hypotension (0.4% versus 0.2%), and syncope (0.1% versus 0%).

Orthostatic vital signs should be monitored in patients who are vulnerable to hypotension (e.g., elderly patients, patients with dehydration, hypovolemia, concomitant treatment with antihypertensive medication), patients with known cardiovascular disease (history of myocardial infarction, ischemic heart disease, heart failure, or conduction abnormalities), and patients with cerebrovascular disease. REXULTI has not been evaluated in patients with a recent history of myocardial infarction or unstable cardiovascular disease. Such patients were excluded from the premarketing clinical trials.

5.10 Falls

Antipsychotics, including REXULTI, may cause somnolence, postural hypotension, motor, and sensory instability, which may lead to falls and, consequently, fractures or other injuries. For patients with diseases, conditions, or medications that could exacerbate these effects, complete fall risk assessments when initiating antipsychotic treatment and recurrently for patients on long-term antipsychotic therapy.

5.11 Seizures

Like other antipsychotic drugs, REXULTI may cause seizures. This risk is greatest in patients with a history of seizures or with conditions that lower the seizure threshold. Conditions that lower the seizure threshold may be more prevalent in older patients.

5.12 Body Temperature Dysregulation

Atypical antipsychotics may disrupt the body's ability to reduce core body temperature. Strenuous exercise, exposure to extreme heat, dehydration, and anticholinergic medications may contribute to an elevation in core body temperature; use REXULTI with caution in patients who may experience these conditions.

5.13 Dysphagia

Esophageal dysmotility and aspiration have been associated with antipsychotic drug use. Antipsychotic drugs, including REXULTI, should be used cautiously in patients at risk for aspiration.

5.14 Potential for Cognitive and Motor Impairment

REXULTI, like other antipsychotics, has the potential to impair judgment, thinking, or motor skills. In the 6-week placebo-controlled clinical trials in patients with MDD, somnolence (including sedation and hypersomnia) was reported in 4% of REXULTI plus ADT-treated patients compared to 1% of placebo plus ADT-treated patients.

In the 6-week placebo-controlled clinical trials in adult patients with schizophrenia, somnolence (including sedation and hypersomnia) was reported in 5% of REXULTI-treated patients compared to 3% of placebo-treated patients.

Patients should be cautioned about operating hazardous machinery, including motor vehicles, until they are reasonably certain that REXULTI therapy does not affect them adversely.

6 ADVERSE REACTIONS

The following adverse reactions are discussed in more detail in other sections of the labeling:

- Increased Mortality in Elderly Patients with Dementia-Related Psychosis *[see Boxed Warning, Warnings and Precautions (5.1)]*
- Suicidal Thoughts and Behaviors in Adolescents and Young Adults *[see Boxed Warning, Warnings and Precautions (5.2)]*
- Cerebrovascular Adverse Reactions Including Stroke in Elderly Patients with Dementia-Related Psychosis *[see Warnings and Precautions (5.3)]*
- Neuroleptic Malignant Syndrome (NMS) *[see Warnings and Precautions (5.4)]*
- Tardive Dyskinesia *[see Warnings and Precautions (5.5)]*
- Metabolic Changes *[see Warnings and Precautions (5.6)]*
- Pathological Gambling and Other Compulsive Behaviors *[see Warnings and Precautions (5.7)]*
- Leukopenia, Neutropenia, and Agranulocytosis *[see Warnings and Precautions (5.8)]*
- Orthostatic Hypotension and Syncope *[see Warnings and Precautions (5.9)]*
- Falls *[see Warnings and Precautions (5.10)]*
- Seizures *[see Warnings and Precautions (5.11)]*
- Body Temperature Dysregulation *[see Warnings and Precautions (5.12)]*
- Dysphagia *[see Warnings and Precautions (5.13)]*
- Potential for Cognitive and Motor Impairment *[see Warnings and Precautions (5.14)]*

6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in clinical practice.

Major Depressive Disorder

The safety of REXULTI was evaluated in 1054 adult patients (18 to 65 years of age) diagnosed with MDD who participated in two 6-week placebo-controlled, fixed-dose clinical trials in patients with major depressive disorder in which REXULTI was administered at doses of 1 mg to 3 mg daily as adjunctive treatment to continued antidepressant therapy; patients in the placebo group continued to receive antidepressant therapy *[see Clinical Studies (14.1)]*.

Adverse Reactions Reported as Reasons for Discontinuation of Treatment

A total of 3% (17/643) of REXULTI-treated patients and 1% (3/411) of placebo-treated patients discontinued due to adverse reactions.

Common Adverse Reactions

Adverse reactions associated with the adjunctive use of REXULTI (incidence of 2% or greater and adjunctive REXULTI incidence greater than adjunctive placebo) that occurred during acute therapy (up to 6-weeks in patients with MDD) are shown in Table 7.

Table 7 Adverse Reactions in Pooled 6-Week Placebo-Controlled, Fixed-Dose MDD Trials in Adults (Studies 1 and 2)*

	Placebo (N=411)	REXULTI			
		1 mg/day (N=226)	2 mg/day (N=188)	3 mg/day (N=229)	All REXULTI (N=643)
Gastrointestinal Disorders					

Constipation	1%	3%	2%	1%	2%
General Disorders and Administration Site Conditions					
Fatigue	2%	3%	2%	5%	3%
Infections and Infestations					
Nasopharyngitis	2%	7%	1%	3%	4%
Investigations					
Weight Increased	2%	7%	8%	6%	7%
Blood Cortisol Decreased	1%	4%	0%	3%	2%
Metabolism and Nutrition					
Increased Appetite	2%	3%	3%	2%	3%
Nervous System Disorders					
Akathisia	2%	4%	7%	14%	9%
Headache	6%	9%	4%	6%	7%
Somnolence	0.5%	4%	4%	6%	5%
Tremor	2%	4%	2%	5%	4%
Dizziness	1%	1%	5%	2%	3%
Psychiatric Disorders					
Anxiety	1%	2%	4%	4%	3%
Restlessness	0%	2%	3%	4%	3%

*Adverse reactions that occurred in ≥2% of REXULTI-treated patients and greater incidence than in placebo-treated patients

Dose-Related Adverse Reactions in the MDD Trials

In Studies 1 and 2, among the adverse reactions that occurred at ≥2% incidence in the patients treated with REXULTI plus ADT, the incidences of akathisia and restlessness increased with increases in dose.

Schizophrenia

Adults

The safety of REXULTI was evaluated in 852 adult patients (18 to 65 years of age) diagnosed with schizophrenia who participated in two 6-week placebo-controlled, fixed-dose clinical trials in which REXULTI was administered at daily doses of 1 mg, 2 mg, and 4 mg *[see Clinical Studies (14.2)]*.

Common Adverse Reactions

Adverse reactions associated with REXULTI (incidence of 2% or greater and REXULTI incidence greater than placebo) during short-term (up to 6 weeks) trials in adult patients with schizophrenia are shown in Table 8.

Table 8 Adverse Reactions in Pooled 6-Week Placebo-Controlled, Fixed-Dose Schizophrenia Trials in Adult Patients (Studies 3 and 4)*

	Placebo (N=368)	REXULTI			
		1 mg/day (N=120)	2 mg/day (N=368)	4 mg/day (N=364)	ALL REXULTI (N=852)
Gastrointestinal Disorders					

Dyspepsia	2%	6%	2%	3%	3%
Diarrhea	2%	1%	3%	3%	3%
Investigations					
Weight Increased	2%	3%	4%	4%	4%
Blood Creatinine Phosphokinase Increased	1%	4%	2%	2%	2%
Nervous System Disorders					
Akathisia	5%	4%	5%	7%	6%
Tremor	1%	2%	2%	3%	3%
Sedation	1%	2%	2%	3%	2%

*Adverse reactions that occurred in ≥2% of REXULTI-treated patients and greater incidence than in placebo-treated patients

Extrapyramidal Symptoms

Major Depressive Disorder

The incidence of reported extrapyramidal symptoms (EPS)-related adverse reactions, excluding akathisia, was 6% for REXULTI plus ADT-treated patients versus 3% for placebo plus ADT-treated patients. The incidence of akathisia events for REXULTI plus ADT-treated patients was 9% versus 2% for placebo plus ADT-treated patients.

In the 6-week placebo-controlled MDD studies , data was objectively collected on the Simpson-Angus Rating Scale (SAS) for EPS, the Barnes Akathisia Rating Scale (BARS) for akathisia and the Abnormal Involuntary Movement Score (AIMS) for dyskinesia. The mean change from baseline at last visit for REXULTI plus ADT-treated patients for the SAS, BARS and AIMS was comparable to placebo-treated patients. The percentage of patients who shifted from normal to abnormal was greater in REXULTI plus ADT-treated patients versus placebo plus ADT-treated patients for the BARS (4% versus 0.6%) and the SAS (4% versus 3%).

Schizophrenia

The incidence of reported EPS-related adverse reactions, excluding akathisia, was 5% for REXULTI-treated patients versus 4% for placebo-treated patients. The incidence of akathisia events for REXULTI-treated patients was 6% versus 5% for placebo-treated patients.

In the 6-week placebo-controlled, fixed-dose schizophrenia studies in adults, data was objectively collected on the Simpson-Angus Rating Scale (SAS) for EPS, the Barnes Akathisia Rating Scale (BARS) for akathisia and the Abnormal Involuntary Movement Scale (AIMS) for dyskinesia. The mean change from baseline at last visit for REXULTI-treated patients for the SAS, BARS and AIMS was comparable to placebo-treated patients. The percentage of patients who shifted from normal to abnormal was greater in REXULTI-treated patients versus placebo for the BARS (2% versus 1%) and the SAS (7% versus 5%).

Dystonia

Symptoms of dystonia may occur in susceptible individuals during the first few days of treatment. Dystonic symptoms include spasm of the neck muscles, sometimes progressing to tightness of the throat, swallowing difficulty, difficulty breathing, and/or protrusion of the tongue. While these symptoms can occur at low doses, they occur more frequently and with greater severity with high potency and at higher doses of first-generation antipsychotic drugs. An elevated risk of acute dystonia is observed in males and younger age groups.

Other Adverse Reactions Observed during the Premarketing Evaluation of REXULTI

Other adverse reactions (≥1% frequency and greater than placebo) within the short-term, placebo-controlled trials in adult patients with MDD and schizophrenia are shown below. The following listing does not include adverse reactions: 1) already listed in previous tables or elsewhere in the labeling, 2) for which a drug cause was remote, 3) which were so general as to be uninformative, 4) which were not considered to have clinically significant implications, or 5) which occurred at a rate equal to or less than placebo.

Eye Disorders: Vision Blurred

Gastrointestinal Disorders: Nausea, Dry Mouth, Salivary Hypersecretion, Abdominal Pain, Flatulence

Infections and Infestations: Urinary Tract Infection

Investigations: Blood Prolactin Increased

Musculoskeletal and Connective Tissue Disorders: Myalgia

Psychiatric Disorders: Abnormal Dreams, Insomnia

Skin and Subcutaneous Tissue Disorders: Hyperhidrosis

Pediatric Patients (13 to 17 years of age)

In an on-going, 2 year, open-label study in pediatric patients 13 to 17 years of age with schizophrenia, in which safety was assessed in 194 patients of which 140 received REXULTI for at least 6 months. Adverse reactions reported in clinical studies for this age group were generally similar to those observed in adult patients.

6.2 Postmarketing Experience

The following adverse reaction has been identified during post-approval use of REXULTI. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

Nervous System disorders: Neuroleptic Malignant Syndrome

7 DRUG INTERACTIONS

7.1 Drugs Having Clinically Important Interactions with REXULTI

Table 9	**Clinically Important Drug Interactions with REXULTI**
Strong CYP3A4 Inhibitors	
Clinical Impact:	Concomitant use of REXULTI with strong CYP3A4 inhibitors increased the exposure of brexpiprazole compared to the use of REXULTI alone *[see Clinical Pharmacology (12.3)]*.
Intervention:	With concomitant use of REXULTI with a strong CYP3A4 inhibitor, reduce the REXULTI dosage *[see Dosage and Administration (2.5)]*.
Strong CYP2D6 Inhibitors*	
Clinical Impact:	Concomitant use of REXULTI with strong CYP2D6 inhibitors increased the exposure of brexpiprazole compared to the use of REXULTI alone *[see Clinical Pharmacology (12.3)]*.
Intervention:	With concomitant use of REXULTI with a strong CYP2D6 inhibitor, reduce the REXULTI dosage *[see Dosage and Administration (2.5)]*.

Both CYP3A4 Inhibitors and CYP2D6 Inhibitors	
Clinical Impact:	Concomitant use of REXULTI with 1) a strong CYP3A4 inhibitor and a strong CYP2D6 inhibitor; or 2) a moderate CYP3A4 inhibitor and a strong CYP2D6 inhibitor; or 3) a strong CYP3A4 inhibitor and a moderate CYP2D6 inhibitor; or 4) a moderate CYP3A4 inhibitor and a moderate CYP2D6 inhibitor increased the exposure of brexpiprazole compared to the use of REXULTI alone *[see Clinical Pharmacology (12.3)].*
Intervention:	With concomitant use of REXULTI with 1) a strong CYP3A4 inhibitor and a strong CYP2D6 inhibitor; or 2) a moderate CYP3A4 inhibitor and a strong CYP2D6 inhibitor; or 3) a strong CYP3A4 inhibitor and a moderate CYP2D6 inhibitor; or 4) a moderate CYP3A4 inhibitor and a moderate CYP2D6 inhibitor, decrease the REXULTI dosage *[see Dosage and Administration (2.5)].*
Strong CYP3A4 Inducers	
Clinical Impact:	Concomitant use of REXULTI and a strong CYP3A4 inducer decreased the exposure of brexpiprazole compared to the use of REXULTI alone *[see Clinical Pharmacology (12.3)].*
Intervention:	With concomitant use of REXULTI with a strong CYP3A4 inducer, increase the REXULTI dosage *[see Dosage and Administration (2.5)].*

*In the clinical trials examining the adjunctive use of REXULTI in the treatment of MDD, dosage was not adjusted for strong CYP2D6 inhibitors (e.g., paroxetine, fluoxetine). Thus, CYP considerations are already factored into general dosing recommendations, and REXULTI may be administered without dosage adjustment in patients with MDD.

7.2 Drugs Having No Clinically Important Interactions with REXULTI

Based on pharmacokinetic studies, no dosage adjustment of REXULTI is required when administered concomitantly with CYP2B6 inhibitors (e.g., ticlopidine) or gastric pH modifiers (e.g., omeprazole). Additionally, no dosage adjustment for substrates of CYP2D6 (e.g., dextromethorphan), CYP3A4 (e.g., lovastatin), CYP2B6 (e.g., bupropion), BCRP (e.g., rosuvastatin), or P-gp (e.g., fexofenadine) is required when administered concomitantly with REXULTI.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Exposure Registry

There is a pregnancy exposure registry that monitors pregnancy outcomes in women exposed to REXULTI during pregnancy. For more information contact the National Pregnancy Registry for Atypical Antipsychotics at 1-866-961-2388 or visit http://womensmentalhealth.org/clinical-and-research-programs/pregnancyregistry/.

Risk Summary

Adequate and well-controlled studies have not been conducted with REXULTI in pregnant women to inform drug-associated risks. However, neonates whose mothers are exposed to antipsychotic drugs, like REXULTI, during the third trimester of pregnancy are at risk for extrapyramidal and/or withdrawal symptoms. In animal reproduction studies, no teratogenicity was observed with oral administration of brexpiprazole to pregnant rats and rabbits during organogenesis at doses up to 73 and 146 times, respectively, of maximum recommended human dose (MRHD) of 4 mg/day on a mg/m^2 basis. However, when pregnant rats were administered brexpiprazole during the period of organogenesis through lactation, the number of perinatal deaths of pups was increased at 73 times the MRHD *[see Data]*. The background risk of major birth defects and miscarriage for the indicated population(s) is unknown. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2 to 4% and 15 to 20%, respectively.

Clinical Considerations

Fetal/Neonatal Adverse Reactions

Extrapyramidal and/or withdrawal symptoms, including agitation, hypertonia, hypotonia, tremor, somnolence, respiratory distress and feeding disorder, have been reported in neonates whose mothers were exposed to antipsychotic drugs during the third trimester of pregnancy. These symptoms have varied in severity. Some neonates recovered within hours or days without specific treatment; others required prolonged hospitalization. Monitor neonates for extrapyramidal and/or withdrawal symptoms and manage symptoms appropriately.

Data

Animal Data

Pregnant rats were treated with oral doses of 3, 10, and 30 mg/kg/day (7.3, 24, and 73 times the MRHD on a mg/m^2 basis) of brexpiprazole during the period of organogenesis. Brexpiprazole was not teratogenic and did not cause adverse developmental effects at doses up to 73 times the MRHD.

Pregnant rabbits were treated with oral doses of 10, 30, and 150 mg/kg/day (49, 146, and 730 times the MRHD) of brexpiprazole during the period of organogenesis. Brexpiprazole was not teratogenic and did not cause adverse developmental effects at doses up to 146 times the MRHD. Findings of decreased body weight, retarded ossification, and increased incidences of visceral and skeletal variations were observed in fetuses at 730 times the MRHD, a dose that induced maternal toxicity.

In a study in which pregnant rats were administered oral doses of 3, 10, and 30 mg/kg/day (7.3, 24, and 73 times the MRHD) during the period of organogenesis and through lactation, the number of live-born pups was decreased, and early postnatal deaths increased at a dose 73 times the MRHD. Impaired nursing by dams, and low birth weight and decreased body weight gain in pups were observed at 73 times, but not at 24 times, the MRHD.

8.2 Lactation

Risk Summary

Lactation studies have not been conducted to assess the presence of brexpiprazole in human milk, the effects of brexpiprazole on the breastfed infant, or the effects of brexpiprazole on milk production. Brexpiprazole is present in rat milk. The development and health benefits of breastfeeding should be considered along with the mother's clinical need for REXULTI and any potential adverse effects on the breastfed infant from REXULTI or from the underlying maternal condition.

8.4 Pediatric Use

Schizophrenia

Safety and effectiveness of REXULTI for treatment of schizophrenia have been established in pediatric patients 13 years of age and older. Use of REXULTI in this population is supported by evidence from adequate and well-controlled studies in adults with schizophrenia, pharmacokinetic data from adults and pediatric patients, and safety data in pediatric patients 13 to 17 years of age *[see Warnings and Precautions (5.6), Adverse Reactions (6.1), Clinical Pharmacology (12.3)]*.

Major Depressive Disorder

Safety and effectiveness in pediatric patients with major depressive disorder have not been established. Antidepressants increased the risk of suicidal thoughts and behaviors in pediatric patients *[see Boxed Warning, Warnings and Precautions (5.2)]*.

8.5 Geriatric Use

Clinical studies of the efficacy of REXULTI did not include any patients aged 65 or older to determine whether they respond differently from younger patients. In general, dose selection for an elderly patient should be cautious, usually starting at the low end of the dosing range, reflecting the greater frequency of decreased hepatic, renal, and cardiac function, concomitant diseases, and other drug therapy.

Based on the results of a safety, tolerability, and pharmacokinetics trial, the pharmacokinetics of once daily oral administration of brexpiprazole (up to 3 mg/day for 14 days) as an adjunct therapy in the treatment of elderly patients (70 to 85 years old, N=11) with MDD were comparable to those observed in adult patients with MDD.

Antipsychotic drugs increase the risk of death in elderly patients with dementia-related psychosis. REXULTI is not approved for the treatment of patients with dementia-related psychosis *[see Boxed Warning, Warnings and Precautions (5.1)]*.

8.6 CYP2D6 Poor Metabolizers

Dosage adjustment is recommended in known CYP2D6 poor metabolizers because these patients have higher brexpiprazole concentrations than normal metabolizers of CYP2D6. Approximately 8% of Caucasians and 3 to 8% of Black/African Americans cannot metabolize CYP2D6 substrates and are classified as poor metabolizers *[see Dosage and Administration (2.5), Clinical Pharmacology (12.3)]*.

8.7 Hepatic Impairment

Reduce the maximum recommended dosage in patients with moderate to severe hepatic impairment (Child-Pugh score ≥7). Patients with moderate to severe hepatic impairment (Child-Pugh score ≥7) generally had higher exposure to brexpiprazole than patients with normal hepatic function *[see Clinical Pharmacology (12.3)]*. Greater exposure may increase the risk of REXULTI-associated adverse reactions *[see Dosage and Administration (2.3)]*.

8.8 Renal Impairment

Reduce the maximum recommended dosage in patients with moderate, severe, or end-stage renal impairment (CrCl<60 mL/minute). Patients with impaired renal function (CrCl<60 mL/minute) had higher exposure to brexpiprazole than patients with normal renal function *[see Clinical Pharmacology (12.3)]*. Greater exposure may increase the risk of REXULTI-associated adverse reactions *[see Dosage and Administration (2.4)]*.

8.9 Other Specific Populations

No dosage adjustment for REXULTI is required on the basis of a patient's sex, race, or smoking status *[see Clinical Pharmacology (12.3)]*.

9 DRUG ABUSE AND DEPENDENCE

9.1 Controlled Substance

REXULTI is not a controlled substance.

9.2 Abuse

Animals given access to REXULTI did not self-administer the drug, suggesting that REXULTI does not have rewarding properties.

9.3 Dependence

Humans and animals that received chronic REXULTI administration did not demonstrate any withdrawal signs upon drug discontinuation. This suggests that REXULTI does not produce physical dependence.

10 OVERDOSAGE

There is limited clinical trial experience regarding human overdosage with REXULTI.

Consult a Certified Poison Control Center (**1-800-222-1222** or **www.poison.org**) for up-to-date guidance and advice regarding a REXULTI overdosage. Management of overdose should concentrate on supportive therapy, maintaining an adequate airway, oxygenation and ventilation, and management of symptoms. Close medical supervision and monitoring should continue until the patient recovers.

Charcoal

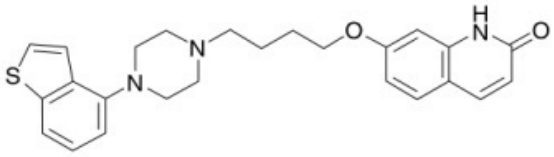
Oral activated charcoal and sorbitol (50 g/240 mL), administered one hour after ingesting oral brexpiprazole, decreased brexpiprazole C_{max} and area under the curve (AUC) by approximately 5% to 23% and 31% to 39% respectively; however, there is insufficient information available on the therapeutic potential of activated charcoal in treating an overdose with REXULTI.

Hemodialysis

There is no information on the effect of hemodialysis in treating an overdose with REXULTI; hemodialysis is unlikely to be useful because brexpiprazole is highly bound to plasma proteins.

11 DESCRIPTION

Brexpiprazole, an atypical antipsychotic, is available as REXULTI® (brexpiprazole) tablets. Brexpiprazole is 7-{4-[4-(1-Benzothiophen-4-yl)piperazin-1-yl]butoxy}quinolin-2(1*H*)-one. The empirical formula is $C_{25}H_{27}N_3O_2S$, and its molecular weight is 433.57. The chemical structure is:



REXULTI tablets are for oral administration and are available in 0.25 mg, 0.5 mg, 1 mg, 2 mg, 3 mg, and 4 mg strengths. Inactive ingredients include lactose monohydrate, corn starch, microcrystalline cellulose, hydroxypropyl cellulose, low-substituted hydroxypropyl cellulose, magnesium stearate, hypromellose, and talc. Colorants include titanium dioxide, iron oxide, and ferrosoferric oxide.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

The mechanism of action of brexpiprazole in the treatment of major depressive disorder or schizophrenia is unknown. However, the efficacy of brexpiprazole 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.

12.2 Pharmacodynamics

Brexpiprazole has affinity (expressed as K_i) for multiple monoaminergic receptors including 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), and noradrenergic α_{1A} (3.8 nM), α_{1B} (0.17 nM), α_{1D} (2.6 nM), and α_{2C} (0.59 nM) receptors. Brexpiprazole acts as a partial agonist at the 5-HT_{1A}, D_2, and D_3 receptors and as an antagonist at 5-HT_{2A}, 5-HT_{2B}, 5-HT_7, α_{1A}, α_{1B}, α_{1D}, and α_{2C} receptors. Brexpiprazole also exhibits affinity for histamine H_1 receptor (19 nM) and for muscarinic M_1 receptor (67% inhibition at 10 µM).

Cardiac Electrophysiology

At a dose 3 times the MRHD for the treatment of schizophrenia and 4 times the MRHD for adjunctive therapy to antidepressants for the treatment of MDD, REXULTI does not prolong the QTc interval to any clinically relevant extent.

12.3 Pharmacokinetics

Absorption

After single-dose administration of REXULTI tablets, the peak plasma brexpiprazole concentrations occurred within 4 hours after administration, and the absolute oral bioavailability was 95%. Brexpiprazole steady-state concentrations were attained within 10 to 12 days of dosing.

REXULTI can be administered with or without food. Administration of a 4 mg REXULTI tablet with a standard high-fat meal did not significantly affect the C_{max} or AUC of brexpiprazole. After single and multiple once daily dose administration, brexpiprazole exposure (C_{max} and AUC) increased in proportion to the dose administered. *In vitro* studies of brexpiprazole did not indicate that brexpiprazole is a substrate of efflux transporters such as MDRI (P-gp) and BCRP.

Distribution

The volume of distribution of brexpiprazole following intravenous administration is high (1.56 ± 0.42 L/kg), indicating extravascular distribution. Brexpiprazole is highly protein bound in plasma (greater than 99%) to serum albumin and α1-acid glycoprotein, and its protein binding is not affected by renal or hepatic impairment. Based on results of *in vitro* studies, brexpiprazole protein binding is not affected by warfarin, diazepam, or digitoxin.

Elimination

Metabolism

Based on *in vitro* metabolism studies of brexpiprazole using recombinant human cytochrome P450 (CYP1A1, 1A2, 2A6, 2B6, 2C8, 2C9, 2C19, 2D6, 2E1, and 3A4), the metabolism of brexpiprazole was shown to be mainly mediated by CYP3A4 and CYP2D6.

In vivo brexpiprazole is metabolized primarily by CYP3A4 and CYP2D6 enzymes. After single- and multiple-dose administrations, brexpiprazole and its major metabolite, DM-3411, were the predominant drug moieties

in the systemic circulation. At steady-state, DM-3411 represented 23% to 48% of brexpiprazole exposure (AUC) in plasma. DM-3411 is considered not to contribute to the therapeutic effects of brexpiprazole.

Based on *in vitro* data, brexpiprazole showed little to no inhibition of CYP450 isozymes.

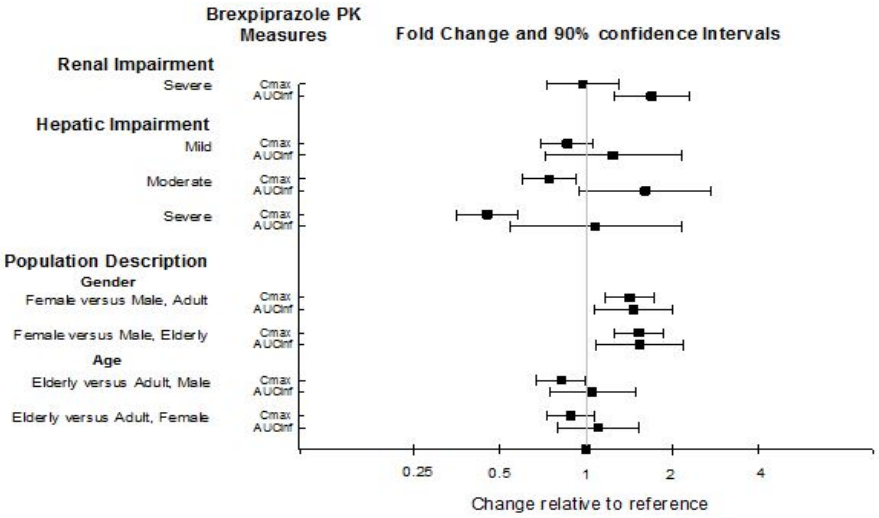
Excretion

Following a single oral dose of [^{14}C]-labeled brexpiprazole, approximately 25% and 46% of the administered radioactivity was recovered in the urine and feces, respectively. Less than 1% of unchanged brexpiprazole was excreted in the urine, and approximately 14% of the oral dose was recovered unchanged in the feces. Apparent oral clearance of a brexpiprazole oral tablet after once daily administration is 19.8 (±11.4) mL/h/kg. After multiple once-daily administrations of REXULTI, the terminal elimination half-lives of brexpiprazole and its major metabolite, DM-3411, were 91 hours and 86 hours, respectively.

Studies in Specific Populations

Exposure of brexpiprazole in specific populations are summarized in Figure 1. Population pharmacokinetic (PK) analysis indicated exposure of brexpiprazole in patients with moderate renal impairment was higher compared to patients with normal renal function.

Figure 1 Effect of Intrinsic Factors on Brexpiprazole Pharmacokinetics



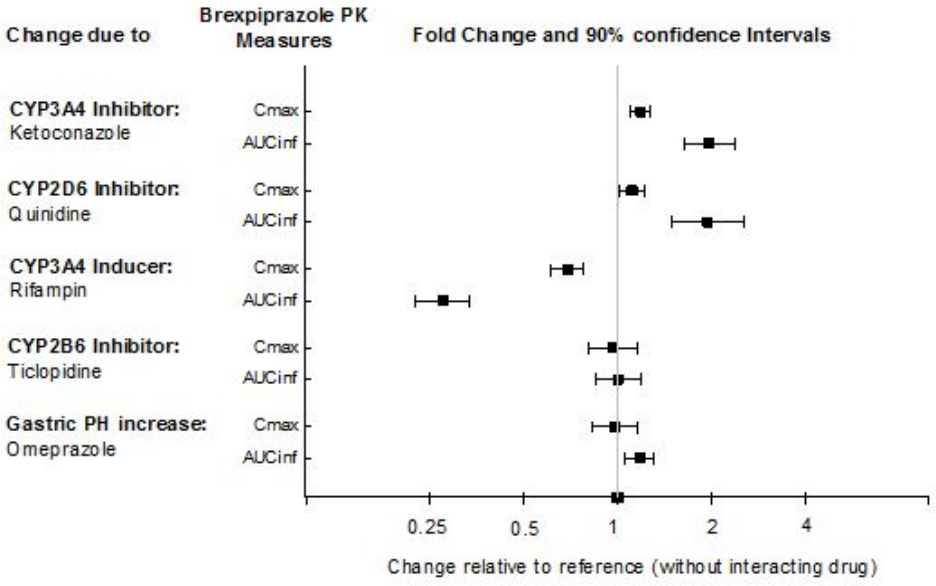
Pediatric Patients

A multiple dose PK study (0.5, 1, 2, 3 or 4 mg/day) has been conducted in 43 pediatric patients aged 13 years to 17 years old. Population PK analysis indicated systemic exposure (C_{max} and AUC) of brexpiprazole in pediatric patients (13 to 17 years of age) was comparable to that in adult patients across the dose range from 0.5 to 4 mg.

Drug Interaction Studies

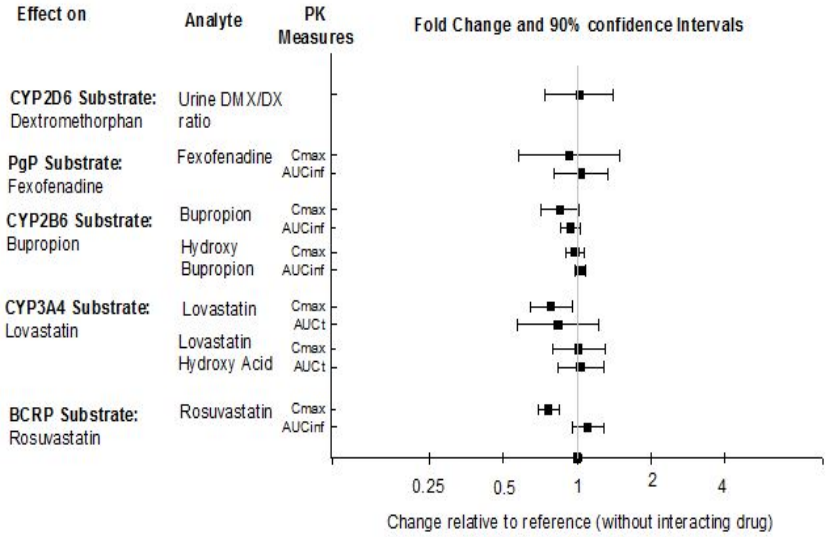
Effect of other drugs on the exposures of brexpiprazole are summarized in Figure 2. Based on simulation, a 5.1-fold increase in AUC values at steady-state is expected when extensive metabolizers of CYP2D6 are administered with both strong CYP2D6 and CYP3A4 inhibitors. A 4.8-fold increase in mean AUC values at steady-state is expected in poor metabolizers of CYP2D6 administered with strong CYP3A4 inhibitors *[see Drug Interactions (7.1)]*.

Figure 2 The Effect of Other Drugs on Brexpiprazole Pharmacokinetics



The effect of REXULTI on the exposures of other drugs are summarized in Figure 3.

Figure 3 The Effect of REXULTI on Pharmacokinetics of Other Drugs



13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenesis

Lifetime carcinogenicity studies were conducted in ICR mice and Sprague Dawley rats. Brexpiprazole was administered orally for two years to male and female mice at doses of 0.75, 2, and 5 mg/kg/day (0.9 to 6.1 times the oral MRHD of 4 mg/day based on mg/m^2 body surface area) and to male and female rats at doses of 1, 3, and 10 mg/kg and 3, 10, and 30 mg/kg/day, respectively (2.4 to 24 and 7.3 to 73 times the oral MRHD, males and females). In female mice, the incidence of mammary gland adenocarcinoma was increased at all doses, and the incidence of adenosquamous carcinoma was increased at 2.4 and 6.1 times

the MRHD. No increase in the incidence of tumors was observed in male mice. In the rat study, brexpiprazole was not carcinogenic in either sex at doses up to 73 times the MRHD.

Proliferative and/or neoplastic changes in the mammary and pituitary glands of rodents have been observed following chronic administration of antipsychotic drugs and are considered to be prolactin mediated. The potential for increasing serum prolactin level of brexpiprazole was shown in both mice and rats. The relevance for human risk of the findings of prolactin-mediated endocrine tumors in rodents is unknown.

Mutagenesis

Brexpiprazole was not mutagenic when tested in the *in vitro* bacterial reverse mutation assay (Ames test). Brexpiprazole was negative for clastogenic activity in the *in vivo* micronucleus assay in rats and was not genotoxic in the *in vivo/in vitro* unscheduled DNA synthesis assay in rats. *In vitro* with mammalian cells brexpiprazole was clastogenic but only at doses that induced cytotoxicity. Based on a weight of evidence, brexpiprazole is not considered to present a genotoxic risk to humans.

Impairment of Fertility

Female rats were treated with oral doses of 0.3, 3, or 30 mg/kg/day (0.7, 7.3, and 73 times the oral MRHD on a mg/m^2 basis) prior to mating with untreated males and continuing through conception and implantation. Estrus cycle irregularities and decreased fertility were observed at 3 and 30 mg/kg/day. Prolonged duration of pairing and increased preimplantation losses were observed at 30 mg/kg/day.

Male rats were treated with oral doses of 3, 10, or 100 mg/kg/day (7.3, 24, and 240 times the oral MRHD on a mg/m^2 basis) for 63 days prior to mating with untreated females and throughout the 14 days of mating. No differences were observed in the duration of mating or fertility indices in males at any dose of brexpiprazole.

14 CLINICAL STUDIES

14.1 Adjunctive Treatment of Major Depressive Disorder

The efficacy of REXULTI in the adjunctive treatment of major depressive disorder (MDD) was evaluated in two 6-week double-blind, placebo-controlled, fixed-dose trials of adult patients meeting DSM-IV-TR criteria for MDD, with or without symptoms of anxiety, who had an inadequate response to prior antidepressant therapy (1 to 3 courses) in the current episode and who had also demonstrated an inadequate response throughout the 8 weeks of prospective antidepressant treatment (with escitalopram, fluoxetine, paroxetine controlled-release, sertraline, duloxetine delayed release, or venlafaxine extended release). Inadequate response during the prospective antidepressant treatment phase was defined as having persistent symptoms without substantial improvement throughout the course of treatment.

Patients in Study 228 (hereafter “Study 1”) were randomized to REXULTI 2 mg once a day or placebo. Patients in Study 227 (hereafter “Study 2”) were randomized to REXULTI 1 or 3 mg once a day or placebo. For patients randomized to REXULTI, all patients initiated treatment at 0.5 mg once daily during Week 1. At Week 2, the REXULTI dosage was increased to 1 mg in all treatment groups, and either maintained at 1 mg or increased to 2 mg or 3 mg once daily, based on treatment assignment, from Week 3 onwards. The dosages were then maintained for the 4 remaining weeks.

The primary endpoint was change from baseline to Week 6 in the Montgomery-Asberg Depression Rating Scale (MADRS), a 10-item clinician-related scale used to assess the degree of depressive symptomatology, with 0 representing no symptoms and 60 representing worst symptoms.

At randomization, the mean MADRS total score was 27. In Studies 1 and 2, REXULTI (plus ADT) 2 mg/day and 3 mg/day were superior to placebo plus ADT in reducing mean MADRS total scores. Results from the

primary efficacy parameters for both fixed dose trials are shown below in Table 10. Figure 4 below shows the time course of response based on the primary efficacy measure (MADRS) in Study 1.

Table 10 Summary of Efficacy Results for Studies 1 and 2 for the Adjunctive Treatment of MDD in Adults

Study	Treatment Group	N	Primary Efficacy Measure: MADRS		
			Mean Baseline Score (SD)	LS Mean Change from Baseline (SE)	Placebo-subtracted Difference[a] (95% CI)
1	REXULTI (2 mg/day) + ADT*	175	26.9 (5.7)	-8.4 (0.6)	-3.2 (-4.9, -1.5)
	Placebo + ADT	178	27.3 (5.6)	-5.2 (0.6)	--
2	REXULTI (1 mg/day) + ADT	211	26.5 (5.6)	-7.6 (0.5)	-1.3 (-2.7, 0.1)
	REXULTI (3 mg/day) + ADT	213	26.5 (5.3)	-8.3 (0.5)	-2.0 (-3.4, -0.5)
	Placebo + ADT	203	26.5 (5.2)	-6.3 (0.5)	--

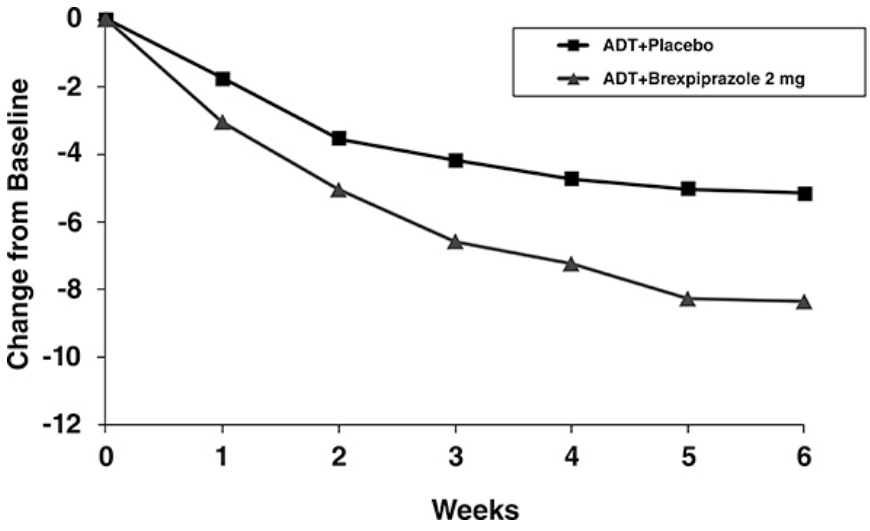
SD: standard deviation; SE: standard error; LS Mean: least-squares mean; CI: unadjusted confidence interval

*Dosages statistically significantly superior to placebo

[a]Difference (drug minus placebo) in least-squares mean change from baseline

An examination of population subgroups did not suggest differential response based on age, gender, race, or choice of prospective antidepressant.

Figure 4 Change from Baseline in MADRS Total Score by Study Visit (Week) in Patients with MDD in Adults (Study 1)



14.2 Schizophrenia

The efficacy of REXULTI in the treatment of adults with schizophrenia was demonstrated in two 6-week randomized, double-blind, placebo-controlled, fixed-dose clinical trials in patients who met DSM-IV-TR criteria for schizophrenia.

In both studies, Study 231 (hereafter “Study 3”) and Study 230 (hereafter “Study 4”), patients were randomized to REXULTI 2 or 4 mg once per day or placebo. Patients in the REXULTI groups initiated treatment at 1 mg once daily on Days 1 to 4. The REXULTI dosage was increased to 2 mg on Days 5 to 7.

The dosage was then either maintained at 2 mg once daily or increased to 4 mg once daily, depending on treatment assignment, for the 5 remaining weeks.

The primary efficacy endpoint of both trials was the change from baseline to Week 6 in the Positive and Negative Syndrome Scale (PANSS) total score. The PANSS is a 30-item scale that measures positive symptoms of schizophrenia (7 items), negative symptoms of schizophrenia (7 items), and general psychopathology (16 items), each rated on a scale of 1 (absent) to 7 (extreme); the total PANSS scores range from 30 (best) to 210 (worst).

In Study 3, REXULTI at both 2 mg/day and 4 mg/day was superior to placebo on the PANSS total score. In Study 4, REXULTI 4 mg/day was superior to placebo on the PANSS total score (Table 11). Figure 5 shows the time course of response based on the primary efficacy measure (change from baseline in PANSS total score) in Study 3.

Examination of population subgroups based on age, gender, and race did not suggest differential responsiveness.

Table 11 Summary of Efficacy Results for Studies of Schizophrenia in Adults (Studies 3 and 4)

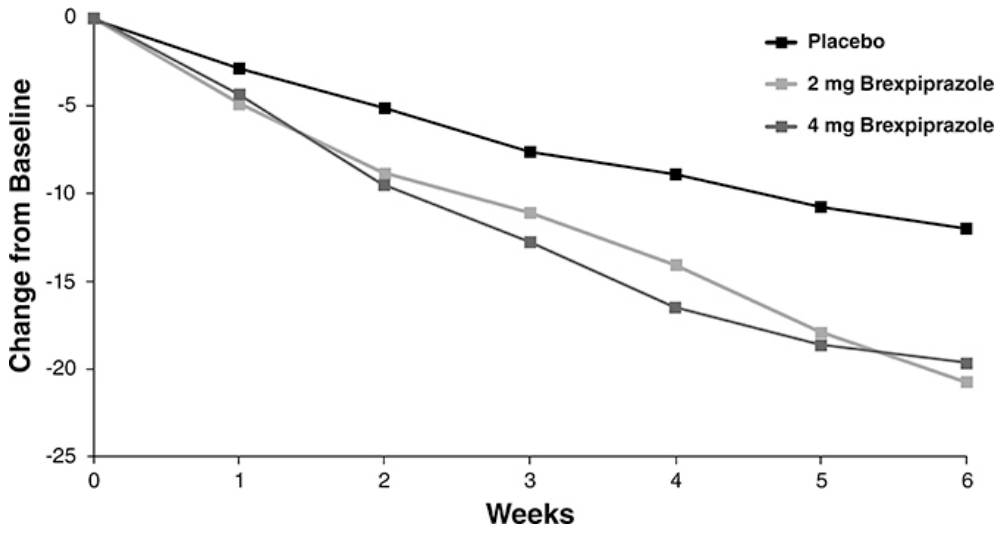
Study	Treatment Group	N	Primary Efficacy Measure: PANSS		
			Mean Baseline Score (SD)	LS Mean Change from Baseline (SE)	Placebo-subtracted Difference[a] (95% CI)
3	REXULTI (2 mg/day)*	180	95.9 (13.8)	-20.7 (1.5)	-8.7 (-13.1, -4.4)
	REXULTI (4 mg/day)*	178	94.7 (12.1)	-19.7 (1.5)	-7.6 (-12.0, -3.1)
	Placebo	178	95.7 (11.5)	-12.0 (1.6)	--
4	REXULTI (2 mg/day)	179	96.3 (12.9)	-16.6 (1.5)	-3.1 (-7.2, 1.1)
	REXULTI (4 mg/day)*	181	95.0 (12.4)	-20.0 (1.5)	-6.5 (-10.6, -2.4)
	Placebo	180	94.6 (12.8)	-13.5 (1.5)	--

SD: standard deviation; SE: standard error; LS Mean: least-squares mean; CI: unadjusted confidence interval

* Dosages statistically significantly superior to placebo

[a]Difference (drug minus placebo) in least-squares mean change from baseline

Figure 5 Change from Baseline in PANSS Total Score by Study Visit (Week) in Adult Patients with Schizophrenia (Study 3)

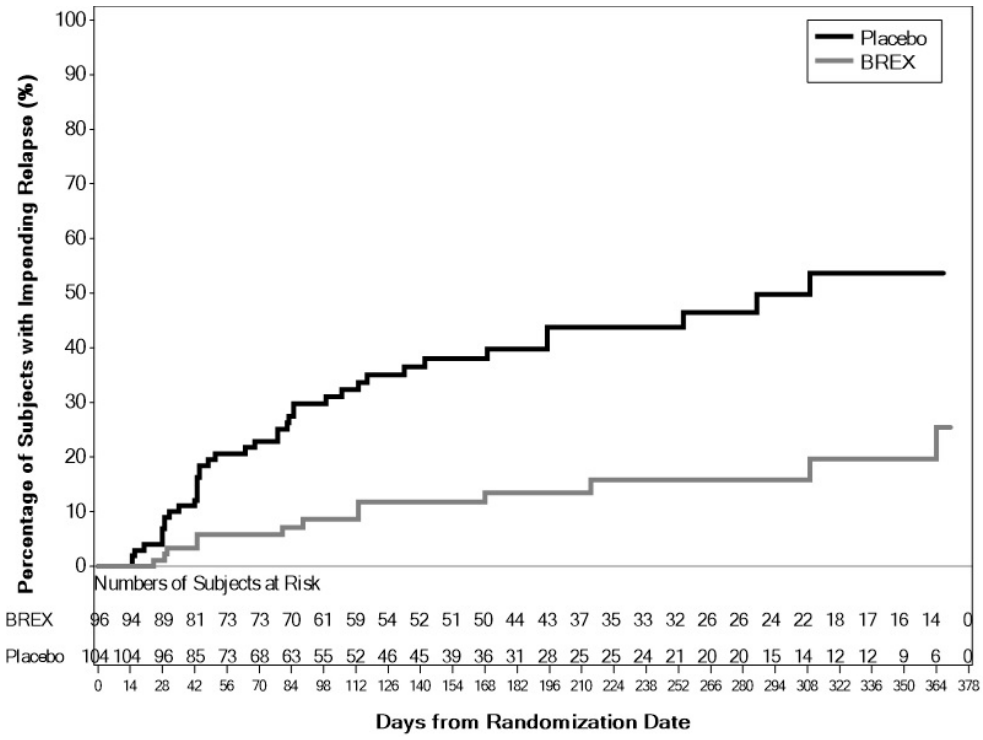


The safety and efficacy of REXULTI as maintenance treatment in adults with schizophrenia aged 18 to 65 years were demonstrated in the maintenance phase of a randomized withdrawal trial (Study 331-10-232, hereafter “Study 5”). Patients were stabilized for at least 12 weeks on 1 to 4 mg/day of REXULTI (N=202). They were then randomized in the double-blind treatment phase to either continue REXULTI at their achieved stable dose (N=97), or to switch to placebo (N=105).

The primary endpoint in Study 5 was time from randomization to impending relapse during the double-blind phase, defined as: 1) Clinical Global Improvement score of ≥5 (minimally worse) and an increase to a score > 4 on PANSS conceptual disorganization, hallucinatory behavior, suspiciousness, or unusual thought content items, with either a ≥2 increase on a specific item or ≥4 point increase on the combined four PANSS items, 2) hospitalization due to worsening of psychotic symptoms, 3) current suicidal behavior, or 4) violent/aggressive behavior.

A pre-specified interim analysis demonstrated a statistically significantly longer time to relapse in patients randomized to the REXULTI group compared to placebo-treated patients. The trial was subsequently terminated early because maintenance of efficacy had been demonstrated. The Kaplan-Meier curves of the cumulative proportion of patients with relapse during the double-blind treatment phase for REXULTI and placebo groups are shown in Figure 6. The key secondary endpoint, the proportion of patients who met the criteria for impending relapse, was statistically significantly lower in REXULTI-treated patients compared with placebo group.

Figure 6 Kaplan-Meier Estimation of Percent Impending Relapse in Study 5



Note: A total of 202 patients were randomized. Among them, one placebo patient did not take investigational medicinal product and one brexpiprazole patient did not have post-randomization efficacy evaluations. These two patients were excluded from the efficacy analysis.

16 HOW SUPPLIED/STORAGE AND HANDLING

16.1 How Supplied

REXULTI (brexpiprazole) tablets have markings on one side and are available in the following strengths and package configurations (see below):

- 0.25 mg tablets are light brown, round, shallow convex, bevel-edged body with “BRX” and “0.25” imprinted on one side

  NDC 59148-035-13 Bottles of 30
- 0.5 mg tablets: are light orange, round, shallow convex, bevel-edged body with “BRX” and “0.5” imprinted on one side

  NDC 59148-036-13 Bottles of 30
- 1 mg tablets are light yellow, round, shallow convex, bevel-edged body with “BRX” and “1” imprinted on one side

  NDC 59148-037-13 Bottles of 30
- 2 mg tablets are light green, round, shallow convex, bevel-edged body with “BRX” and “2” imprinted on one side

  NDC 59148-038-13 Bottles of 30
- 3 mg tablets are light purple, round, shallow convex, bevel-edged body with “BRX” and “3” imprinted on one side

  NDC 59148-039-13 Bottles of 30
- 4 mg tablets are white, round, shallow convex, bevel-edged body with “BRX” and “4” imprinted on one side

  NDC 59148-040-13 Bottles of 30

16.2 Storage

Store REXULTI tablets at 20°C to 25°C (68°F to 77°F); excursions permitted to 15°C to 30°C (59°F to 86°F) [see USP Controlled Room Temperature].

17 PATIENT COUNSELING INFORMATION

Advise the patient or caregiver to read the FDA-approved patient labeling (Medication Guide).

Suicidal Thoughts and Behaviors

Advise patients and caregivers to look for the emergence of suicidality, especially early during treatment and when the dosage is adjusted up or down, and instruct them to report such symptoms to the healthcare provider *[see Boxed Warning, Warnings and Precautions (5.2)]*.

Dosage and Administration

Advise patients that REXULTI can be taken with or without food. Advise patients regarding importance of following dosage escalation instructions *[see Dosage and Administration (2.1), (2.2)]*.

Neuroleptic Malignant Syndrome (NMS)

Counsel patients about a potentially fatal adverse reaction - neuroleptic malignant syndrome (NMS) - that has been reported in association with administration of antipsychotic drugs. Advise patients to contact a

healthcare provider or report to the emergency room if they experience signs or symptoms of NMS *[see Warnings and Precautions (5.4)]*.

Tardive Dyskinesia

Counsel patients on the signs and symptoms of tardive dyskinesia and to contact their healthcare provider if these abnormal movements occur *[see Warnings and Precautions (5.5)]*.

Metabolic Changes

Educate patients about the risk of metabolic changes, how to recognize symptoms of hyperglycemia and diabetes mellitus, and the need for specific monitoring, including blood glucose, lipids, and weight *[see Warnings and Precautions (5.6)]*.

Pathological Gambling and Other Compulsive Behaviors

Advise patients and their caregivers of the possibility that they may experience compulsive urges to shop, intense urges to gamble, compulsive sexual urges, binge eating and/or other compulsive urges and the inability to control these urges while taking REXULTI. In some cases, but not all, the urges were reported to have stopped when the dose was reduced or stopped *[see Warnings and Precautions (5.7)]*.

Leukopenia, Neutropenia and Agranulocytosis

Advise patients with a pre-existing low WBC or a history of drug-induced leukopenia/neutropenia that they should have their CBC monitored while taking REXULTI *[see Warnings and Precautions (5.8)]*.

Orthostatic Hypotension and Syncope

Educate patients about the risk of orthostatic hypotension and syncope, especially early in treatment, and also at times of reinitiating treatment or increases in dosage *[see Warnings and Precautions (5.9)]*.

Heat Exposure and Dehydration

Counsel patients regarding appropriate care in avoiding overheating and dehydration *[see Warnings and Precautions (5.12)]*.

Interference with Cognitive and Motor Performance

Caution patients about performing activities requiring mental alertness, such as operating hazardous machinery or operating a motor vehicle, until they are reasonably certain that REXULTI therapy does not adversely affect their ability to engage in such activities *[see Warnings and Precautions (5.14)]*.

Concomitant Medications

Advise patients to inform their healthcare providers of any changes to their current prescription or over-the-counter medications because there is a potential for clinically significant interactions *[see Drug Interactions (7.1)]*.

Pregnancy

Advise patients that third trimester use of REXULTI may cause extrapyramidal and/or withdrawal symptoms in a neonate and to notify their healthcare provider with a known or suspected pregnancy. Advise patients that there is a pregnancy exposure registry that monitors pregnancy outcomes in women exposed to REXULTI during pregnancy *[see Use in Specific Populations (8.1)]*.

Manufactured by Otsuka Pharmaceutical Co., Ltd., Tokyo 101-8535, Japan
Distributed and Marketed by Otsuka America Pharmaceutical, Inc., Rockville, MD 20850 USA

Marketed by Lundbeck, Deerfield, IL 60015 USA

MEDICATION GUIDE
REXULTI® (REX-ul-TE)
(brexpiprazole)
tablets

What is the most important information I should know about REXULTI?

REXULTI may cause serious side effects, including:

- **Increased risk of death in elderly people with dementia-related psychosis.** Medicines like REXULTI can raise the risk of death in elderly people who have lost touch with reality (psychosis) due to confusion and memory loss (dementia). REXULTI is not approved for the treatment of people with dementia-related psychosis.
- **Increased risk of suicidal thoughts and actions.** Antidepressant medicines may increase suicidal thoughts and actions in some children, adolescents, and young adults **especially within the first few months of treatment or when the dose is changed.**
  - Depression and other mental illnesses are the most important causes of suicidal thoughts and actions.

  How can I watch for and try to prevent suicidal thoughts and actions in myself or a family member?
  - Pay close attention to any changes, especially sudden changes in mood, behaviors, thoughts, or feelings. This is very important when REXULITI or the antidepressant medicine is started or when the dose is changed.
  - Call your healthcare provider right away to report new or sudden changes in mood, behavior, thoughts, or feelings, or if you develop suicidal thoughts or actions.
  - Keep all follow-up visits with your healthcare provider as scheduled. Call your healthcare provider between visits as needed, especially if you have concerns about symptoms.

  Call a healthcare provider right away if you or your family member have any of the following symptoms, especially if they are new, worse, or worry you:
  - thoughts about suicide or dying
  - new or worsening depression
  - feeling very agitated or restless
  - trouble sleeping (insomnia)
  - acting aggressive, being angry, or violent
  - an extreme increase in activity or talking (mania)
  - attempts to commit suicide
  - new or worsening anxiety
  - panic attacks
  - new or worsening irritability
  - acting on dangerous impulses
  - other unusual changes in behavior or mood

What is REXULTI?

REXULTI is a prescription medicine used:

- with other antidepressant medicines to treat major depressive disorder (MDD) in adults.
- to treat schizophrenia in adults and children ages 13 years and older.

It is not known if REXULTI is safe and effective in children with MDD.

It is not known if REXULTI is safe and effective in children under 13 years of age with schizophrenia.

Do not take REXULTI if you are allergic to brexpiprazole or any of the ingredients in REXULTI. See the end of this Medication Guide for a complete list of ingredients in REXULTI.

Before taking REXULTI, tell your healthcare provider about all of your medical conditions, including if you:

- have or have had heart problems or a stroke
- have or have had low or high blood pressure
- have or have had diabetes or high blood sugar or a family history of diabetes or high blood sugar. Your healthcare provider should check your blood sugar before you start REXULTI and during treatment with REXULTI.
- have of have had high levels of total cholesterol, LDL cholesterol, or triglycerides, or low levels of HDL cholesterol
- have or have had seizures (convulsions)
- have or have had kidney or liver problems
- have or have had a low white blood cell count
- are pregnant or plan to become pregnant. REXULTI may harm your unborn baby. Taking REXULTI during your third trimester of pregnancy may cause your baby to have abnormal muscle movements or withdrawal symptoms after birth.
  - Tell your healthcare provider if you become pregnant or think you are pregnant during treatment with REXULTI.
  - If you become pregnant during treatment with REXULTI, talk to your healthcare provider about registering with the National Pregnancy Registry for Atypical Antipsychotics. You can register by calling 1-866-961-2388 or visit http://womensmentalhealth.org/clinical-and-research-programs/pregnancyregistry/.

- are breastfeeding or plan to breastfeed. It is not known if REXULTI passes into your breast milk. Talk to your healthcare provider about the best way to feed your baby during treatment with REXULTI.

Tell your healthcare provider about all the medicines you take, including prescription and over-the-counter medicines, vitamins, and herbal supplements.

REXULTI and other medicines may affect each other causing possible serious side effects. REXULTI may affect the way other medicines work, and other medicines may affect how REXULTI works.

Your healthcare provider can tell you if it is safe to take REXULTI with your other medicines. Do not start or stop any medicines during treatment with REXULTI without first talking to your healthcare provider.

Know the medicines you take. Keep a list of them to show your healthcare provider and pharmacist when you get a new medicine.

How should I take REXULTI?

- Take REXULTI exactly as your healthcare provider tells you to take it. Your healthcare provider may change your dose if needed. Do not change the dose or stop taking REXULTI without first talking to your healthcare provider.
- Take REXULTI 1 time each day with or without food.
- If you take too much REXULTI, call your healthcare provider or a certified Poison Control Center at 1-800-222-1222 or go to www.poison.org, or go to the nearest hospital emergency room right away.

What should I avoid while taking REXULTI?

- Do not drive a car, operate machinery, or do other dangerous activities until you know how REXULTI affects you. REXULTI may make you feel drowsy.
- Do not become too hot or dehydrated during treatment with REXULTI.
  - Do not exercise too much.
  - In hot weather, stay inside in a cool place if possible.
  - Stay out of the sun.
  - Do not wear too much clothing or heavy clothing.
  - Drink plenty of water.

What are the possible side effects of REXULTI?

REXULTI may cause serious side effects, including:

- **See "What is the most important information I should know about REXULTI?"**
- **Stroke (cerebrovascular problems) in elderly people with dementia-related psychosis that can lead to death.**
- **Neuroleptic malignant syndrome (NMS) is a serious condition that can lead to death.** Call your healthcare provider or go to the nearest hospital emergency room right away if you have some or all of the following signs and symptoms of NMS:
  - high fever
  - changes in your breathing, heart rate, and blood pressure
  - stiff muscles
  - confusion
  - increased sweating
- **Uncontrolled body movements (tardive dyskinesia).** REXULTI may cause movements that you cannot control in your face, tongue, or other body parts. Tardive dyskinesia may not go away, even if you stop taking REXULTI. Tardive dyskinesia may also start after you stop taking REXULTI.
- **Problems with your metabolism such as:**
  - **high blood sugar (hyperglycemia) and diabetes.** Increases in blood sugar can happen in some people who take REXULTI. Extremely high blood sugar can lead to coma or death. Your healthcare provider should check your blood sugar before you start, or soon after you start REXULTI and then regularly during long term treatment with REXULTI.

    Call your healthcare provider if you have any of these symptoms of high blood sugar during treatment with REXULTI:
    - feel very thirsty
    - feel very hungry
    - feel sick to your stomach
    - need to urinate more than usual
    - feel weak or tired
    - feel confused, or your breath smells fruity
  - **increased fat levels (cholesterol and triglycerides) in your blood.** Your healthcare provider should check the fat levels in your blood before you start, or soon after you start REXULTI, and then periodically during treatment with REXULTI.
  - **weight gain.** You and your healthcare provider should check your weight before you start and often during treatment with REXULTI.

- **Unusual and uncontrollable (compulsive) urges.** Some people taking REXULTI have had strong unusual urges, to gamble and gambling that cannot be controlled (compulsive gambling). Other compulsive urges include sexual urges, shopping, and eating or binge eating. If you or your family members notice that you are having unusual strong urges, talk to your healthcare provider.
- **Low white blood cell count.** Your healthcare provider may do blood tests during the first few months of treatment with REXULTI.
- **Decreased blood pressure (orthostatic hypotension).** You may feel lightheaded or faint when you rise too quickly from a sitting or lying position.
- **Falls.** REXULTI may make you sleepy or dizzy, may cause a decrease in your blood pressure when changing position (orthostatic hypotension), and can slow your thinking and motor skills which may lead to falls that can cause fractures or other injuries.
- **Seizures (convulsions).**
- **Problems controlling your body temperature so that you feel too warm.** See **"What should I avoid while taking REXULTI?"**
- **Difficulty swallowing** that can cause food or liquid to get into your lungs.
- **Sleepiness, drowsiness, feeling tired, difficulty thinking and doing normal activities.** See "What should I avoid while taking REXULTI?"

The most common side effects of REXULTI include weight gain and restlessness or feeling like you need to move (akathisia).

These are not all the possible side effects of REXULTI.

Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

How should I store REXULTI?

- Store REXULTI at room temperature between 68°F to 77°F (20°C to 25°C).

Keep REXULTI and all medicines out of the reach of children.

General information about the safe and effective use of REXULTI.

Medicines are sometimes prescribed for purposes other than those listed in a Medication Guide. Do not use REXULTI for a condition for which it was not prescribed. Do not give REXULTI to other people, even if they have the same symptoms you have. It may harm them. You can ask your pharmacist or healthcare provider for information about REXULTI that is written for healthcare professionals.

What are the ingredients in REXULTI?

Active ingredient: brexpiprazole

Inactive ingredients: corn starch, ferrosoferric oxide, hydroxypropyl cellulose, hypromellose, iron oxide, lactose monohydrate, low-substituted hydroxypropyl cellulose, magnesium stearate, microcrystalline cellulose, talc, titanium dioxide

Manufactured by Otsuka Pharmaceutical Co., Ltd., Tokyo 101-8535, Japan
Distributed and Marketed by Otsuka America Pharmaceutical, Inc., Rockville, MD 20850 USA
Marketed by Lundbeck, Deerfield, IL 60015 USA

For more information about REXULTI, go to www.REXULTI.com or call 1-800-441-6763.

This Medication Guide has been approved by the U.S. Food and Drug Administration. Revised 12/2021