Brand Name	Rexulti
Active Ingredient(s)	brexpiprazole
Strength	0.25 mg 0.5 mg 1 mg 2 mg 3 mg 4 mg
Dosage Form	tablet
Inactive Ingredients	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.
NDC	59148-035-13 59148-036-13 59148-037-13 59148-038-13 59148-039-13 59148-040-13
DIN	02461749 02461757 02461765 02461773 02461781 02461803
Canadian Distributor	Otsuka Pharmaceutical Co., Ltd 2-9 Kanda-Tsukasamachi, Chiyoda-Ku Tokyo 101-8535 Japan
NDA Number	NDA205422
US Distributor (NDA Holder)	Otsuka America Pharmaceutical, Inc. 150 Saunders Road; Lake Forest, Illinois 60045 USA
Manufacturer (Final Packager)	Otsuka Pharmaceutical Co., Ltd 2-9, Kanda-Tsukasamachi, Chiyoda-ku, Tokyo 101-8535, Japan
API Manufacturer	Not available
Relationship to Sponsor	The Sponsor may have or have had agreements with the U.S. manufacturer for rebates. The Sponsor has no relationship with the foreign manufacturer.

Current FDA-approved Package Insert

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 without agitation associated with dementia due to Alzheimer's disease. (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	5/2023
Indications and Usage (1)	5/2023
Dosage and Administration (2.1, 2.3, 2.4, 2.5, 2.6)	5/2023
Warnings and Precautions (5.1, 5.3, 5.4, 5.6, 5.9, 5.14)	5/2023

----------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)
- Treatment of agitation associated with dementia due to Alzheimer's disease (1, 14.3)

  Limitations of Use: REXULTI is not indicated as an as needed ("prn") treatment for agitation associated with dementia due to Alzheimer's disease (1)

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

Administer REXULTI once daily with or without food. (2, 12.3)

Indication	Starting Dosage	Recommended Target Dosage	Maximum Dosage
MDD Adults (2.2)	0.5 mg/day or 1 mg/day	2 mg/day	3 mg/day
Schizophrenia Adults (2.3)	1 mg/day	2 to 4 mg/day	4 mg/day
Schizophrenia Pediatric (13 - 17 years) (2.3)	0.5 mg/day	2 to 4 mg/day	4 mg/day
Agitation associated with dementia due to Alzheimer's disease (2.4)	0.5 mg/day	2 mg/day	3 mg/day

- *Moderate to Severe Hepatic Impairment:* Maximum recommended dosage is 2 mg once daily for patients with MDD or agitation associated with dementia due to Alzheimer's disease and 3 mg once daily for patients with schizophrenia. (2.5)
- *CrCl<60 mL/minute:* Maximum recommended dosage is 2 mg once daily for patients with MDD or agitation associated with dementia due to Alzheimer's disease and 3 mg once daily for patients with schizophrenia. (2.6)
- See Full Prescribing Information for dosage modifications for CYP2D6 poor metabolizers and for concomitant use with CYP inhibitors or inducers. (2.7)

----------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, somnolence, and akathisia (≥5% and at least twice the rate for placebo)
- *Schizophrenia*: Weight increased (≥4% and at least twice the rate for placebo)
- *Agitation associated with dementia due to Alzheimer's disease:* Nasopharyngitis, dizziness (≥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 (2.7)
Strong CYP2D6* or CYP3A4 inhibitors	Administer half of recommended dosage.
Strong/moderate CYP2D6 with Strong/moderate CYP3A4 inhibitors	Administer a quarter of the recommended dosage.
Known CYP2D6 poor metabolizers taking strong/moderate CYP3A4 inhibitors	Administer a quarter of the recommended dosage.
Strong CYP3A4 inducers	Double the recommended dosage 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: 5/2023

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 without agitation associated with dementia due to Alzheimer's disease *[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
- 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 *[see Clinical Studies (14.3)]*.

2 DOSAGE AND ADMINISTRATION

2.1 Administration Information

Administer REXULTI orally, once daily with or without food *[see Clinical Pharmacology (12.3)]*

2.2 Recommended Dosage for Adjunctive Treatment of Major Depressive Disorder (Adults)

The recommended starting REXULTI dosage for the adjunctive treatment of MDD in adults is 0.5 mg or 1 mg once daily .Titrate to 1 mg once daily, then titrate to the target dosage of 2 mg once daily (based on the patient's clinical response and tolerability, increase the dosage at weekly intervals). The maximum recommended daily dosage is 3 mg. Periodically reassess to determine the continued need and appropriate dosage for treatment.

2.3 Recommended Dosage for Schizophrenia (Adults and Pediatric Patients 13 to 17 Years)

Adults

The recommended starting REXULTI dosage for the treatment of schizophrenia in adults is 1 mg once daily on Days 1 to 4. Titrate to 2 mg once daily on Day 5 through Day 7. On Day 8, the dosage can be increased to the maximum recommended daily dosage of 4 mg based on clinical response and tolerability. The recommended target dosage is 2 mg to 4 mg once daily.

Pediatric Patients (13 to 17 years of age)

The recommended starting REXULTI dosage for the treatment of schizophrenia in pediatric patients 13 to 17 years of age is 0.5 mg taken orally once daily on Days 1 to 4. On Days 5 through 7, titrate to 1 mg per day and on Day 8 titrate to 2 mg based on clinical response and tolerability. Weekly dose increases can be made in 1 mg increments. A recommended target dosage is 2 to 4 mg once daily. The maximum recommended daily dosage is 4 mg.

2.4 Recommended Dosage for Agitation Associated with Dementia Due to Alzheimer's Disease

The recommended starting REXULTI dosage for the treatment of agitation associated with dementia due to Alzheimer's disease is 0.5 mg taken once daily on Days 1 to 7. Increase the dosage on Days 8 through 14 to 1 mg once daily, and on Day 15 to 2 mg once daily. The recommended target dose is 2 mg once daily. The dosage can be increased to the maximum recommended daily dosage of 3 mg once daily after at least 14 days, based on clinical response and tolerability.

2.5 Recommended Dosage in Patients with Hepatic Impairment

The maximum recommended dosage in patients with moderate to severe hepatic impairment (Child-Pugh score ≥7) is *[see Use in Specific Populations (8.7), Clinical Pharmacology (12.3)]*.

- 2 mg once daily in patients with MDD or agitation associated with dementia due to Alzheimer's disease, and
- 3 mg orally once daily in patients with schizophrenia

2.6 Recommended Dosage in Patients with Renal Impairment

The maximum recommended dosage in patients with creatinine clearance CrCl<60 mL/minute is *[see Use in Specific Populations (8.8), Clinical Pharmacology (12.3)]*.

- 2 mg orally once daily in patients with MDD or agitation associated with dementia due to Alzheimer's disease and
- 3 mg orally once daily in patients with schizophrenia

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

Dosage modifications are recommended in patients who are known cytochrome P450 (CYP) 2D6 poor metabolizers and in patients taking concomitant CYP3A4 inhibitors, CYP2D6 inhibitors, or strong CYP3A4 inducers (see Table 1). If the concomitant drug is discontinued, adjust the REXULTI dosage to its original level. If the concomitant 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 Modifications of REXULTI for CYP2D6 Poor Metabolizers and for Concomitant Use with CYP3A4 Inhibitors, CYP2D6 Inhibitors, or CYP3A4 Inducers

Factors	Adjusted REXULTI Dosage
CYP2D6 Poor Metabolizers	
CYP2D6 poor metabolizers	Administer half of the recommended dosage.
Known CYP2D6 poor metabolizers taking strong/moderate	Administer a quarter of the recommended

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

Factors	Adjusted REXULTI Dosage
CYP3A4 inhibitors	dosage.
Patients Taking CYP2D6 Inhibitors and/or CYP3A4 Inhibitors	
Strong CYP2D6 inhibitors*	Administer half of the recommended dosage.
Strong CYP3A4 inhibitors	Administer half of the recommended dosage.
Strong/moderate CYP2D6 inhibitors with strong/moderate CYP3A4 inhibitors	Administer a quarter of the recommended dosage.
Patients Taking CYP3A4 Inducers	
Strong CYP3A4 inducers	Double the recommended dosage over 1 to 2 weeks.

*In the clinical studies examining the use of REXULTI for the adjunctive 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 the 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 without agitation associated with dementia due to Alzheimer's disease *[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 24 years of age 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 Table 2.

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 without agitation associated with dementia due to Alzheimer's disease *[see Boxed Warning, Warnings and Precautions (5.1)]*.

5.4 Neuroleptic Malignant Syndrome (NMS)

Neuroleptic Malignant Syndrome (NMS), a potentially fatal symptom complex, 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 (irregular pulse or blood pressure, tachycardia, diaphoresis and cardiac dysrhythmia). 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 impossible to predict which patients will 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 appear to increase as the duration of treatment and the cumulative dose increases. The syndrome can develop after relatively brief treatment periods, 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 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 occurrence of tardive dyskinesia. Chronic antipsychotic treatment should generally be reserved for patients who suffer from a chronic illness that 1) is known to respond to antipsychotic drugs and 2) for whom alternative, equally 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. The need for continued treatment should be reassessed periodically.

If signs and symptoms of tardive dyskinesia appear in a patient treated with 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 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. 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.

Adjunctive Treatment of Major Depressive Disorder: In the 6-week placebo-controlled, fixed-dose clinical studies 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 studies 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.

Schizophrenia 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.

Agitation Associated with Dementia Due to Alzheimer's Disease: In the 12-week placebo-controlled, fixed-dose studies in patients (51 to 90 years of age) with agitation associated with dementia due to Alzheimer's disease, the proportions of patients with shifts in fasting glucose from normal (<100 mg/dL) to high (≥126 mg/dL) or impaired (≥100 and <126 mg/dL) to high were similar in patients treated with REXULTI (14%) and patients treated with placebo (16%).

Of the patients who were previously treated with REXULTI for 12-weeks and continued into a 12-week, active-treatment extension study, 15% of patients with normal baseline fasting glucose experienced a shift from normal (<100 mg/dL) to high (≥126 mg/dL) fasting glucose while taking REXULTI; 30% of patients with impaired fasting glucose experienced shifts from impaired fasting glucose (≥100 and <126 mg/dL) to high fasting glucose. Combined, 20% of patients with normal or impaired fasting glucose experienced shifts to high fasting glucose.

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.

Adjunctive Treatment of Major Depressive Disorder: In the 6-week placebo-controlled, fixed-dose clinical studies 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 Studies

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 studies 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 Studies 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.

Schizophrenia [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).

Agitation Associated with Dementia Due to Alzheimer's Disease: In the 12-week placebo-controlled, fixed-dose clinical studies in patients (55 to 90 years of age) with agitation associated with dementia due to Alzheimer's disease, changes in total cholesterol, LDL cholesterol, and HDL cholesterol were similar in REXULTI- and placebo-treated patients.

Table 5 shows the proportions of patients with changes in fasting triglycerides in REXULTI- and placebo-treated patients.

Table 5 Change in Fasting Triglycerides in the 12-Week Placebo-Controlled, Fixed-Dose Agitation Associated with Dementia Due to Alzheimer's Disease Studies				
Proportion of Patients with Shifts Baseline to Post-Baseline				
Triglycerides	Placebo	1 mg/day	2 mg/day	3 mg/day
Normal to High (<150 and 200 to <500 mg/dL)	6% (10/157)*	9% (9/99)*	13% (17/133)*	6% (6/94)*
Borderline to High (150 and <200mg/dL to 200 and <500 mg/dL)	12% (3/26)*	33% (2/6)*	28% (7/25)*	26% (6/23)*
Normal/Borderline to High (<200 mg/dL to 200 and <500 mg/dL)	7% (13/183)*	11% (11/105)*	15% (24/158)*	10% (12/117)*

*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

Of the patients who were previously treated with REXULTI for 12 weeks and continued into a 12-week, active-treatment extension study, 9% of patients taking REXULTI showed shifts in baseline fasting total cholesterol from normal (<200 mg/dL) to high (≥240 mg/dL), and 16% of patients taking REXULTI showed shifts in baseline HDL cholesterol from normal to low (≥40 to <40 mg/dL). Of the patients with normal baseline triglycerides, 18% experienced shifts from normal (<150 mg/dL) to high (200 to <500 mg/dL).

Weight Gain

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

Adjunctive Treatment of Major Depressive Disorder: 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 patients with MDD.

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

	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 7 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 7 Increases in Body Weight in the 6-Week Placebo-Controlled, Fixed-Dose Schizophrenia Studies 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.

Schizophrenia [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 study, 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.

Agitation Associated with Dementia Due to Alzheimer's Disease: In the 12-week placebo-controlled, fixed-dose clinical studies in patients (51 to 90 years of age) with agitation associated with dementia due to Alzheimer's disease, the proportion of the patients with a ≥7% increase in body weight (kg) at any visit were 2% in REXULTI compared to 0% in placebo group.

In patients who were previously treated with REXULTI for 12 weeks and who continued into a 12-week, active-treatment extension study, there was no mean change in weight (kg) from baseline to last visit in association with REXULTI. In this extension study, 4% of patients demonstrated ≥7% increase in body weight, and 5% demonstrated a ≥7% decrease in body weight from baseline to last visit.

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%). In 12-week, placebo-controlled clinical studies of REXULTI in patients with agitation associated with dementia due to Alzheimer's disease, the incidence of orthostatic hypotension-related adverse reactions in patients treated with REXULTI compared to patients treated with placebo included: dizziness (3% versus 3%), orthostatic hypotension (1% versus 1%), and syncope (0.2% versus 0.8%).

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 studies.

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 studies 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 studies 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.

In the 12-week placebo-controlled, fixed-dose clinical studies in patients (51 to 90 years of age) with agitation associated with dementia due to Alzheimer's disease, somnolence (including sedation) was reported in 3% of patients treated with REXULTI compared to 1% of patients treated with placebo.

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.

Adjunctive Treatment in Major Depressive Disorder (MDD)

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 studies 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.

Adverse Reactions in REXULTI Studies for Adjunctive MDD in Adults

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 8.

Table 8 Adverse Reactions in ≥2% of REXULTI-Treated Patients and Greater than Placebo in Pooled 6-Week Placebo-Controlled, Fixed-Dose Adjunctive MDD Studies in Adults (Study 1 and Study 2)

		REXULTI			
	Placebo (N=411) %	**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

Dose-Related Adverse Reactions in the Adjunctive MDD Studies

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 studies in which REXULTI was administered at daily doses of 1 mg, 2 mg, and 4 mg *[see Clinical Studies (14.2)]*.

Adverse Reactions Occurring at an Incidence of 2% or More in Patients Treated with REXULTI for Schizophrenia

Adverse reactions associated with REXULTI (incidence of 2% or greater and REXULTI incidence greater than placebo) during short-term (up to 6 weeks) studies in adult patients with schizophrenia are shown in Table 9.

Table 9 Adverse Reactions in ≥2% of REXULTI-Treated Patients and Greater than Placebo in Pooled 6-Week Placebo-Controlled, Fixed-Dose Schizophrenia Studies in Adult Patients (Study 3 and Study 4)

		REXULTI			
	Placebo (N=368) %	**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

Agitation Associated with Dementia Due to Alzheimer's Disease

The safety of REXULTI was evaluated in 503 patients (51 to 90 years of age), with a probable diagnosis of agitation associated with dementia due to Alzheimer's disease, who participated in two 12-week placebo-controlled, fixed-dose clinical studies in which REXULTI was administered at daily doses of 2 mg to 3 mg *[see Clinical Studies (14.3)]*.

Discontinuation of Treatment Due to Adverse Reactions

In two 12-week placebo-controlled, fixed-dose, clinical studies, a total of 5.6% (28/503) of patients treated with REXULTI and 4.8% (12/251) of patients treated with placebo discontinued due to adverse reactions.

Adverse Reactions Occurring at an Incidence of 2% or More in Patients Treated with REXULTI for Agitation Associated with Dementia Due to Alzheimer's Disease

Adverse reactions associated with REXULTI (incidence ≥2% and greater than placebo) during the 12-week fixed-dose clinical studies in geriatric patients for treatment of agitation associated with dementia due to Alzheimer's disease are shown in Table 10.

Table 10 Adverse Reactions in ≥2% of REXULTI-Treated Patients and Greater than Placebo in Pooled 12-Week Placebo-Controlled, Fixed-Dose Agitation Associated with Dementia due to Alzheimer's Disease Studies (Study 6 and Study 7)

		REXULTI			
	Placebo (N=251) %	**1 mg/day* (N=137) %**	**2 mg/day (N=213) %**	**3 mg/day (N=153) %**	**ALL REXULTI (N=503) %**
Infections and Infestations					
Nasopharyngitis	2	4	2	3	3
Urinary Tract Infection	1	2	3	3	3
Nervous System Disorders					
Dizziness†	2	1	5	3	3
Headache	8	9	9	7	8
Somnolence‡	1	2	3	4	3
Psychiatric Disorders					
Insomnia§	3	5	5	2	4

*1 mg once day REXULTI dosage is not a recommended dosage for the treatment of agitation associated with dementia due to Alzheimer's disease *[see Dosage and Administration (2.4)]*.

†Dizziness and Vertigo are grouped to Dizziness

‡Sedation and somnolence are group to somnolence.

§Initial insomnia and insomnia are grouped to insomnia

Extrapyramidal Symptoms

Adjunctive Treatment of 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%).

Agitation Associated with Dementia Due to Alzheimer's Disease

The incidence of reported EPS-related adverse reactions, excluding akathisia, was 3% for REXULTI-treated patients versus 2% for placebo-treated patients. The incidence of akathisia events for REXULTI-treated patients was 1% versus 0% for placebo-treated patients.

In the 12-week placebo-controlled, fixed-dose studies in agitation associated with dementia due to Alzheimer's disease, 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 SAS (6% versus 2%).

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 Clinical Trial 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

Investigations: Blood Prolactin Increased

Musculoskeletal and Connective Tissue Disorders: Myalgia

Psychiatric Disorders: Abnormal Dreams

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

See Table 11 for clinically important drug interactions with REXULTI.

Table 11 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 (2.7)]*.
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 (2.7)]*.

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 (2.7)].*
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 (2.7)].*

*In the clinical studies 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 of REXULTI 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

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)]*.

Adjunctive Treatment of Major Depressive Disorder (MDD) and Schizophrenia

Of the total number of REXULTI-treated patients in the clinical studies for the adjunctive therapy to antidepressants for MDD and for schizophrenia, 248 (3%) were 65 years of age and older (which included 45 (18%) patients who were 75 years of age and older). Clinical studies of REXULTI in these patients did not include sufficient numbers of patients 65 years of age and older to determine whether they respond differently from younger adult patients. In general, dosage selection for the treatment of MDD or schizophrenia in a geriatric 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.

Agitation Associated with Dementia Due to Alzheimer's Disease

The total number of REXULTI-treated patients 65 years of age and older in the clinical studies for agitation associated with dementia due to Alzheimer's disease (Studies 6 and 7) was 448 (86%) including 170 (33%) patients 65 to 74 years of age, 228 (44%) patients 75 to 84 years of age, and 50 (10%) patients 85 years of age and older *[see Clinical Studies (14.3)]*.

In clinical studies of REXULTI for the treatment of agitation associated with dementia due to Alzheimer's disease did not include sufficient numbers of younger adult patients to determine if patients 65 years of age and older respond differently than younger adult patients.

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 (2.7), Clinical Pharmacology (12.3)]*.

8.7 Hepatic Impairment

The maximum recommended dosage in patients with moderate to severe hepatic impairment (Child-Pugh score ≥7) is lower than those with mild hepatic impairment and those with normal hepatic function *[see Dosage and Administration (2.4)]*. Patients with moderate to severe hepatic impairment 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 .

8.8 Renal Impairment

The maximum recommended dosage in patients with CrCl<60 mL/minute is lower than those with mild renal impairment and those with normal renal function *[see Dosage and Administration (2.6)]*. Patients with renal

impairment 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.

8.9 Other Specific Populations

The recommended dosage for REXULTI is the same in males and females, in different racial groups, and in smokers and nonsmokers *[see Clinical Pharmacology (12.3)]*.

9 DRUG ABUSE AND DEPENDENCE

9.1 Controlled Substance

REXULTI contains brexpiprazole, which 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.

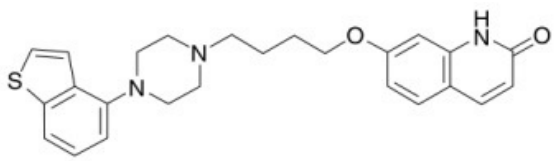
Management of a REXULTI overdose should concentrate on supportive therapy, maintaining an adequate airway, oxygenation and ventilation, and management of symptoms. Close medical supervision and monitoring should continue until the patient recovers. Consider contacting the Poison Help Line (1-800-222-1222) or a medical toxicologist for additional overdosage management recommendations.

Oral activated charcoal and sorbitol (50 g/240 mL), administered one hour after ingesting oral REXULTI, 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.

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 REXULTI in the adjunctive treatment of major depressive disorder, treatment of agitation associated with dementia due to Alzheimer's disease, or treatment of schizophrenia is unknown. However, the efficacy of REXULTI may be mediated through a combination of partial agonist activity at serotonin 5-HT_{1A} and dopamine D_2 receptors, and antagonist activity at serotonin 5-HT_{2A} receptors.

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 or agitation associated with dementia due to Alzheimer's disease, 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.

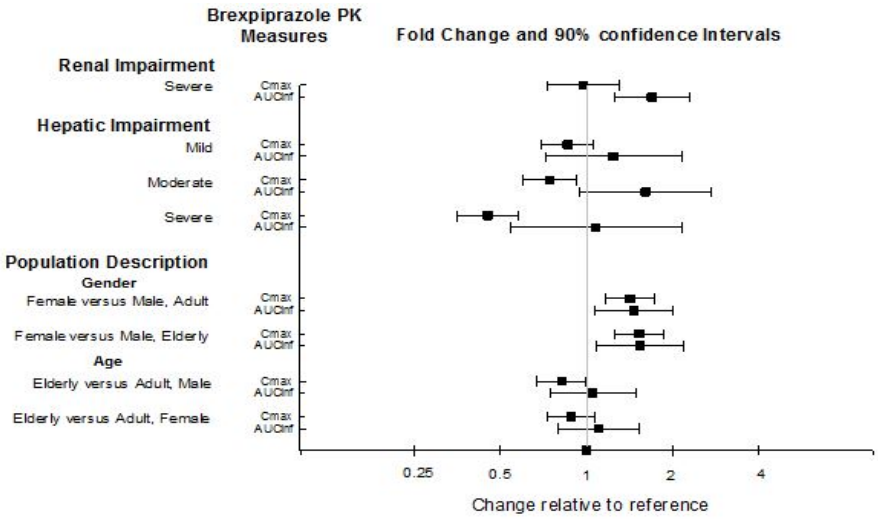
Excretion

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

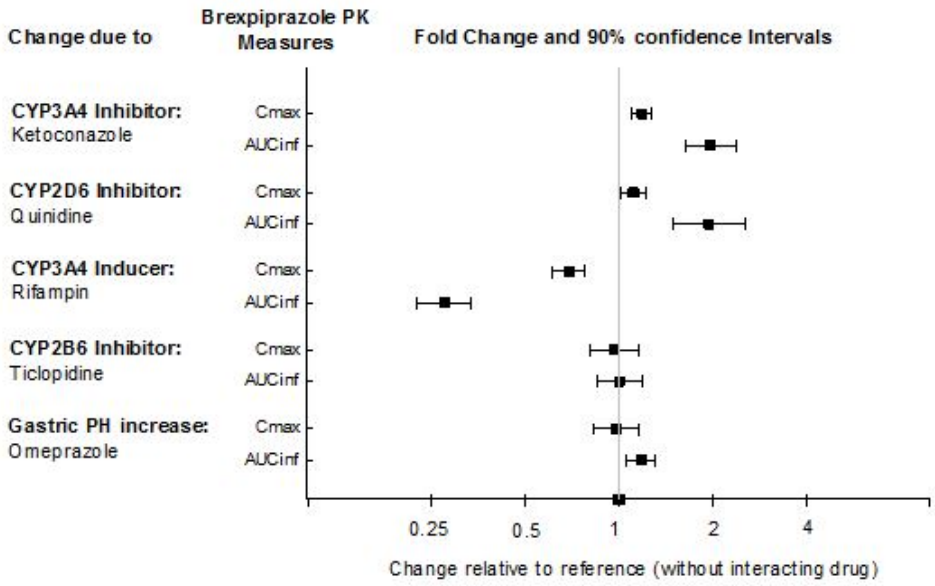
A multiple dose PK study (0.5, 1, 2, 3 or 4 mg/day) has been conducted in 43 pediatric patients aged 13 years to 17 years old. Population PK analysis indicated systemic exposure (C_{max} and AUC) of brexpiprazole in

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

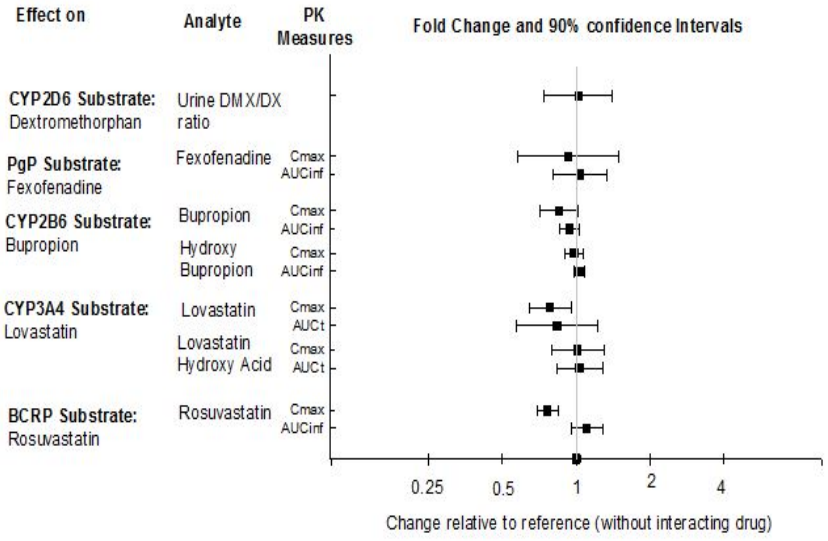
Effect of other drugs on the exposures of brexpiprazole are summarized in Figure 2. Based on simulation, a 5.1-fold increase in AUC values at steady-state is expected when extensive metabolizers of CYP2D6 are administered with both strong CYP2D6 and CYP3A4 inhibitors. A 4.8-fold increase in mean AUC 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 studies 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 1 (NCT01360645) were randomized to REXULTI 2 mg once a day or placebo. Patients in Study 2 (NCT01360632) 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 once daily and 3 mg once daily were superior to placebo plus ADT in reducing mean MADRS total scores. Results from the primary efficacy parameters for both fixed dose studies are shown below in Table 12. Figure 4 below shows the time course of response based on the primary efficacy measure (MADRS) in Study 1.

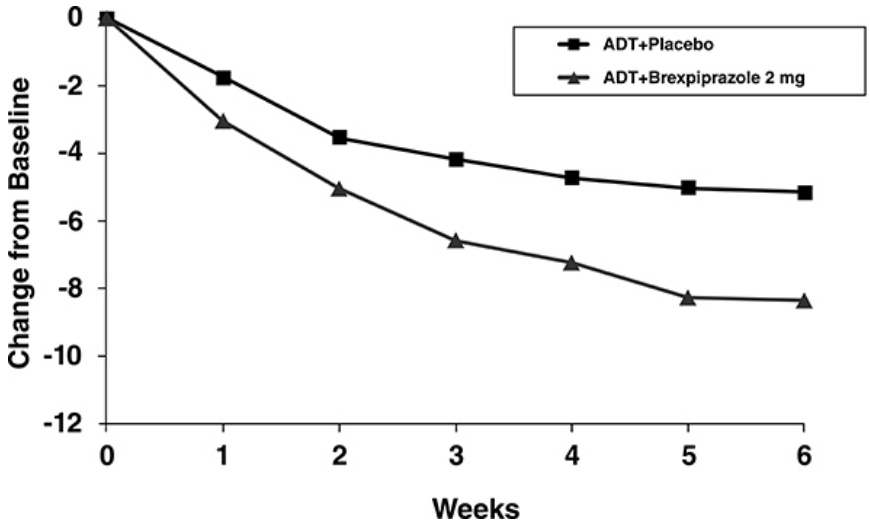
Table 12 Change in MADRS from Baseline at Week 6 in Adult Patients for Adjunctive Treatment of MDD (Study 1 and Study 2)

Study	Treatment Group	N	Mean Baseline Score (SD)	LS Mean Change from Baseline (SE)	Placebo-subtracted Difference* (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
*Difference (drug minus placebo) in least-squares mean change from baseline
†Dosages statistically significantly superior to placebo

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 studies in patients who met DSM-IV-TR criteria for schizophrenia.

In both studies, Study 3 (NCT01396421) and Study 4 (NCT01393613), 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 studies 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 once daily and 4 mg once daily was superior to placebo on the PANSS total score. In Study 4, REXULTI 4 mg once daily was superior to placebo on the PANSS total score (Table 13). Figure 5 shows the time course of response based on the primary efficacy measure (change from baseline in PANSS total score) in Study 3.

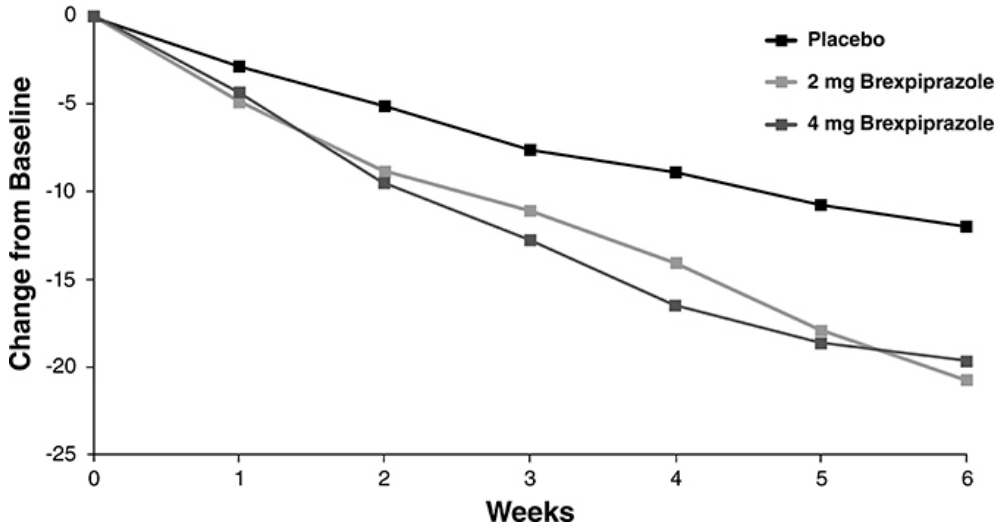
Examination of population subgroups based on age, sex, and race did not suggest differential responsiveness.

Table 13 Change in PANSS Total Score from Baseline at Week 6 in Adult Patients in Studies of Schizophrenia (Study 3 and Study 4)

Study	Treatment Group	N	Mean Baseline Score (SD)	LS Mean Change from Baseline (SE)	Placebo-subtracted Difference* (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
*Difference (drug minus placebo) in least-squares mean change from baseline
†Dosages statistically significantly superior to placebo

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



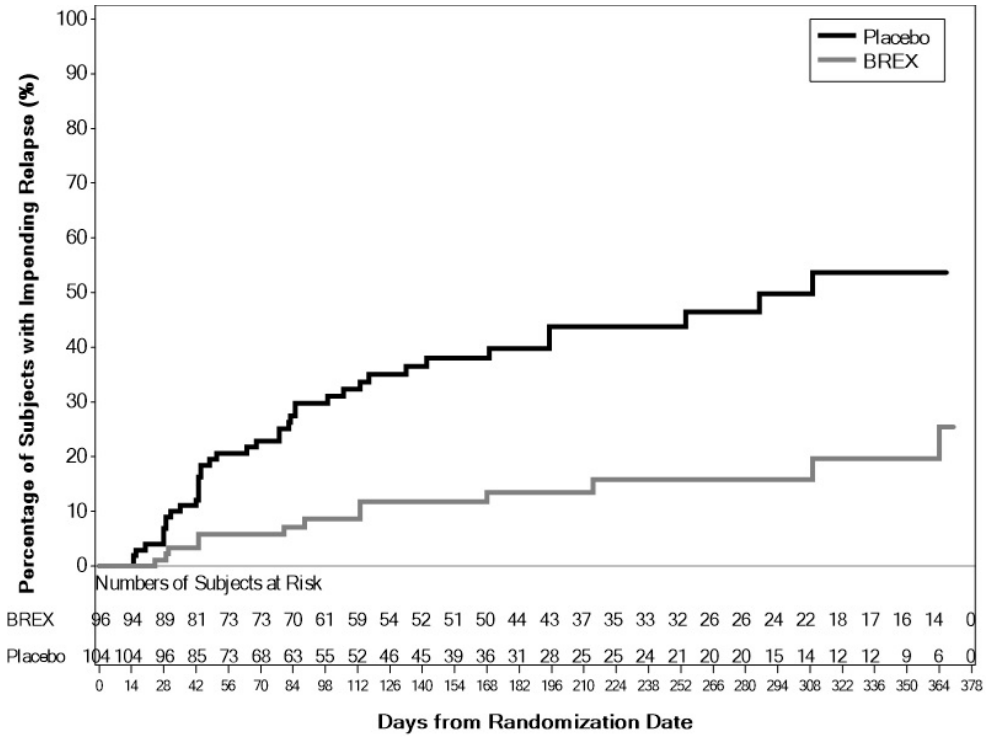
The safety and efficacy of REXULTI as maintenance treatment in adults with schizophrenia aged 18 to 65 years were demonstrated in the maintenance phase of a randomized withdrawal study (Study 5, NCT01668797). Patients were stabilized for at least 12 weeks on 1 to 4 mg/day of REXULTI (N=202). They were 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 study 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 patient in the placebo group did not take investigational medicinal product and one patient in the REXULTI group did not have post-randomization efficacy evaluations. These two patients were excluded from the efficacy analysis.

14.3 Agitation Associated with Dementia Due to Alzheimer's Disease

The efficacy of REXULTI in the treatment of agitation associated with dementia due to Alzheimer's disease was demonstrated in two 12-week, randomized, double-blind, placebo-controlled, fixed-dose studies (Study 6, NCT01862640 and Study 7, NCT03548584). In these studies, patients were required to:

- Have a diagnosis of probable Alzheimer's disease according to NINCDS-ADRDA criteria,
- Have a Mini-Mental State Examination (MMSE) score of ≥5 and ≤22 and have a total score of ≥4 by the agitation/aggression item of the NPI/NPI-NH, and
- Exhibit sufficient agitation behaviors at time of entry to warrant use of pharmacotherapy, after excluding other factors.

Patients in:

- Study 6 were randomized to an oral dosage of either REXULTI 1 mg once a day, REXULTI 2 mg once a day, or placebo. Patients in both REXULTI groups started on 0.25 mg once daily for approximately three days, then received 0.5 mg once daily for approximately 12 days. Subsequently, patients in the 1 mg group received 1 mg once daily for the remainder of the 12-week study, and patients in the 2 mg group received 1 mg once daily for approximately two weeks and then received 2 mg for the remainder of the study.
- Study 7 were randomized to an oral dose of either REXULTI 2 mg or 3 mg once a day (combined treatment arm) or placebo. Patients in both REXULTI groups started on 0.5 mg once daily for 7 days, then received 1 mg once daily for 7 days and then 2 mg once daily for 14 days. Subsequently, patients in the 2 mg group received 2 mg once daily for the remainder of the 12-week study, and patients in the 3 mg group received 3 mg once daily for the remainder of the study.

Study 6 included 433 patients with a mean age of 74 years old, and a range of 51 and 90 years old; 45% were male; 96%, 3%, and 1%, were White, Black or African American, and Asian, respectively; and 16% and 83% were Latino/Hispanic and not Latino/Hispanic, respectively. Study 7 included 345 patients with a mean age of 74 years old, and a range of 56 and 90 years old; 44% were male; 95%, 4%, and 1% were White, Black or African American, and Asian, respectively; and 31% and 69% were Latino/Hispanic and not Latino/Hispanic, respectively.

The primary efficacy endpoint in these two studies was the change from baseline in the Cohen-Mansfield Agitation Inventory total (CMAI) score at Week 12. The CMAI is a clinician rated questionnaire consisting of 29 items, which assess the frequency of manifestations of agitated behaviors in elderly patients, based on caregiver input. Three specific factors can be derived from the CMAI scale: 1) Aggressive Behavior (e.g., screaming, throwing things, cursing/verbal aggression, kicking, pushing scratching, hurting self or others); 2) Physically Non-Aggressive Behavior (e.g., repetitive mannerisms, general restlessness, pacing); and 3) Verbally Agitated Behavior (e.g., complaining, repetitive questions, constant requests for attention). Each CMAI behavior was rated on a scale of 1 (never) to 7 (very frequent agitated behaviors); the total CMAI scores range from 29 (best) to 203 (worst). A negative change indicates improvement.

In Trial 6, patients in the REXULTI 2 mg group showed improved total CMAI scores compared to patients in the placebo group at Week 12. In Trial 7, patients in the REXULTI 2 mg/3 mg group showed improved total CMAI scores compared to patients in the placebo group at Week 12.

As shown in Table 14 and Figure 7, the mean change from baseline in the total CMAI score after 12 weeks in the 2 mg/or 3 mg REXULTI group was statistically significantly superior to the placebo group. The 1 mg REXULTI group did not demonstrate significantly greater mean changes at baseline from the placebo group in the total CMAI score in this patient population. The 1 mg once day REXULTI dosage is not approved and is not recommended for the treatment of agitation associated with dementia due to Alzheimer's disease *[see Dosage and Administration (2.4)]*.

Table 14: Change in CMAI Total Score* from Baseline at Week 12 in Patients with Agitation Associated with Dementia Due to Alzheimer's Disease (Study 6 and Study 7)

Study	Treatment Group	N	Mean Baseline Score (SD)	LS Mean Change from Baseline (SE)	Placebo-subtracted Difference† (95% CI)
6	REXULTI 1 mg/day	134	70.5 (16.0)	-17.6 (1.3)	0.2 (-3.4, 3.9)
	REXULTI 2 mg/day‡	138	71.0 (16.6)	-21.6 (1.3)	-3.8 (-7.4, -0.2)
	Placebo	131	72.2 (17.9)	-17.8 (1.3)	—
7	REXULTI 2 mg/day or 3 mg/day‡	225	80.6 (16.6)	-22.6 (1.1)	-5.3 (-8.8, -1.9)
	Placebo	116	79.2 (17.5)	-17.3 (1.4)	—

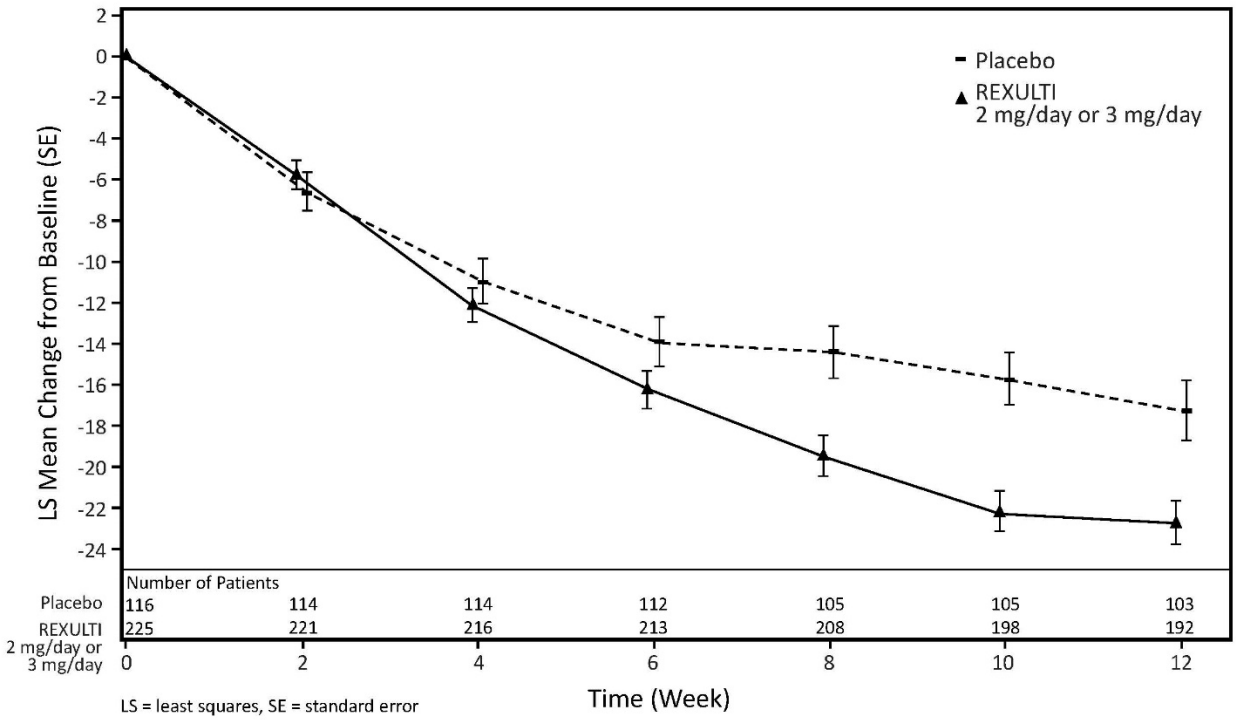
SD: standard deviation; SE: standard error; LS Mean: least-squares mean; CI: unadjusted confidence interval

*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.

†Difference (drug minus placebo) in least-squares mean change from baseline

‡Dosages statistically significantly superior to placebo.

Figure 7: Change from Baseline in Total CMAI Score by Study Week in Patients with Agitation Associated with Dementia Due to Alzheimer's Disease (Study 7)



16 HOW SUPPLIED/STORAGE AND HANDLING

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

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)]*.

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)]*.

Potential for Cognitive and Motor Impairment

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

 11US23IBR0001

MEDICATION GUIDE
REXULTI® (REX-ul-TE)
(brexpiprazole)
tablets, for oral use

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 without agitation that may happen with dementia due to Alzheimer's disease.
- **Increased risk of suicidal thoughts and actions.** REXULTI and antidepressant medicines may increase suicidal thoughts and actions in some people 24 years of age and younger, **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 REXULTI 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:

- along with antidepressant medicines to treat major depressive disorder (MDD) in adults
- to treat schizophrenia in adults and children ages 13 years and older
- to treat agitation that may happen with dementia due to Alzheimer's disease

REXULTI should not be used as an "as needed" treatment for agitation that may happen with dementia due to Alzheimer's disease.

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. Talk to your healthcare provider about the risk to your unborn baby if you take REXULTI during pregnancy.
    - Tell your healthcare provider if you become pregnant or think you are pregnant during treatment with REXULTI.
    - There is a pregnancy exposure registry for women who are exposed to REXULTI during pregnancy. 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 Poison Help Line at 1-800-222-1222 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?"**
- **Cerebrovascular problems, including stroke, 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
    - stiff muscles
    - confusion
    - changes in your pulse, blood pressure, heart rate, and breathing
    - 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 new or unusual strong urges or behaviors, 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) and fainting.** You may feel dizzy, lightheaded, or pass out (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, sleepiness, dizziness, common cold symptoms, 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 health professionals.

What are the ingredients in REXULTI?

Active ingredient: brexpiprazole

Inactive ingredients: lactose monohydrate, corn starch, microcrystalline cellulose, hydroxypropyl cellulose, low-substituted hydroxypropyl cellulose, magnesium stearate, hypromellose, and talc

For color: titanium dioxide, iron oxide, and ferrosoferric oxide

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

This Medication Guide has been approved by the U.S. Food and Drug Administration. Revised: 5/2023

11US23IBR0002

Proposed Package Insert

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 without agitation associated with dementia due to Alzheimer's disease. (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	5/2023
Indications and Usage (1)	5/2023
Dosage and Administration (2.1, 2.3, 2.4, 2.5, 2.6)	5/2023
Warnings and Precautions (5.1, 5.3, 5.4, 5.6, 5.9, 5.14)	5/2023

----------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)
- Treatment of agitation associated with dementia due to Alzheimer's disease (1, 14.3)

  Limitations of Use: REXULTI is not indicated as an as needed ("prn") treatment for agitation associated with dementia due to Alzheimer's disease (1)

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

Administer REXULTI once daily with or without food. (2, 12.3)

Indication	Starting Dosage	Recommended Target Dosage	Maximum Dosage
MDD Adults (2.2)	0.5 mg/day or 1 mg/day	2 mg/day	3 mg/day
Schizophrenia Adults (2.3)	1 mg/day	2 to 4 mg/day	4 mg/day
Schizophrenia Pediatric (13 - 17 years) (2.3)	0.5 mg/day	2 to 4 mg/day	4 mg/day
Agitation associated with dementia due to Alzheimer's disease (2.4)	0.5 mg/day	2 mg/day	3 mg/day

- *Moderate to Severe Hepatic Impairment:* Maximum recommended dosage is 2 mg once daily for patients with MDD or agitation associated with dementia due to Alzheimer's disease and 3 mg once daily for patients with schizophrenia. (2.5)
- *CrCl<60 mL/minute:* Maximum recommended dosage is 2 mg once daily for patients with MDD or agitation associated with dementia due to Alzheimer's disease and 3 mg once daily for patients with schizophrenia. (2.6)
- See Full Prescribing Information for dosage modifications for CYP2D6 poor metabolizers and for concomitant use with CYP inhibitors or inducers. (2.7)

----------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, somnolence, and akathisia (≥5% and at least twice the rate for placebo)
- *Schizophrenia*: Weight increased (≥4% and at least twice the rate for placebo)
- *Agitation associated with dementia due to Alzheimer's disease:* Nasopharyngitis, dizziness (≥4% and at least twice the rate for placebo)

To report SUSPECTED ADVERSE REACTIONS, contact LifeScience Logistics at 1-855-738-6171 or FDA at 1-800-FDA-1088 or *www.fda.gov/medwatch*.

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

Factors	Dosage Adjustments for REXULTI (2.7)
Strong CYP2D6* or CYP3A4 inhibitors	Administer half of recommended dosage.
Strong/moderate CYP2D6 with Strong/moderate CYP3A4 inhibitors	Administer a quarter of the recommended dosage.
Known CYP2D6 poor metabolizers taking strong/moderate CYP3A4 inhibitors	Administer a quarter of the recommended dosage.
Strong CYP3A4 inducers	Double the recommended dosage 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: 5/2023

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 without agitation associated with dementia due to Alzheimer's disease *[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
- 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 *[see Clinical Studies (14.3)]*.

2 DOSAGE AND ADMINISTRATION

2.1 Administration Information

Administer REXULTI orally, once daily with or without food *[see Clinical Pharmacology (12.3)]*

2.2 Recommended Dosage for Adjunctive Treatment of Major Depressive Disorder (Adults)

The recommended starting REXULTI dosage for the adjunctive treatment of MDD in adults is 0.5 mg or 1 mg once daily .Titrate to 1 mg once daily, then titrate to the target dosage of 2 mg once daily (based on the patient's clinical response and tolerability, increase the dosage at weekly intervals). The maximum recommended daily dosage is 3 mg. Periodically reassess to determine the continued need and appropriate dosage for treatment.

2.3 Recommended Dosage for Schizophrenia (Adults and Pediatric Patients 13 to 17 Years)

Adults

The recommended starting REXULTI dosage for the treatment of schizophrenia in adults is 1 mg once daily on Days 1 to 4. Titrate to 2 mg once daily on Day 5 through Day 7. On Day 8, the dosage can be increased to the maximum recommended daily dosage of 4 mg based on clinical response and tolerability. The recommended target dosage is 2 mg to 4 mg once daily.

Pediatric Patients (13 to 17 years of age)

The recommended starting REXULTI dosage for the treatment of schizophrenia in pediatric patients 13 to 17 years of age is 0.5 mg taken orally once daily on Days 1 to 4. On Days 5 through 7, titrate to 1 mg per day and on Day 8 titrate to 2 mg based on clinical response and tolerability. Weekly dose increases can be made in 1 mg increments. A recommended target dosage is 2 to 4 mg once daily. The maximum recommended daily dosage is 4 mg.

2.4 Recommended Dosage for Agitation Associated with Dementia Due to Alzheimer's Disease

The recommended starting REXULTI dosage for the treatment of agitation associated with dementia due to Alzheimer's disease is 0.5 mg taken once daily on Days 1 to 7. Increase the dosage on Days 8 through 14 to 1 mg once daily, and on Day 15 to 2 mg once daily. The recommended target dose is 2 mg once daily. The dosage can be increased to the maximum recommended daily dosage of 3 mg once daily after at least 14 days, based on clinical response and tolerability.

2.5 Recommended Dosage in Patients with Hepatic Impairment

The maximum recommended dosage in patients with moderate to severe hepatic impairment (Child-Pugh score ≥7) is *[see Use in Specific Populations (8.7), Clinical Pharmacology (12.3)]*.

- 2 mg once daily in patients with MDD or agitation associated with dementia due to Alzheimer's disease, and
- 3 mg orally once daily in patients with schizophrenia

2.6 Recommended Dosage in Patients with Renal Impairment

The maximum recommended dosage in patients with creatinine clearance CrCl<60 mL/minute is *[see Use in Specific Populations (8.8), Clinical Pharmacology (12.3)]*.

- 2 mg orally once daily in patients with MDD or agitation associated with dementia due to Alzheimer's disease and
- 3 mg orally once daily in patients with schizophrenia

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

Dosage modifications are recommended in patients who are known cytochrome P450 (CYP) 2D6 poor metabolizers and in patients taking concomitant CYP3A4 inhibitors, CYP2D6 inhibitors, or strong CYP3A4 inducers (see Table 1). If the concomitant drug is discontinued, adjust the REXULTI dosage to its original level. If the concomitant 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 Modifications of REXULTI for CYP2D6 Poor Metabolizers and for Concomitant Use with CYP3A4 Inhibitors, CYP2D6 Inhibitors, or CYP3A4 Inducers

Factors	Adjusted REXULTI Dosage
CYP2D6 Poor Metabolizers	
CYP2D6 poor metabolizers	Administer half of the recommended dosage.
Known CYP2D6 poor metabolizers taking strong/moderate	Administer a quarter of the recommended

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

Factors	Adjusted REXULTI Dosage
CYP3A4 inhibitors	dosage.
Patients Taking CYP2D6 Inhibitors and/or CYP3A4 Inhibitors	
Strong CYP2D6 inhibitors*	Administer half of the recommended dosage.
Strong CYP3A4 inhibitors	Administer half of the recommended dosage.
Strong/moderate CYP2D6 inhibitors with strong/moderate CYP3A4 inhibitors	Administer a quarter of the recommended dosage.
Patients Taking CYP3A4 Inducers	
Strong CYP3A4 inducers	Double the recommended dosage over 1 to 2 weeks.

*In the clinical studies examining the use of REXULTI for the adjunctive 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 the 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 without agitation associated with dementia due to Alzheimer's disease *[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 24 years of age 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 Table 2.

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 without agitation associated with dementia due to Alzheimer's disease *[see Boxed Warning, Warnings and Precautions (5.1)]*.

5.4 Neuroleptic Malignant Syndrome (NMS)

Neuroleptic Malignant Syndrome (NMS), a potentially fatal symptom complex, 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 (irregular pulse or blood pressure, tachycardia, diaphoresis and cardiac dysrhythmia). 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 impossible to predict which patients will 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 appear to increase as the duration of treatment and the cumulative dose increases. The syndrome can develop after relatively brief treatment periods, 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 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 occurrence of tardive dyskinesia. Chronic antipsychotic treatment should generally be reserved for patients who suffer from a chronic illness that 1) is known to respond to antipsychotic drugs and 2) for whom alternative, equally 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. The need for continued treatment should be reassessed periodically.

If signs and symptoms of tardive dyskinesia appear in a patient treated with 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 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. 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.

Adjunctive Treatment of Major Depressive Disorder: In the 6-week placebo-controlled, fixed-dose clinical studies 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 studies 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.

Schizophrenia 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.

Agitation Associated with Dementia Due to Alzheimer's Disease: In the 12-week placebo-controlled, fixed-dose studies in patients (51 to 90 years of age) with agitation associated with dementia due to Alzheimer's disease, the proportions of patients with shifts in fasting glucose from normal (<100 mg/dL) to high (≥126 mg/dL) or impaired (≥100 and <126 mg/dL) to high were similar in patients treated with REXULTI (14%) and patients treated with placebo (16%).

Of the patients who were previously treated with REXULTI for 12-weeks and continued into a 12-week, active-treatment extension study, 15% of patients with normal baseline fasting glucose experienced a shift from normal (<100 mg/dL) to high (≥126 mg/dL) fasting glucose while taking REXULTI; 30% of patients with impaired fasting glucose experienced shifts from impaired fasting glucose (≥100 and <126 mg/dL) to high fasting glucose. Combined, 20% of patients with normal or impaired fasting glucose experienced shifts to high fasting glucose.

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.

Adjunctive Treatment of Major Depressive Disorder: In the 6-week placebo-controlled, fixed-dose clinical studies 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 Studies

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 studies 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 Studies 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.

Schizophrenia [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).

Agitation Associated with Dementia Due to Alzheimer's Disease: In the 12-week placebo-controlled, fixed-dose clinical studies in patients (55 to 90 years of age) with agitation associated with dementia due to Alzheimer's disease, changes in total cholesterol, LDL cholesterol, and HDL cholesterol were similar in REXULTI- and placebo-treated patients.

Table 5 shows the proportions of patients with changes in fasting triglycerides in REXULTI- and placebo-treated patients.

Table 5 Change in Fasting Triglycerides in the 12-Week Placebo-Controlled, Fixed-Dose Agitation Associated with Dementia Due to Alzheimer's Disease Studies				
Proportion of Patients with Shifts Baseline to Post-Baseline				
Triglycerides	Placebo	1 mg/day	2 mg/day	3 mg/day
Normal to High (<150 and 200 to <500 mg/dL)	6% (10/157)*	9% (9/99)*	13% (17/133)*	6% (6/94)*
Borderline to High (150 and <200mg/dL to 200 and <500 mg/dL)	12% (3/26)*	33% (2/6)*	28% (7/25)*	26% (6/23)*
Normal/Borderline to High (<200 mg/dL to 200 and <500 mg/dL)	7% (13/183)*	11% (11/105)*	15% (24/158)*	10% (12/117)*

*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

Of the patients who were previously treated with REXULTI for 12 weeks and continued into a 12-week, active-treatment extension study, 9% of patients taking REXULTI showed shifts in baseline fasting total cholesterol from normal (<200 mg/dL) to high (≥240 mg/dL), and 16% of patients taking REXULTI showed shifts in baseline HDL cholesterol from normal to low (≥40 to <40 mg/dL). Of the patients with normal baseline triglycerides, 18% experienced shifts from normal (<150 mg/dL) to high (200 to <500 mg/dL).

Weight Gain

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

Adjunctive Treatment of Major Depressive Disorder: 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 patients with MDD.

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

	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 7 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 7 Increases in Body Weight in the 6-Week Placebo-Controlled, Fixed-Dose Schizophrenia Studies 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.

Schizophrenia [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 study, 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.

Agitation Associated with Dementia Due to Alzheimer's Disease: In the 12-week placebo-controlled, fixed-dose clinical studies in patients (51 to 90 years of age) with agitation associated with dementia due to Alzheimer's disease, the proportion of the patients with a ≥7% increase in body weight (kg) at any visit were 2% in REXULTI compared to 0% in placebo group.

In patients who were previously treated with REXULTI for 12 weeks and who continued into a 12-week, active-treatment extension study, there was no mean change in weight (kg) from baseline to last visit in association with REXULTI. In this extension study, 4% of patients demonstrated ≥7% increase in body weight, and 5% demonstrated a ≥7% decrease in body weight from baseline to last visit.

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%). In 12-week, placebo-controlled clinical studies of REXULTI in patients with agitation associated with dementia due to Alzheimer's disease, the incidence of orthostatic hypotension-related adverse reactions in patients treated with REXULTI compared to patients treated with placebo included: dizziness (3% versus 3%), orthostatic hypotension (1% versus 1%), and syncope (0.2% versus 0.8%).

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 studies.

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 studies 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 studies 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.

In the 12-week placebo-controlled, fixed-dose clinical studies in patients (51 to 90 years of age) with agitation associated with dementia due to Alzheimer's disease, somnolence (including sedation) was reported in 3% of patients treated with REXULTI compared to 1% of patients treated with placebo.

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.

Adjunctive Treatment in Major Depressive Disorder (MDD)

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 studies 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.

Adverse Reactions in REXULTI Studies for Adjunctive MDD in Adults

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 8.

Table 8 Adverse Reactions in ≥2% of REXULTI-Treated Patients and Greater than Placebo in Pooled 6-Week Placebo-Controlled, Fixed-Dose Adjunctive MDD Studies in Adults (Study 1 and Study 2)

		REXULTI			
	Placebo (N=411) %	**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

Dose-Related Adverse Reactions in the Adjunctive MDD Studies

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 studies in which REXULTI was administered at daily doses of 1 mg, 2 mg, and 4 mg *[see Clinical Studies (14.2)]*.

Adverse Reactions Occurring at an Incidence of 2% or More in Patients Treated with REXULTI for Schizophrenia

Adverse reactions associated with REXULTI (incidence of 2% or greater and REXULTI incidence greater than placebo) during short-term (up to 6 weeks) studies in adult patients with schizophrenia are shown in Table 9.

Table 9 Adverse Reactions in ≥2% of REXULTI-Treated Patients and Greater than Placebo in Pooled 6-Week Placebo-Controlled, Fixed-Dose Schizophrenia Studies in Adult Patients (Study 3 and Study 4)

		REXULTI			
	Placebo (N=368) %	**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

Agitation Associated with Dementia Due to Alzheimer's Disease

The safety of REXULTI was evaluated in 503 patients (51 to 90 years of age), with a probable diagnosis of agitation associated with dementia due to Alzheimer's disease, who participated in two 12-week placebo-controlled, fixed-dose clinical studies in which REXULTI was administered at daily doses of 2 mg to 3 mg *[see Clinical Studies (14.3)]*.

Discontinuation of Treatment Due to Adverse Reactions

In two 12-week placebo-controlled, fixed-dose, clinical studies, a total of 5.6% (28/503) of patients treated with REXULTI and 4.8% (12/251) of patients treated with placebo discontinued due to adverse reactions.

Adverse Reactions Occurring at an Incidence of 2% or More in Patients Treated with REXULTI for Agitation Associated with Dementia Due to Alzheimer's Disease

Adverse reactions associated with REXULTI (incidence ≥2% and greater than placebo) during the 12-week fixed-dose clinical studies in geriatric patients for treatment of agitation associated with dementia due to Alzheimer's disease are shown in Table 10.

Table 10 Adverse Reactions in ≥2% of REXULTI-Treated Patients and Greater than Placebo in Pooled 12-Week Placebo-Controlled, Fixed-Dose Agitation Associated with Dementia due to Alzheimer's Disease Studies (Study 6 and Study 7)

		REXULTI			
	Placebo (N=251) %	**1 mg/day* (N=137) %**	**2 mg/day (N=213) %**	**3 mg/day (N=153) %**	**ALL REXULTI (N=503) %**
Infections and Infestations					
Nasopharyngitis	2	4	2	3	3
Urinary Tract Infection	1	2	3	3	3
Nervous System Disorders					
Dizziness†	2	1	5	3	3
Headache	8	9	9	7	8
Somnolence‡	1	2	3	4	3
Psychiatric Disorders					
Insomnia§	3	5	5	2	4

*1 mg once day REXULTI dosage is not a recommended dosage for the treatment of agitation associated with dementia due to Alzheimer's disease *[see Dosage and Administration (2.4)]*.

†Dizziness and Vertigo are grouped to Dizziness

‡Sedation and somnolence are group to somnolence.

§Initial insomnia and insomnia are grouped to insomnia

Extrapyramidal Symptoms

Adjunctive Treatment of 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%).

Agitation Associated with Dementia Due to Alzheimer's Disease

The incidence of reported EPS-related adverse reactions, excluding akathisia, was 3% for REXULTI-treated patients versus 2% for placebo-treated patients. The incidence of akathisia events for REXULTI-treated patients was 1% versus 0% for placebo-treated patients.

In the 12-week placebo-controlled, fixed-dose studies in agitation associated with dementia due to Alzheimer's disease, 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 SAS (6% versus 2%).

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 Clinical Trial 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

Investigations: Blood Prolactin Increased

Musculoskeletal and Connective Tissue Disorders: Myalgia

Psychiatric Disorders: Abnormal Dreams

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

See Table 11 for clinically important drug interactions with REXULTI.

Table 11 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 (2.7)]*.
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 (2.7)]*.

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 (2.7)].*
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 (2.7)].*

*In the clinical studies 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 of REXULTI 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

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)]*.

Adjunctive Treatment of Major Depressive Disorder (MDD) and Schizophrenia

Of the total number of REXULTI-treated patients in the clinical studies for the adjunctive therapy to antidepressants for MDD and for schizophrenia, 248 (3%) were 65 years of age and older (which included 45 (18%) patients who were 75 years of age and older). Clinical studies of REXULTI in these patients did not include sufficient numbers of patients 65 years of age and older to determine whether they respond differently from younger adult patients. In general, dosage selection for the treatment of MDD or schizophrenia in a geriatric 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.

Agitation Associated with Dementia Due to Alzheimer's Disease

The total number of REXULTI-treated patients 65 years of age and older in the clinical studies for agitation associated with dementia due to Alzheimer's disease (Studies 6 and 7) was 448 (86%) including 170 (33%) patients 65 to 74 years of age, 228 (44%) patients 75 to 84 years of age, and 50 (10%) patients 85 years of age and older *[see Clinical Studies (14.3)]*.

In clinical studies of REXULTI for the treatment of agitation associated with dementia due to Alzheimer's disease did not include sufficient numbers of younger adult patients to determine if patients 65 years of age and older respond differently than younger adult patients.

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 (2.7), Clinical Pharmacology (12.3)]*.

8.7 Hepatic Impairment

The maximum recommended dosage in patients with moderate to severe hepatic impairment (Child-Pugh score ≥7) is lower than those with mild hepatic impairment and those with normal hepatic function *[see Dosage and Administration (2.4)]*. Patients with moderate to severe hepatic impairment 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 .

8.8 Renal Impairment

The maximum recommended dosage in patients with CrCl<60 mL/minute is lower than those with mild renal impairment and those with normal renal function *[see Dosage and Administration (2.6)]*. Patients with renal

impairment 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.

8.9 Other Specific Populations

The recommended dosage for REXULTI is the same in males and females, in different racial groups, and in smokers and nonsmokers *[see Clinical Pharmacology (12.3)]*.

9 DRUG ABUSE AND DEPENDENCE

9.1 Controlled Substance

REXULTI contains brexpiprazole, which 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.

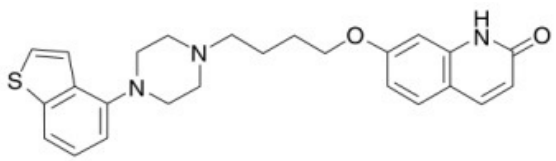
Management of a REXULTI overdose should concentrate on supportive therapy, maintaining an adequate airway, oxygenation and ventilation, and management of symptoms. Close medical supervision and monitoring should continue until the patient recovers. Consider contacting the Poison Help Line (1-800-222-1222) or a medical toxicologist for additional overdosage management recommendations.

Oral activated charcoal and sorbitol (50 g/240 mL), administered one hour after ingesting oral REXULTI, 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.

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 REXULTI in the adjunctive treatment of major depressive disorder, treatment of agitation associated with dementia due to Alzheimer's disease, or treatment of schizophrenia is unknown. However, the efficacy of REXULTI may be mediated through a combination of partial agonist activity at serotonin 5-HT_{1A} and dopamine D_2 receptors, and antagonist activity at serotonin 5-HT_{2A} receptors.

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 or agitation associated with dementia due to Alzheimer's disease, 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.

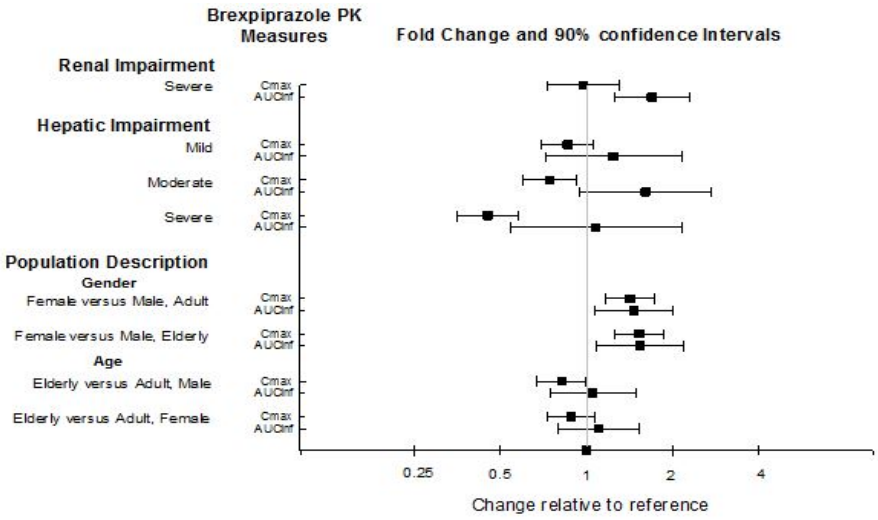
Excretion

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

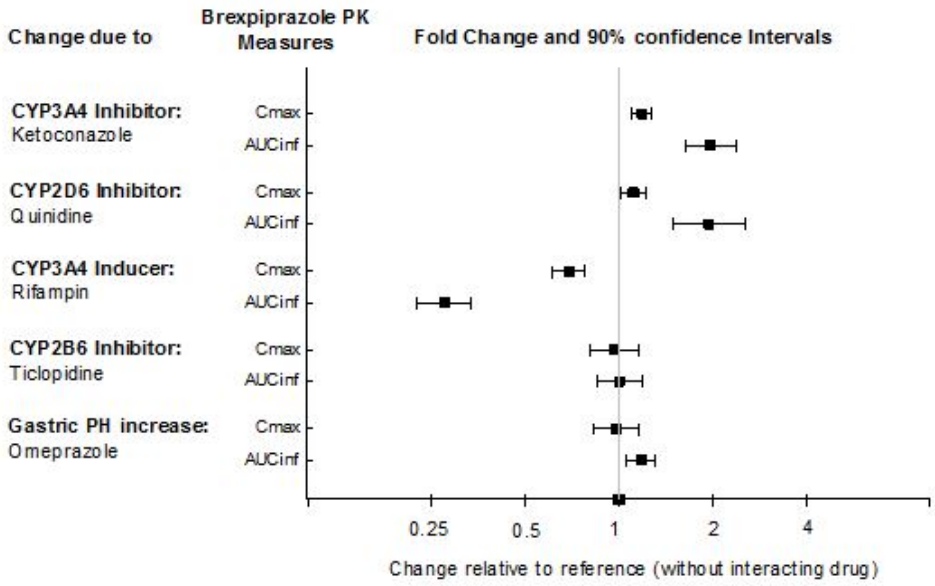
A multiple dose PK study (0.5, 1, 2, 3 or 4 mg/day) has been conducted in 43 pediatric patients aged 13 years to 17 years old. Population PK analysis indicated systemic exposure (C_{max} and AUC) of brexpiprazole in

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

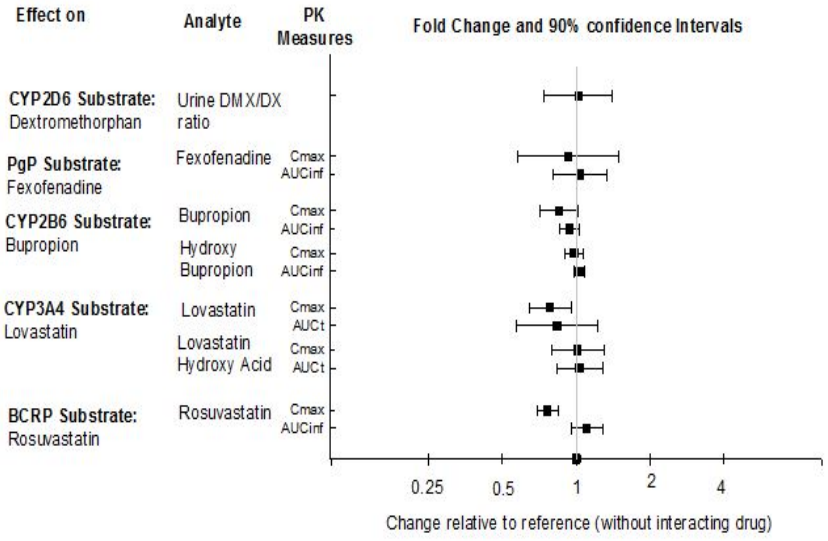
Effect of other drugs on the exposures of brexpiprazole are summarized in Figure 2. Based on simulation, a 5.1-fold increase in AUC values at steady-state is expected when extensive metabolizers of CYP2D6 are administered with both strong CYP2D6 and CYP3A4 inhibitors. A 4.8-fold increase in mean AUC 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 studies 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 1 (NCT01360645) were randomized to REXULTI 2 mg once a day or placebo. Patients in Study 2 (NCT01360632) 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 once daily and 3 mg once daily were superior to placebo plus ADT in reducing mean MADRS total scores. Results from the primary efficacy parameters for both fixed dose studies are shown below in Table 12. Figure 4 below shows the time course of response based on the primary efficacy measure (MADRS) in Study 1.

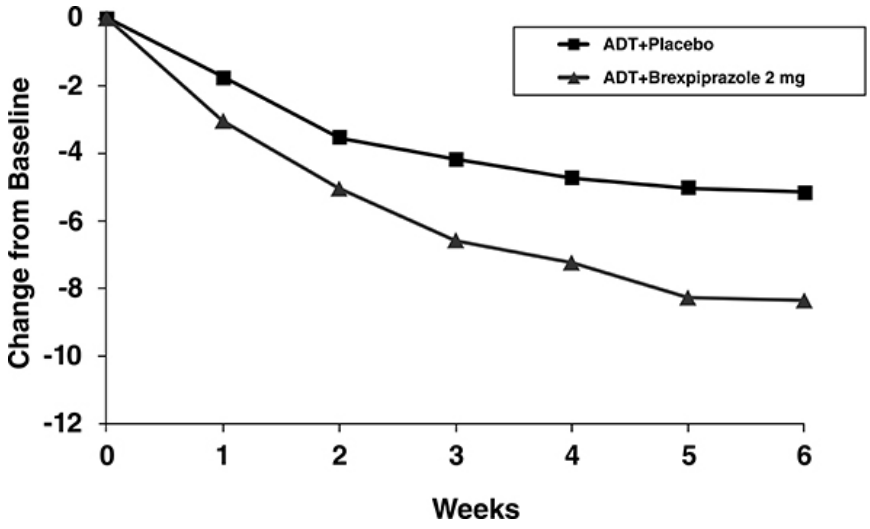
Table 12 Change in MADRS from Baseline at Week 6 in Adult Patients for Adjunctive Treatment of MDD (Study 1 and Study 2)

Study	Treatment Group	N	Mean Baseline Score (SD)	LS Mean Change from Baseline (SE)	Placebo-subtracted Difference* (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
*Difference (drug minus placebo) in least-squares mean change from baseline
†Dosages statistically significantly superior to placebo

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 studies in patients who met DSM-IV-TR criteria for schizophrenia.

In both studies, Study 3 (NCT01396421) and Study 4 (NCT01393613), 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 studies 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 once daily and 4 mg once daily was superior to placebo on the PANSS total score. In Study 4, REXULTI 4 mg once daily was superior to placebo on the PANSS total score (Table 13). Figure 5 shows the time course of response based on the primary efficacy measure (change from baseline in PANSS total score) in Study 3.

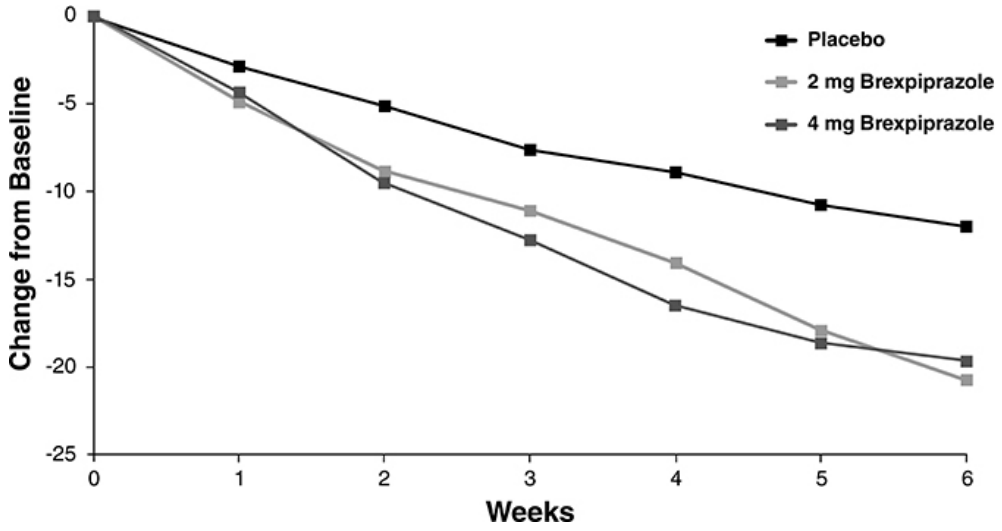
Examination of population subgroups based on age, sex, and race did not suggest differential responsiveness.

Table 13 Change in PANSS Total Score from Baseline at Week 6 in Adult Patients in Studies of Schizophrenia (Study 3 and Study 4)

Study	Treatment Group	N	Mean Baseline Score (SD)	LS Mean Change from Baseline (SE)	Placebo-subtracted Difference* (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
*Difference (drug minus placebo) in least-squares mean change from baseline
†Dosages statistically significantly superior to placebo

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



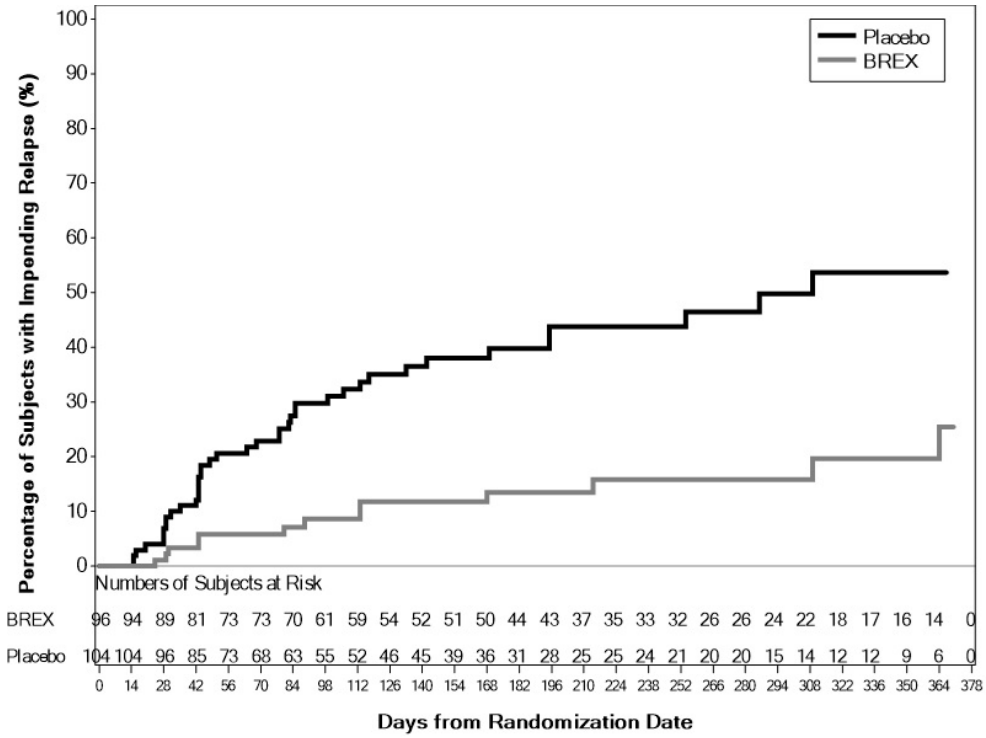
The safety and efficacy of REXULTI as maintenance treatment in adults with schizophrenia aged 18 to 65 years were demonstrated in the maintenance phase of a randomized withdrawal study (Study 5, NCT01668797). Patients were stabilized for at least 12 weeks on 1 to 4 mg/day of REXULTI (N=202). They were 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 study 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 patient in the placebo group did not take investigational medicinal product and one patient in the REXULTI group did not have post-randomization efficacy evaluations. These two patients were excluded from the efficacy analysis.

14.3 Agitation Associated with Dementia Due to Alzheimer's Disease

The efficacy of REXULTI in the treatment of agitation associated with dementia due to Alzheimer's disease was demonstrated in two 12-week, randomized, double-blind, placebo-controlled, fixed-dose studies (Study 6, NCT01862640 and Study 7, NCT03548584). In these studies, patients were required to:

- Have a diagnosis of probable Alzheimer's disease according to NINCDS-ADRDA criteria,
- Have a Mini-Mental State Examination (MMSE) score of ≥5 and ≤22 and have a total score of ≥4 by the agitation/aggression item of the NPI/NPI-NH, and
- Exhibit sufficient agitation behaviors at time of entry to warrant use of pharmacotherapy, after excluding other factors.

Patients in:

- Study 6 were randomized to an oral dosage of either REXULTI 1 mg once a day, REXULTI 2 mg once a day, or placebo. Patients in both REXULTI groups started on 0.25 mg once daily for approximately three days, then received 0.5 mg once daily for approximately 12 days. Subsequently, patients in the 1 mg group received 1 mg once daily for the remainder of the 12-week study, and patients in the 2 mg group received 1 mg once daily for approximately two weeks and then received 2 mg for the remainder of the study.
- Study 7 were randomized to an oral dose of either REXULTI 2 mg or 3 mg once a day (combined treatment arm) or placebo. Patients in both REXULTI groups started on 0.5 mg once daily for 7 days, then received 1 mg once daily for 7 days and then 2 mg once daily for 14 days. Subsequently, patients in the 2 mg group received 2 mg once daily for the remainder of the 12-week study, and patients in the 3 mg group received 3 mg once daily for the remainder of the study.

Study 6 included 433 patients with a mean age of 74 years old, and a range of 51 and 90 years old; 45% were male; 96%, 3%, and 1%, were White, Black or African American, and Asian, respectively; and 16% and 83% were Latino/Hispanic and not Latino/Hispanic, respectively. Study 7 included 345 patients with a mean age of 74 years old, and a range of 56 and 90 years old; 44% were male; 95%, 4%, and 1% were White, Black or African American, and Asian, respectively; and 31% and 69% were Latino/Hispanic and not Latino/Hispanic, respectively.

The primary efficacy endpoint in these two studies was the change from baseline in the Cohen-Mansfield Agitation Inventory total (CMAI) score at Week 12. The CMAI is a clinician rated questionnaire consisting of 29 items, which assess the frequency of manifestations of agitated behaviors in elderly patients, based on caregiver input. Three specific factors can be derived from the CMAI scale: 1) Aggressive Behavior (e.g., screaming, throwing things, cursing/verbal aggression, kicking, pushing scratching, hurting self or others); 2) Physically Non-Aggressive Behavior (e.g., repetitive mannerisms, general restlessness, pacing); and 3) Verbally Agitated Behavior (e.g., complaining, repetitive questions, constant requests for attention). Each CMAI behavior was rated on a scale of 1 (never) to 7 (very frequent agitated behaviors); the total CMAI scores range from 29 (best) to 203 (worst). A negative change indicates improvement.

In Trial 6, patients in the REXULTI 2 mg group showed improved total CMAI scores compared to patients in the placebo group at Week 12. In Trial 7, patients in the REXULTI 2 mg/3 mg group showed improved total CMAI scores compared to patients in the placebo group at Week 12.

As shown in Table 14 and Figure 7, the mean change from baseline in the total CMAI score after 12 weeks in the 2 mg/or 3 mg REXULTI group was statistically significantly superior to the placebo group. The 1 mg REXULTI group did not demonstrate significantly greater mean changes at baseline from the placebo group in the total CMAI score in this patient population. The 1 mg once day REXULTI dosage is not approved and is not recommended for the treatment of agitation associated with dementia due to Alzheimer's disease *[see Dosage and Administration (2.4)]*.

Table 14: Change in CMAI Total Score* from Baseline at Week 12 in Patients with Agitation Associated with Dementia Due to Alzheimer's Disease (Study 6 and Study 7)

Study	Treatment Group	N	Mean Baseline Score (SD)	LS Mean Change from Baseline (SE)	Placebo-subtracted Difference† (95% CI)
6	REXULTI 1 mg/day	134	70.5 (16.0)	-17.6 (1.3)	0.2 (-3.4, 3.9)
	REXULTI 2 mg/day‡	138	71.0 (16.6)	-21.6 (1.3)	-3.8 (-7.4, -0.2)
	Placebo	131	72.2 (17.9)	-17.8 (1.3)	—
7	REXULTI 2 mg/day or 3 mg/day‡	225	80.6 (16.6)	-22.6 (1.1)	-5.3 (-8.8, -1.9)
	Placebo	116	79.2 (17.5)	-17.3 (1.4)	—

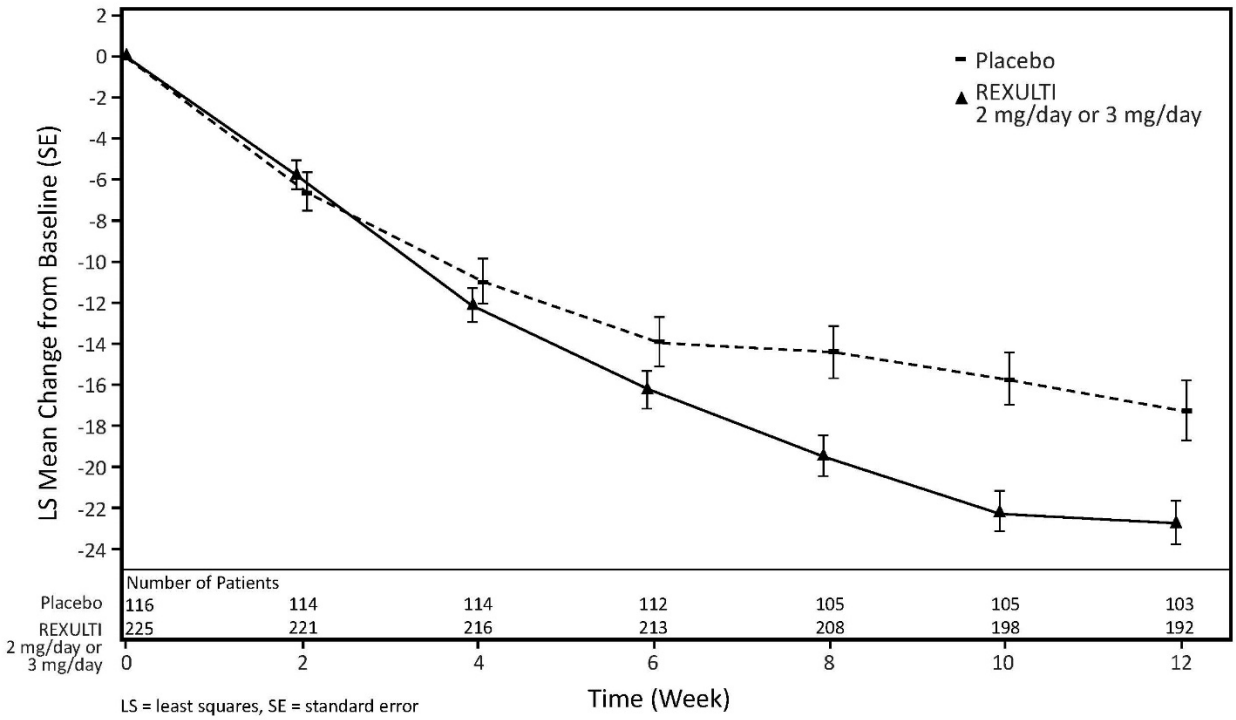
SD: standard deviation; SE: standard error; LS Mean: least-squares mean; CI: unadjusted confidence interval

*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.

†Difference (drug minus placebo) in least-squares mean change from baseline

‡Dosages statistically significantly superior to placebo.

Figure 7: Change from Baseline in Total CMAI Score by Study Week in Patients with Agitation Associated with Dementia Due to Alzheimer's Disease (Study 7)



16 HOW SUPPLIED/STORAGE AND HANDLING

How Supplied

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- 0.25 mg tablets are light brown, round, shallow convex, bevel-edged body with “BRX” and “0.25” imprinted on one side
  NDC 42067-250-30 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 42067-252-30 Bottles of 30
- 1 mg tablets are light yellow, round, shallow convex, bevel-edged body with “BRX” and “1” imprinted on one side
  NDC 42067-254-30 Bottles of 30
- 2 mg tablets are light green, round, shallow convex, bevel-edged body with “BRX” and “2” imprinted on one side
  NDC 42067-256-30 Bottles of 30
- 3 mg tablets are light purple, round, shallow convex, bevel-edged body with “BRX” and “3” imprinted on one side
  NDC 42067-258-30 Bottles of 30
- 4 mg tablets are white, round, shallow convex, bevel-edged body with “BRX” and “4” imprinted on one side
  NDC 42067-260-30 Bottles of 30

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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)]*.

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)]*.

Potential for Cognitive and Motor Impairment

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)]*.

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MEDICATION GUIDE
REXULTI® (REX-ul-TE)
(brexpiprazole)
tablets, for oral use

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 without agitation that may happen with dementia due to Alzheimer's disease.
- **Increased risk of suicidal thoughts and actions.** REXULTI and antidepressant medicines may increase suicidal thoughts and actions in some people 24 years of age and younger, **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 REXULTI 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:

- along with antidepressant medicines to treat major depressive disorder (MDD) in adults
- to treat schizophrenia in adults and children ages 13 years and older
- to treat agitation that may happen with dementia due to Alzheimer's disease

REXULTI should not be used as an "as needed" treatment for agitation that may happen with dementia due to Alzheimer's disease.

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. Talk to your healthcare provider about the risk to your unborn baby if you take REXULTI during pregnancy.
    - Tell your healthcare provider if you become pregnant or think you are pregnant during treatment with REXULTI.
    - There is a pregnancy exposure registry for women who are exposed to REXULTI during pregnancy. 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 Poison Help Line at 1-800-222-1222 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?"**
- **Cerebrovascular problems, including stroke, 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
    - stiff muscles
    - confusion
    - changes in your pulse, blood pressure, heart rate, and breathing
    - 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 new or unusual strong urges or behaviors, 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) and fainting.** You may feel dizzy, lightheaded, or pass out (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, sleepiness, dizziness, common cold symptoms, 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 health professionals.

What are the ingredients in REXULTI?

Active ingredient: brexpiprazole

Inactive ingredients: lactose monohydrate, corn starch, microcrystalline cellulose, hydroxypropyl cellulose, low-substituted hydroxypropyl cellulose, magnesium stearate, hypromellose, and talc

For color: titanium dioxide, iron oxide, and ferrosoferric oxide

Manufactured by Otsuka Pharmaceutical Co., Ltd., Tokyo 101-8535, Japan
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Marketed by Lundbeck, Deerfield, IL 60015 USA

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Annotated Label Comparisons

PI Comparisons FDA VS. FLCPDIP
Differences
Updated information Adverse Reactions Contact
How Supplied/Storage and Handling added SIP804 language
Patient Information added SIP804 language
Listed new NDC #
Added Importation language & Importer name & address
Listed only drug strength purchased for program

FDA

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

Most common adverse reactions in adults were (6.1):

- *MDD*: Weight increased, somnolence, and akathisia (≥5% and at least twice the rate for placebo)
- *Schizophrenia*: Weight increased (≥4% and at least twice the rate for placebo)
- *Agitation associated with dementia due to Alzheimer's disease:* Nasopharyngitis, dizziness (≥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*.

16 HOW SUPPLIED/STORAGE AND HANDLING

How Supplied

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  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
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FLSIP

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Proposed Package Label

Label Comparisons FDA VS. FLCPDIP
Differences
NDC
GTN
Bar Codes FPO with Associated NDCs
SIP804 Importation Language
Label SIZE due to production process & adding SIP804 language
Importer Name & Address
Brand logos FPO low resolution. Native art files requested upon SIP804 approval.

Comparisons
FDA to FLSIP

Recent FDA Approved Label	US Proprietary Name	US Generic Name	US Strength	NDC	NDA or ANDA	Applicant Holder Name	Applicant Holder Address	US Active Ingredients	Date Labeling Prepared for FLSIP	FLSIP Proprietary Name	FLSIP Generic Name	FLSIP Strength	LSL NDC	Relabeler Name	Applicant Holder Name	Applicant Holder Address	Active Ingredients	FDA Comments
May-23	Rexulti	BREXPIPRAZOLE	0.25 mg	59148-035-13	205422	OTSUKA	Rockville, MD 20850	BREXPIPRAZOLE	Aug-23	Rexulti	BREXPIPRAZOLE	0.25 mg	42067-250-30	LifeScience Logistics, LLC	OTSUKA	Rockville, MD 20850	BREXPIPRAZOLE	none
May-23	Rexulti	BREXPIPRAZOLE	0.5 mg	59148-036-13	205422	OTSUKA	Rockville, MD 20850	BREXPIPRAZOLE	Aug-23	Rexulti	BREXPIPRAZOLE	0.5 mg	42067-252-30	LifeScience Logistics, LLC	OTSUKA	Rockville, MD 20850	BREXPIPRAZOLE	none
May-23	Rexulti	BREXPIPRAZOLE	1 mg	59148-037-13	205422	OTSUKA	Rockville, MD 20850	BREXPIPRAZOLE	Aug-23	Rexulti	BREXPIPRAZOLE	1 mg	42067-254-30	LifeScience Logistics, LLC	OTSUKA	Rockville, MD 20850	BREXPIPRAZOLE	none
May-23	Rexulti	BREXPIPRAZOLE	2 mg	59148-038-13	205422	OTSUKA	Rockville, MD 20850	BREXPIPRAZOLE	Aug-23	Rexulti	BREXPIPRAZOLE	2 mg	42067-256-30	LifeScience Logistics, LLC	OTSUKA	Rockville, MD 20850	BREXPIPRAZOLE	none
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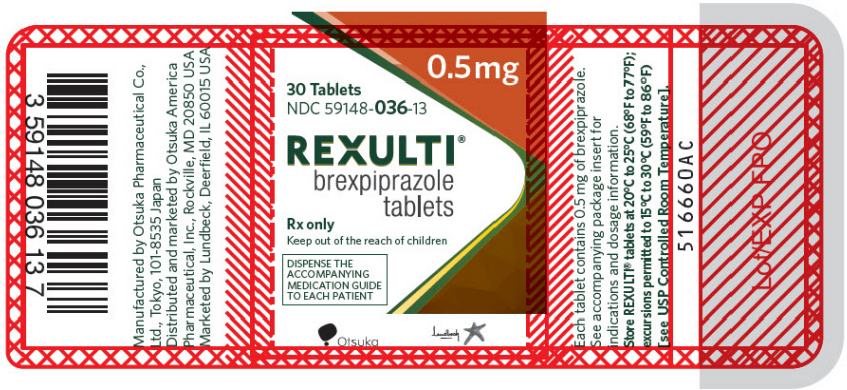
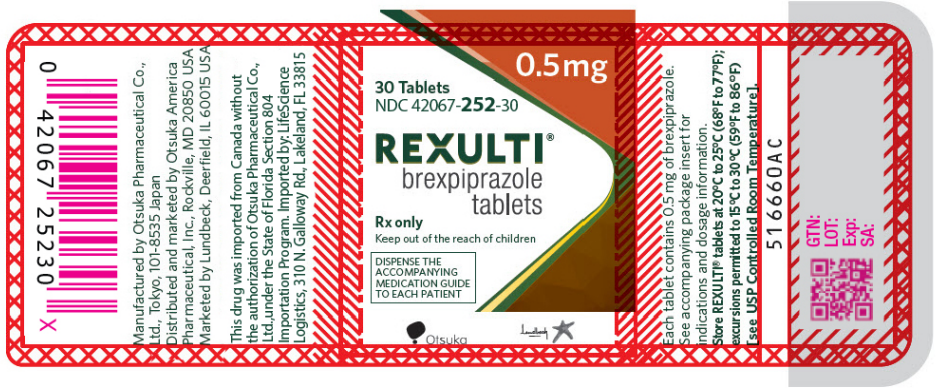
May-23	Rexulti	BREXPIPRAZOLE	4 mg	59148-040-13	205422	OTSUKA	Rockville, MD 20850	BREXPIPRAZOLE	Aug-23	Rexulti	BREXPIPRAZOLE	4 mg	42067-260-30	LifeScience Logistics, LLC	OTSUKA	Rockville, MD 20850	BREXPIPRAZOLE	none





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Recent FDA Approved Label	US Proprietary Name	US Generic Name	US Strength	NDC	NDA or ANDA	Applicant Holder Name	Applicant Holder Address	US Active Ingredients	Date Labeling Prepared for FLSIP	FLSIP Proprietary Name	FLSIP Generic Name	FLSIP Strength	LSL NDC	Relabeler Name	Applicant Holder Name	Applicant Holder Address	Active Ingredients	FDA Comments
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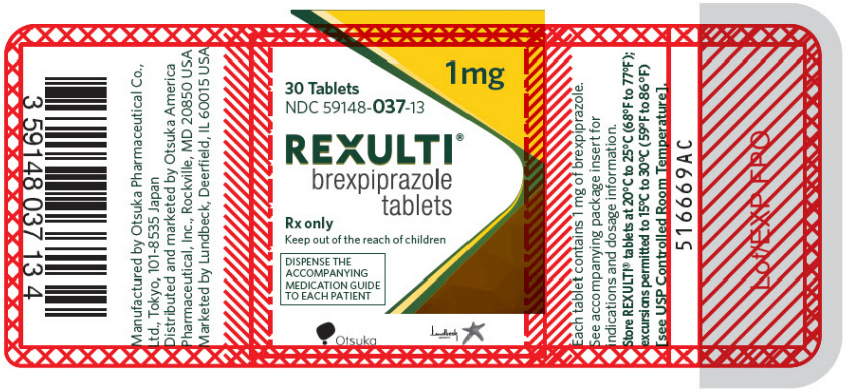

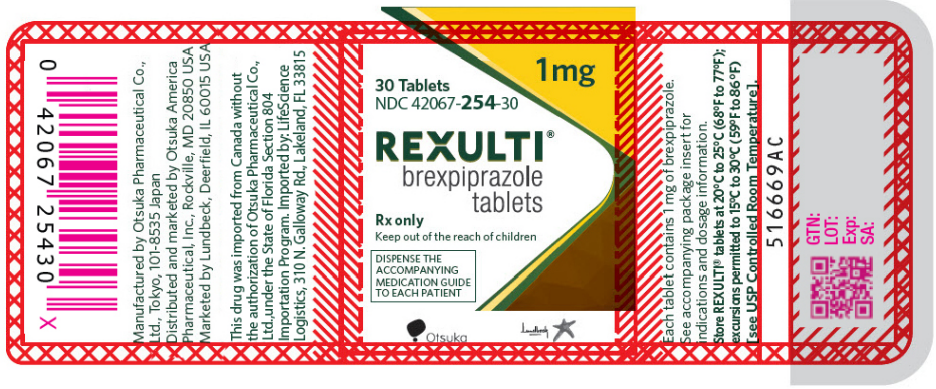

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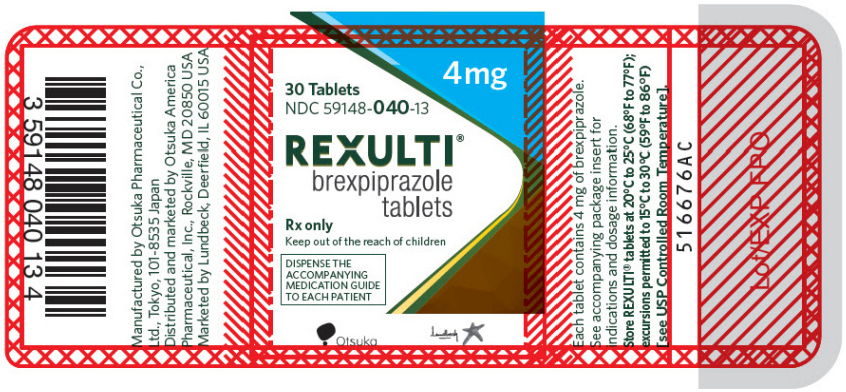

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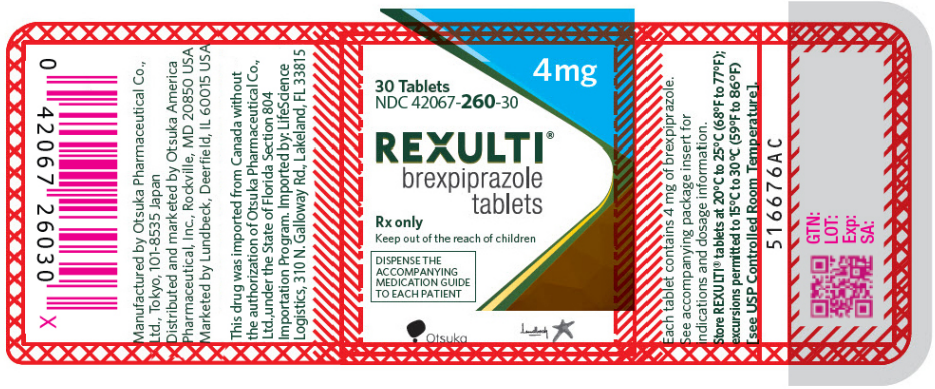

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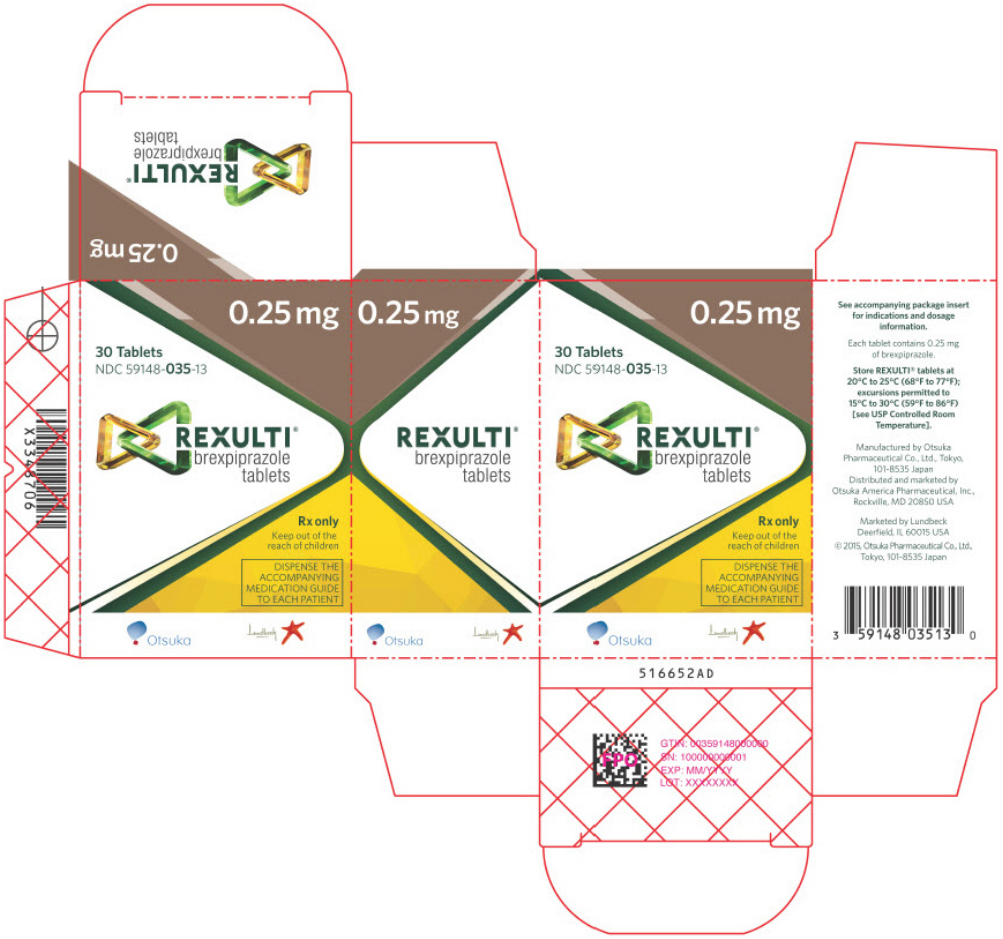

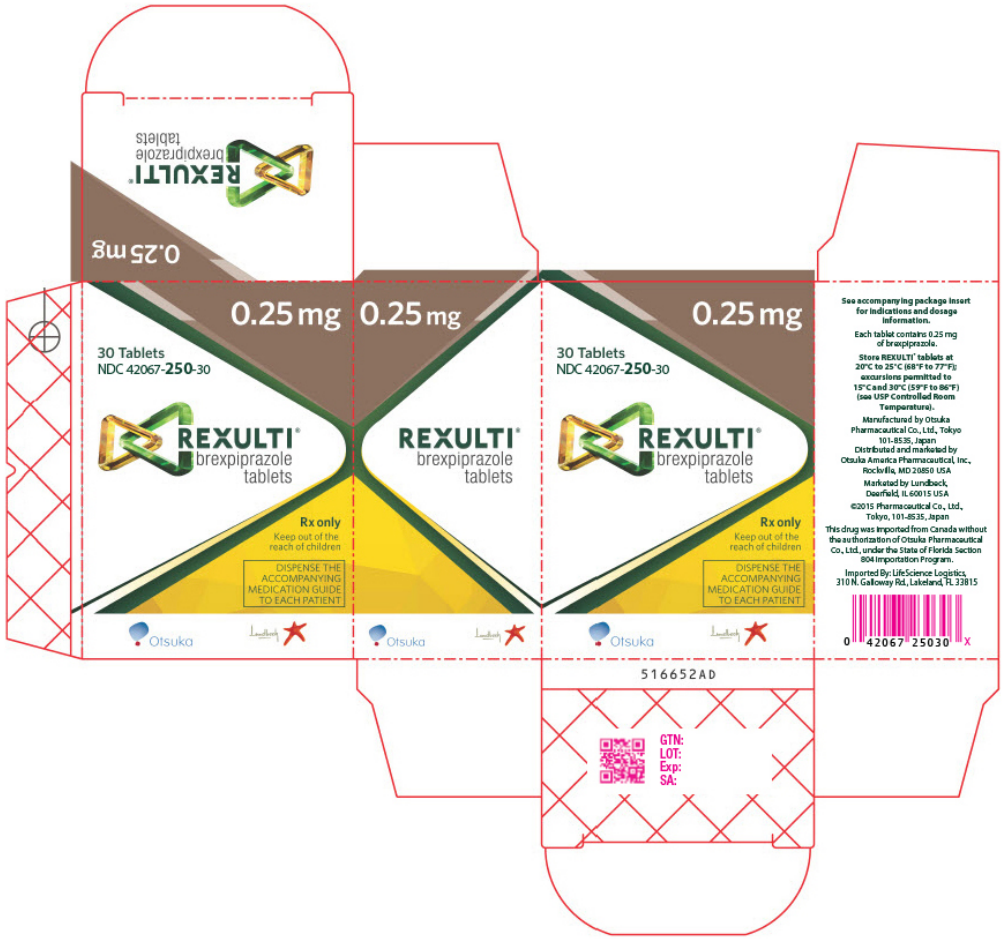

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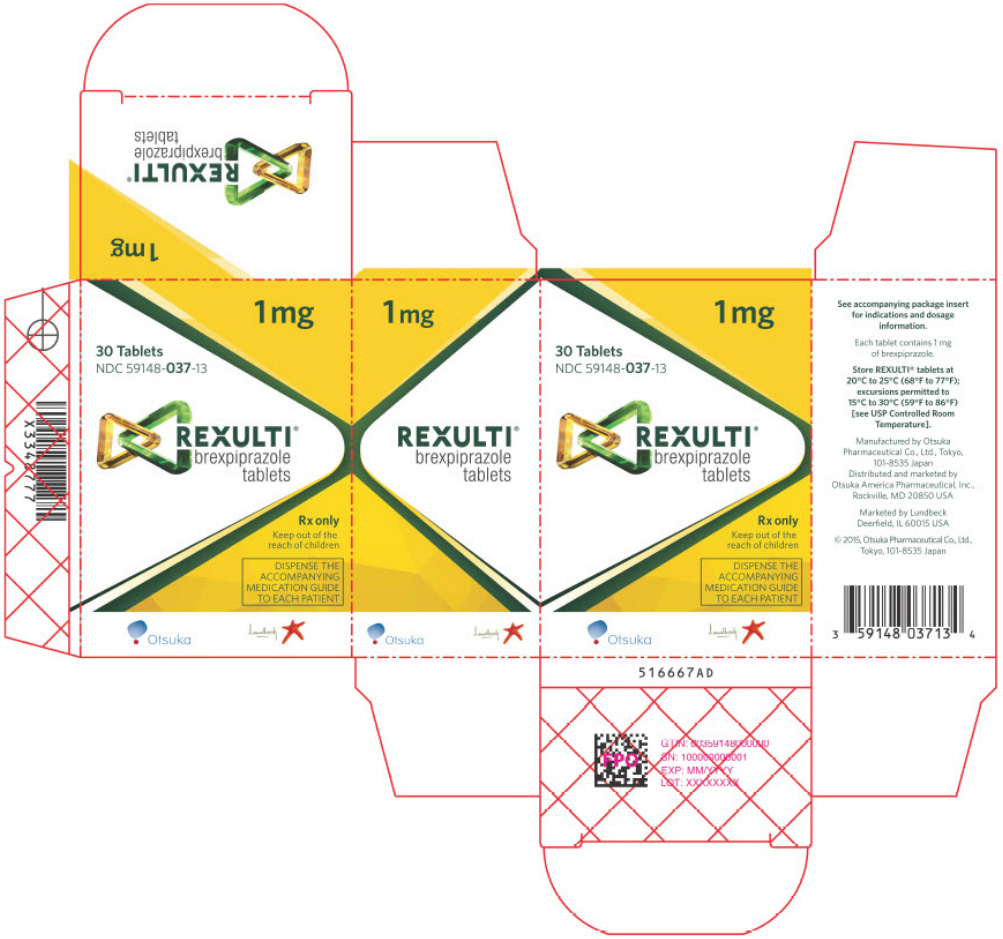

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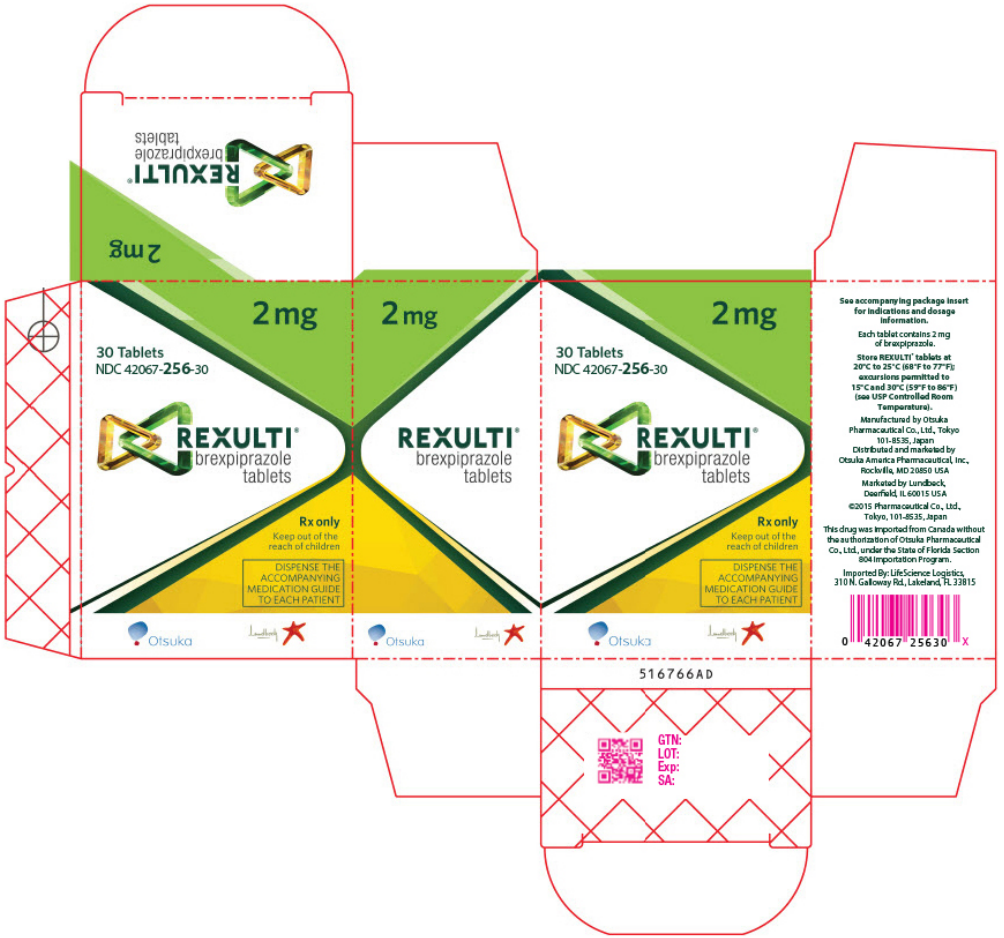

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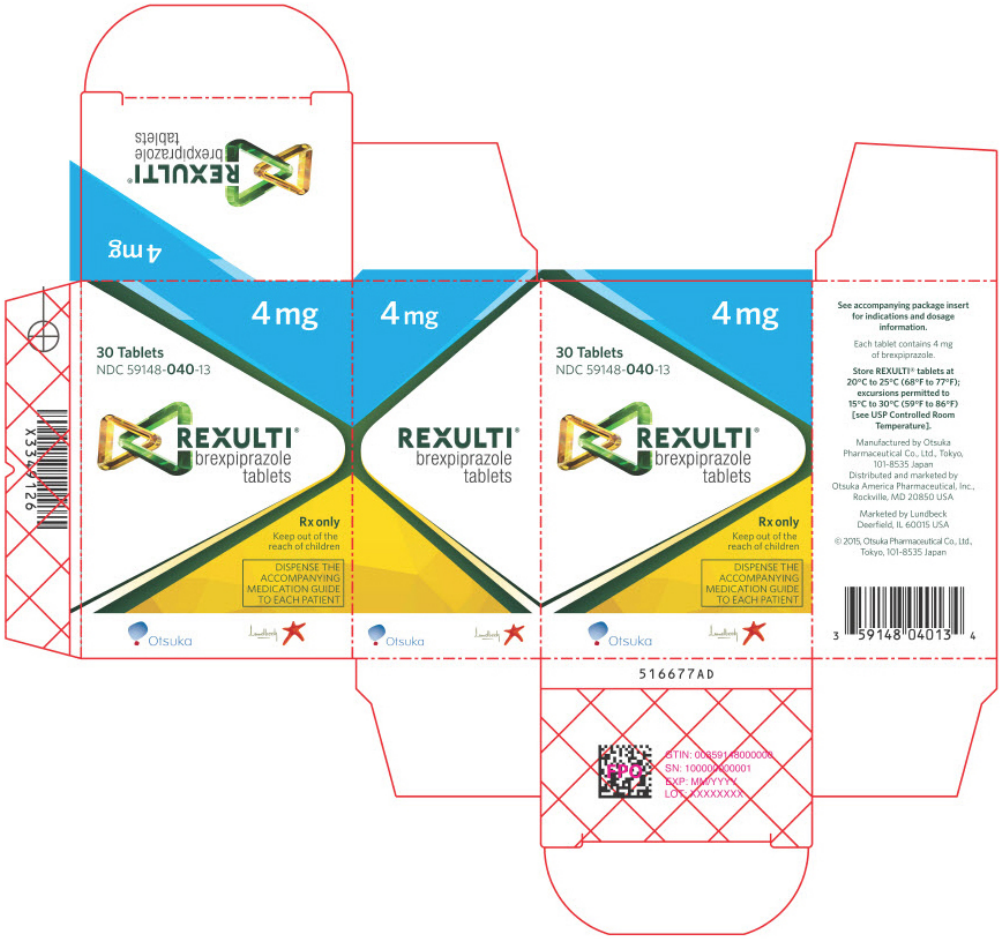
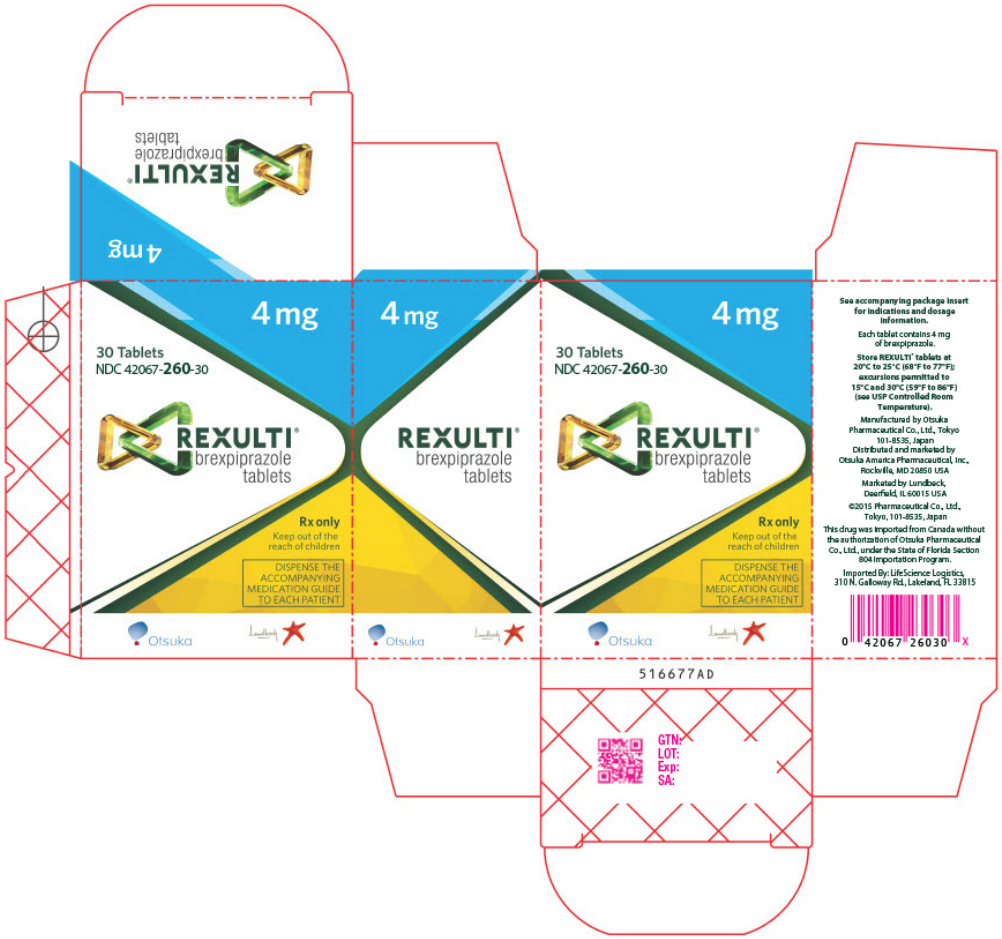




Canadian To FDA Drug Comparisons

Comparisons
Canada to FDA

Active Ingredient	Canadian Submission Number	Canadian Proprietary Name	Canadian Generic Name	DIN	Date Labeling Approved	Company Name	Address	Canadian Strength	Dosage Form	# of active Ingred.	Canadian Ingredients	US Proprietary Name	US Generic Name	US Strength	NDC	NDA or ANDA	Applicant Holder Name	US Active Ingredients	Comments for FDA
Brexpiprazole	242419	Rexulti	Brexpiprazole	02461749	Dec-20	OTSUKA PHARMACEUTICAL CO LTD	2-9 Kanda-Tsukasamachi, Chiyoda-Ku Tokyo Japan 101-8535	0.25 mg	tablet, oral	1	Brexpiprazole	Rexulti	Brexpiprazole	0.25 mg	59148-035-13	205422	OTSUKA	Brexpiprazole	n/a
Brexpiprazole	242419	Rexulti	Brexpiprazole	02461757	Dec-20	OTSUKA PHARMACEUTICAL CO LTD	2-9 Kanda-Tsukasamachi, Chiyoda-Ku Tokyo Japan 101-8535	0.5 mg	tablet, oral	1	Brexpiprazole	Rexulti	Brexpiprazole	0.5 mg	59148-036-13	205422	OTSUKA	Brexpiprazole	n/a
Brexpiprazole	242419	Rexulti	Brexpiprazole	0246765	Dec-20	OTSUKA PHARMACEUTICAL CO LTD	2-9 Kanda-Tsukasamachi, Chiyoda-Ku Tokyo Japan 101-8535	1 mg	tablet, oral	1	Brexpiprazole	Rexulti	Brexpiprazole	1 mg	59148-037-13	205422	OTSUKA	Brexpiprazole	n/a
Brexpiprazole	242419	Rexulti	Brexpiprazole	0246773	Dec-20	OTSUKA PHARMACEUTICAL CO LTD	2-9 Kanda-Tsukasamachi, Chiyoda-Ku Tokyo Japan 101-8535	2 mg	tablet, oral	1	Brexpiprazole	Rexulti	Brexpiprazole	2 mg	59148-038-13	205422	OTSUKA	Brexpiprazole	n/a
Brexpiprazole	242419	Rexulti	Brexpiprazole	02461781	Dec-20	OTSUKA PHARMACEUTICAL CO LTD	2-9 Kanda-Tsukasamachi, Chiyoda-Ku Tokyo Japan 101-8535	3 mg	tablet, oral	1	Brexpiprazole	Rexulti	Brexpiprazole	3 mg	59148-039-13	205422	OTSUKA	Brexpiprazole	n/a
Brexpiprazole	242419	Rexulti	Brexpiprazole	02461803	Dec-20	OTSUKA PHARMACEUTICAL CO LTD	2-9 Kanda-Tsukasamachi, Chiyoda-Ku Tokyo Japan 101-8535	4 mg	tablet, oral	1	Brexpiprazole	Rexulti	Brexpiprazole	4 mg	59148-040-13	205422	OTSUKA	Brexpiprazole	n/a

Canadian Monograph

PRODUCT MONOGRAPH

INCLUDING PATIENT MEDICATION INFORMATION

PrREXULTI®

Brexpiprazole Tablets

0.25 mg, 0.5 mg, 1 mg, 2 mg, 3 mg and 4 mg

Antipsychotic agent

Otsuka Pharmaceutical Co., Ltd.
Tokyo, 101-8535 Japan

Imported by:
Otsuka Canada Pharmaceutical Inc.
Saint-Laurent, QC
H4S 2C9

Marketed by:
Otsuka Canada Pharmaceutical Inc.
Saint-Laurent, QC
H4S 2C9

Lundbeck Canada Inc.
Saint-Laurent, QC
H4S 0A9

Date of Initial Approval:
February 16, 2017

Date of Revision:
September 29, 2020

Submission Control No: 232776

Table of Contents

PrREXULTI®

brexpiprazole

PART I: HEALTH PROFESSIONAL INFORMATION

SUMMARY REXULTI INFORMATION

Route of Administration	Dosage Form / Strength	Nonmedicinal Ingredients
Oral	Tablet, 0.25 mg, 0.5 mg, 1 mg, 2 mg, 3 mg and 4 mg	lactose monohydrate, corn starch, microcrystalline cellulose, hydroxypropyl cellulose, low-substituted hydroxypropyl cellulose, magnesium stearate, hypromellose, talc, titanium dioxide, ferric oxide yellow (0.25 mg, 0.5 mg, 1 mg, 2 mg), ferric oxide red (0.25 mg, 0.5 mg, 3 mg) and ferrosoferric oxide (0.25 mg, 2 mg, 3 mg)

INDICATIONS AND CLINICAL USE

Adults

Schizophrenia
REXULTI (brexpiprazole) is indicated for treatment of schizophrenia in adults.

In clinical trials, REXULTI was found to significantly improve both positive and negative symptoms.

Adjunctive Treatment of Major Depressive Disorder (MDD)
REXULTI is indicated for use as an adjunct to antidepressants for the treatment of major depressive disorder (MDD) in adult patients with an inadequate response to prior antidepressant treatments during the current episode (see CLINICAL TRIALS, Adjunctive Treatment of Major Depressive Disorder).

When considering the use of REXULTI as adjunctive treatment in MDD, clinicians must take into account the safety concerns associated with antipsychotic drugs, a class of drugs to which REXULTI belongs. Safety concerns of this class include: weight gain; hyperlipidemia; hyperglycaemia; Tardive Dyskinesia; and Neuroleptic Malignant Syndrome (see WARNINGS AND PRECAUTIONS, ADVERSE REACTIONS). REXULTI should only be prescribed in

patients with MDD by clinicians who are aware of the importance and are experienced in the early detection and management of the safety issues associated with this class of drugs.

The efficacy and safety of REXULTI in the adjunctive treatment of MDD were demonstrated in 6-week, double-blind, placebo-controlled trials in adult patients. Therefore, the required length of adjunctive treatment with REXULTI is not known. When prescribed as an adjunct to antidepressants in the treatment of MDD, REXULTI should be used for the shortest period of time that is clinically indicated (see CLINICAL TRIALS, Adjunctive Treatment of Major Depressive Disorder; DOSAGE AND ADMINISTRATION, Adjunctive Treatment of Major Depressive Disorder).

Clinical trials evaluating REXULTI in MDD did not include REXULTI monotherapy treatment arms. It is, therefore, not known whether efficacy in adjunct treatment is due to REXULTI alone or from combined treatment with an antidepressant.

Geriatrics (> 65 years of age):
REXULTI is not indicated in elderly patients with dementia (see WARNINGS AND PRECAUTIONS, Serious Warnings and Precaution Box and Special Populations). The safety and efficacy of REXULTI have not been systematically evaluated in patients 65 years of age or older. Caution should be used when treating geriatric patients (see WARNINGS AND PRECAUTIONS, Special Populations and ACTION AND CLINICAL PHARMACOLOGY).

Pediatrics (< 18 years of age):
The safety and efficacy of REXULTI have not been established in patients less than 18 years of age. REXULTI is not indicated in pediatric patients and its use is not recommended in this population (see WARNINGS AND PRECAUTIONS, Special Populations, Pediatrics).

CONTRAINDICATIONS

REXULTI is contraindicated in patients who are hypersensitive to this drug or to any ingredient in the formulation, including any non-medicinal ingredient, or component of the container. For a complete listing, see Dosage Forms, Composition and Packaging (see WARNINGS AND PRECATIONS – Immune, ADVERSE REACTIONS – Post-Market Adverse Drug Reactions).

WARNINGS AND PRECAUTIONS

Serious Warnings and Precautions

WARNING: INCREASED MORTALITY IN ELDERLY PATIENTS WITH DEMENTIA

Increased Mortality in Elderly Patients with Dementia
Elderly patients with dementia treated with atypical antipsychotic drugs are at an increased risk of death compared to placebo. Analyses of thirteen placebo-controlled trials with various atypical antipsychotics (modal duration of 10 weeks) in these patients showed a mean 1.6-fold increase in the death rate in the drug-treated patients. 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 (see WARNINGS AND PRECAUTIONS, Special Populations, Geriatrics (> 65 years of age)). REXULTI is not approved for the treatment of patients with dementia.

General

Body Temperature Regulation
Disruption of the body's ability to reduce core body temperature has been attributed to antipsychotic agents. Appropriate care is advised when prescribing REXULTI for patients who will be experiencing conditions which may contribute to an elevation in core body temperature (e.g., exercising strenuously, exposure to extreme heat, receiving concomitant medication with anticholinergic activity, or being subject to dehydration).

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.

Cardiovascular

Orthostatic Hypotension
In the short-term, placebo-controlled clinical studies of REXULTI in subjects with schizophrenia, the incidence of orthostatic hypotension-related adverse reactions in REXULTI-treated patients compared to placebo subjects included: dizziness (2.3% versus 1.4%), orthostatic hypotension (0.4% versus 0.2%), and syncope (0.1% versus 0%). In the short-term, placebo-controlled clinical studies of REXULTI + ADT in subjects with MDD, the incidence of orthostatic hypotension-related adverse reactions in REXULTI-treated subjects compared to placebo +ADT subjects included: dizziness (2.6% versus 1.6%), dizziness postural (0.1% versus 0.4%), orthostatic hypotension (0.1% versus 0%), and syncope (0.1% versus 0.4%).

Adverse reactions associated with orthostatic hypotension can include dizziness, lightheadedness and tachycardia. Generally, these risks are greatest at the beginning of treatment and during dose escalation. Patients at increased risk of these adverse reactions or at increased risk of developing complications from hypotension include those with dehydration, hypovolemia, treatment with antihypertensive medication, history of cardiovascular disease (e.g., heart failure, myocardial infarction, ischemia, or conduction abnormalities), history of cerebrovascular disease, as well as patients who are antipsychotic-naïve. In such patients, consider using a lower starting dosage and slower titration, and monitor orthostatic vital signs.

Patients with a recent history of myocardial infarction or unstable cardiovascular disease were excluded from clinical trials.

QT Interval

The effects of REXULTI on the QT/QTc interval were evaluated in a dedicated ECG study (see ACTION AND CLINICAL PHARMACOLOGY, Cardiac Electrophysiology). The trial involved administration of REXULTI at a therapeutic dose of 4 mg/day or a supratherapeutic dose of 12 mg/day for 11 days in 147 clinically stable patients with schizophrenia. On day 11, the maximum placebo-adjusted mean change from baseline in the QTcI interval was 8.3 ms (90% CI 3.7, 12.9) at 6 h post-dosing in the brexpiprazole 4 mg/day group (N=62) and 3.1 ms (90% CI -1.7, 8.0) at 4 h post-dosing in the brexpiprazole 12 mg/day group (N=53).

QTc prolongation may lead to an increased risk of ventricular arrhythmias including torsade de pointes. Torsade de pointes is a polymorphic ventricular tachyarrhythmia. Generally, the risk of torsade de pointes increases with the magnitude of QTc prolongation produced by the drug. Torsade de pointes may be asymptomatic or experienced by the patient as dizziness, palpitations, syncope, or seizures. If sustained, torsade de pointes can progress to ventricular fibrillation and sudden cardiac death.

Particular care should be exercised when administering REXULTI to patients who are suspected to be at an increased risk of experiencing torsade de pointes during treatment with a QTc-prolonging drug (see DRUG INTERACTIONS).

Risk factors for torsade de pointes in the general population include, but are not limited to, the following: female gender; age ≥65 years; baseline prolongation of the QT/QTc interval; presence of genetic variants affecting cardiac ion channels or regulatory proteins, especially congenital long QT syndromes; family history of sudden cardiac death at <50 years of age; cardiac disease (e.g., myocardial ischemia or infarction, congestive heart failure, cardiomyopathy, conduction system disease); history of arrhythmias; electrolyte disturbances (e.g., hypokalemia, hypomagnesemia, hypocalcemia) or conditions leading to electrolyte disturbances (e.g., persistent vomiting, eating disorders); bradycardia; acute neurological events (e.g., intracranial or subarachnoid haemorrhage, stroke, intracranial trauma); diabetes mellitus; and autonomic neuropathy.

When drugs that prolong the QTc interval are prescribed, healthcare professionals should counsel their patients concerning the nature and implications of the ECG changes, underlying

diseases and disorders that are considered to represent risk factors, demonstrated and predicted drug-drug interactions, symptoms suggestive of arrhythmia, risk management strategies, and other information relevant to the use of the drug. Patients should be advised to contact their healthcare provider immediately to report any new chest pain or discomfort, changes in heartbeat, palpitations, dizziness, lightheadedness, fainting, or changes in or new use of other medications.

Dependence/Tolerance

Brexpiprazole has not been systematically studied in humans for its potential for abuse, tolerance, or physical dependence. In drug dependence studies in animals, no withdrawal symptoms were observed upon abrupt cessation of dosing in rats and monkeys, and no frequent self-administration of brexpiprazole was observed in monkeys. While the clinical trials did not reveal any tendency for any drug-seeking behavior, these observations were not systematic and it is not possible to predict on the basis of this limited experience the extent to which a CNS-active drug will be misused, diverted, or abused once marketed. Consequently, patients should be evaluated carefully for a history of drug abuse, and such patients should be observed closely for signs of REXULTI misuse or abuse (e.g., development of tolerance, increases in dose, drug-seeking behavior).

Endocrine and Metabolism

Hyperglycemia and Diabetes Mellitus

In both short-term placebo-controlled trials and long-term open label trials with REXULTI, there have been reports of hyperglycemia in subjects treated with REXULTI. Diabetic ketoacidosis has occurred in patients with no reported history of hyperglycemia. Therefore, patients should have baseline and periodic monitoring of blood glucose and body weight.

Assessment of the relationship between atypical antipsychotic use and glucose abnormalities is complicated by the possibility of an increased background risk of diabetes mellitus in patients with schizophrenia and the increasing incidence of diabetes mellitus in the general population. Given these confounders, the relationship between atypical antipsychotic use and hyperglycemia-related adverse events is not completely understood. However, epidemiological studies which did not include REXULTI, suggest an increased risk of treatment-emergent hyperglycemia-related adverse events in patients treated with atypical antipsychotics. Because REXULTI was not marketed at the time these studies were performed, it is not known if brexpiprazole is associated with this increased risk. Precise risk estimates for hyperglycemia-related adverse events in patients treated with atypical antipsychotics are not available.

Patients should have baseline and periodic monitoring of blood glucose and body weight. Any patient treated with atypical antipsychotics should also be monitored for symptoms of hyperglycemia including polydipsia, polyuria, polyphagia, and weakness. Patients who develop symptoms of hyperglycemia during treatment with atypical antipsychotics should undergo fasting blood glucose testing. In some cases, hyperglycemia has resolved when the atypical antipsychotic was discontinued; however, some patients required continuation of anti-diabetic treatment despite discontinuation of the suspect drug. Patients with risk factors for diabetes

mellitus (e.g., obesity, family history of diabetes) who are starting treatment with atypical antipsychotics should undergo fasting blood glucose testing at the beginning of treatment and periodically during treatment. Patients with an established diagnosis of diabetes mellitus who are started on atypical antipsychotics should be monitored regularly for worsening of glucose control.

Weight Gain
Antipsychotic drugs have been associated with metabolic changes, including weight gain. Clinical monitoring of weight is recommended (see ADVERSE REACTIONS, Weight Gain).

Dyslipidemia
Undesirable alterations in lipids have been observed in subjects treated with atypical antipsychotics. Therefore, patients should have baseline and periodic monitoring of fasting lipid profile (see ADVERSE REACTIONS, Fasting Lipids).

Hyperprolactinemia
Like other antipsychotics, REXULTI can elevate prolactin levels. Elevations associated with REXULTI treatment are generally mild and may decline during administration, however, in some infrequent cases the effect may persist during chronic administration (see ADVERSE REACTIONS, Prolactin).

Hyperprolactinemia may suppress hypothalamic GnRH, resulting in reduced pituitary gonadotrophin secretion. This, in turn, may inhibit reproductive function by impairing gonadal steroidogenesis in both female and male patients. Galactorrhea, amenorrhea, gynecomastia, and impotence have been reported with prolactin-elevating compounds. Long-standing hyperprolactinemia when associated with hypogonadism may lead to decreased bone mineral density in both female and male patients.

Tissue culture experiments indicate that approximately one-third of human breast cancers are prolactin dependent *in vitro*, a factor of potential importance if the prescription of these drugs is considered in a patient with previously detected breast cancer. As is common with compounds which increase prolactin release, an increase in mammary gland neoplasia was observed in a REXULTI carcinogenicity study conducted in mice (see TOXICOLOGY). The physiological differences between rats and humans with regard to prolactin make the clinical significance of these findings unclear. To date, neither clinical nor epidemiological studies have shown an association between chronic administration of these drugs and mammary tumorigenesis.

Genitourinary

Although no cases of priapism were reported in clinical trials with REXULTI, rare cases of priapism have been reported with antipsychotic use. With other psychotropic drugs, this adverse reaction did not appear to be dose-dependent and did not correlate with the duration of treatment.

Hematologic

In clinical trial and/or post-marketing experience, events of leukopenia/neutropenia have been

reported temporally related to antipsychotic agents. Agranulocytosis has also been reported. Therefore, it is recommended that patients have their complete blood count (CBC) tested prior to starting REXULTI and then periodically throughout treatment.

Possible risk factors for leukopenia/neutropenia include pre-existing low white blood cell count (WBC) and history of drug-induced leukopenia/neutropenia. Patients with a history of a clinically significant low WBC or drug-induced leukopenia/neutropenia should have their complete blood count (CBC) monitored frequently during the first few months of therapy and discontinuation of REXULTI should be considered at the first sign of a clinically significant decline in WBC in the absence of other causative factors.

Patients with clinically significant neutropenia should be carefully monitored for fever or other symptoms or signs of infection and treated promptly if such symptoms or signs occur. Discontinue REXULTI in patients with severe neutropenia (absolute neutrophil count $<1x10^9$/L) and follow their WBC counts until recovery.

Venous thromboembolism
Venous thromboembolism (VTE), including fatal pulmonary embolism, has been reported with antipsychotic drugs including REXULTI, in case reports and/or observational studies. When prescribing REXULTI all potential risk factors for VTE should be identified and preventative measures undertaken.

Immune

Hypersensitivity
Spontaneous post-market reports of serious hypersensitivity reactions, such as anaphylaxis, angioedema and facial swelling, rash and urticaria, have been reported with REXULTI (see CONTRAINDICATIONS, ADVERSE REACTIONS – Post-Market Adverse Drug Reactions).

Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS)
Post market cases of DRESS have been reported in association with atypical antipsychotic drugs similar to brexpiprazole.

Neurologic

Neuroleptic Malignant Syndrome (NMS)
Neuroleptic malignant syndrome is a potentially fatal symptom complex that has been reported in association with antipsychotic drugs.

Clinical manifestations 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 creatine phosphokinase (CPK), myoglobinuria (rhabdomyolysis), and acute renal failure.

In arriving at a diagnosis, it is important to identify cases where the clinical presentation includes

both serious medical illness (e.g., pneumonia, systemic infection, etc.), and untreated or inadequately treated extrapyramidal signs and symptoms (EPS). Other important considerations in the differential diagnosis include central anticholinergic toxicity, heat stroke, drug fever, and primary central nervous system pathology.

The management of NMS should include 1) immediate discontinuation of all antipsychotic drugs including REXULTI and other drugs not essential to therapy; 2) intensive symptomatic treatment and medical monitoring; and 3) treatment of any concomitant serious medical problems for which specific treatments are available. There is no general agreement about specific pharmacological treatment for uncomplicated NMS.

If a patient requires antipsychotic drug treatment after recovery from NMS, the potential reintroduction of therapy should be very carefully considered. The patient should be carefully monitored, since recurrence of NMS has been reported.

Tardive Dyskinesia
A syndrome of potentially irreversible, involuntary, dyskinetic movements may develop in patients treated with antipsychotic drugs. Although the prevalence of the syndrome is highest among the elderly, especially elderly women, it is impossible to rely upon prevalence estimates to predict, at the inception of antipsychotic treatment, which patients are likely to develop the syndrome. Whether antipsychotic drugs differ in their potential to cause tardive dyskinesia is unknown.

The risk of developing tardive dyskinesia and the likelihood that it will become irreversible increase as the duration of treatment and the total cumulative dose of antipsychotic drugs administered to the patient increases. However, the syndrome can develop, although much less commonly, after relatively brief treatment periods at low doses.

There is no known treatment for established cases of tardive dyskinesia, although the syndrome may remit, partially or completely, if antipsychotic treatment is withdrawn. Antipsychotic treatment itself, however, may suppress (or partially suppress) the signs and symptoms of the syndrome and, thereby, may possibly mask the underlying process. The effect that symptomatic suppression has upon the long-term course of the syndrome is unknown.

Given these considerations, REXULTI should be prescribed in a manner that is most likely to minimize the occurrence of tardive dyskinesia. Chronic antipsychotic treatment should generally be reserved for patients who suffer from a chronic illness that (1) is known to respond to antipsychotic drugs and (2) for whom alternative, equally effective, but potentially less harmful treatments are not available or appropriate. In such patients who do require chronic treatment, the smallest dose and the shortest duration of treatment producing a satisfactory clinical response should be sought. The need for continued treatment should be reassessed periodically.

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.

Seizure/Convulsion
As with other antipsychotic drugs, REXULTI should be used cautiously in patients with a history of seizures or with conditions that lower the seizure threshold. Post-marketing cases of seizures have been reported with REXULTI. Conditions that lower the seizure threshold may be more prevalent in a population of 65 years or older (see ADVERSE REACTIONS – Post-Market Adverse Drug Reactions).

Potential for Cognitive and Motor Impairment
Like other antipsychotics drugs, REXULTI has the potential to impair judgment, thinking, or motor skills. Because REXULTI may cause somnolence and impair motor skills, patients should be cautioned about performing activities requiring mental alertness, such as operating hazardous machinery, including motor vehicles, until they are reasonably certain that REXULTI therapy does not affect them adversely.

Psychiatric

Suicide
Completed suicide, attempted suicide, suicidal behavior and suicidal ideation have been reported during post-market use of REXULTI. The possibility of a suicide attempt is inherent in psychotic illnesses and major depressive disorder (MDD). In addition, depression may be co-morbid with schizophrenia. The risk of suicide-related events during a depressive episode may persist until remission occurs. It is general clinical experience that the risk of suicide may increase in the early stages of recovery. Close supervision and appropriate clinical management of high-risk patients should accompany drug therapy. Prescriptions for REXULTI should be written for the smallest quantity of tablets consistent with good patient management, in order to reduce the risk of overdose (see ADVERSE REACTIONS – Post-Market Adverse Drug Reactions).

Impulse-Control Disorders/Compulsive Behaviors
Post-marketing reports of impulse-control disorders including pathological gambling and compulsive shopping, binge eating, and hypersexuality and other compulsive behaviors have been reported very rarely in patients treated with brexpiprazole. Patients with a prior history of impulse-control disorder may be at increased risk and should be monitored carefully. 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 increased impulse-control disorders or other compulsive behaviors while being treated with brexpiprazole. It should be noted that impulse-control symptoms can be associated with the underlying disorder. 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 while taking brexpiprazole.

Special Populations

Pregnant Women:
Teratogenic effects
There are no adequate and well-controlled studies of REXULTI in pregnant women. It is not known whether REXULTI can cause fetal harm when administered to a pregnant woman or can affect reproductive capacity.

In animal studies, brexpiprazole was not teratogenic and did not cause adverse developmental effects when administered during pregnancy at doses up to 24-fold in rats and 49-fold in rabbits, of the maximum recommended human dose (MRHD) of 4 mg/day on a mg/m^2 body surface area for a 60 kg patient (see TOXICOLOGY, Reproductive Toxicity). In a pregnant and lactating rat study, there was an increase in stillbirths and deaths of offspring at doses ≥ 10 mg/kg/day (24-fold MRHD on a mg/m^2 basis).

Non-teratogenic effects
Neonates exposed to antipsychotic drugs during the third trimester of pregnancy are at risk for extrapyramidal and/or withdrawal symptoms following delivery. There have been reports of agitation, hypertonia, hypotonia, tremor, somnolence, respiratory distress and feeding disorder in these neonates. These complications have varied in severity; while in some cases symptoms have been self-limited, in other cases neonates have required intensive care unit support and prolonged hospitalization.

REXULTI should not be used during pregnancy unless the expected benefits to the mother markedly outweigh the potential risks to the fetus.

Labor and Delivery: The effect of REXULTI on labor and delivery in humans is unknown. Parturition in rats was not affected by brexpiprazole.

Nursing Women: REXULTI was excreted in milk of rats during lactation. It is not known whether REXULTI or its metabolites are excreted in human milk. Because of the potential for serious adverse reactions in nursing infants, it is recommended that women receiving REXULTI should not breast-feed.

Pediatrics: (<18 years of age): The safety and effectiveness of REXULTI in patients under the age of 18 years have not been established and its use is not recommended.

Weight gain has been observed with atypical antipsychotic use in pediatric and adolescent patient populations. Independent of any drug-specific effects, weight gain can be associated with adverse changes in other metabolic parameters (e.g., glucose and lipid metabolism). Abnormal childhood weight and metabolic status can have adverse effects on cardiovascular outcomes in adulthood. Weight gain and adverse effects on other metabolic parameters associated with atypical antipsychotics can be more frequent or severe in pediatric and adolescent patients than in the adult patients.

The long-term safety, including cardiometabolic effects and effects on growth, maturation and

behavioural development in patients under 18 years of age has not been systematically evaluated.

Geriatrics (> 65 years of age): Clinical studies of REXULTI did not include sufficient numbers of patients aged 65 and older to determine whether they respond differently from younger subjects. 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, or cardiac function, and of concomitant disease or other drug therapy (see Serious Warnings and Precautions box, and ACTION AND CLINICAL PHARMACOLOGY).

Use in Elderly Patients with Dementia

Overall Mortality
Elderly patients with dementia treated with atypical antipsychotic drugs showed increased mortality compared to placebo in a meta-analysis of 13 placebo-controlled trials of various atypical antipsychotic drugs. REXULTI is not indicated for the treatment of patients with dementia (e.g. dementia-related psychosis) (see Serious Warnings and Precautions box).

Cerebrovascular Adverse Events, Including Stroke in Elderly Patients with Dementia
In placebo-controlled trials with some atypical antipsychotics, there was a higher incidence of cerebrovascular adverse events (cerebrovascular accidents and transient ischemic attacks) including fatalities compared to placebo-treated subjects. There are insufficient data with REXULTI to know if there is an increased risk of cerebrovascular events associated with REXULTI. REXULTI is not indicated for the treatment of patients with dementia (e.g. dementia-related psychosis) (see also Serious Warnings and Precautions box).

Dysphagia
Esophageal dysmotility and aspiration have been associated with antipsychotic drug use, including REXULTI. Aspiration pneumonia is a common cause of morbidity and mortality in elderly patients, in particular those with advanced Alzheimer's dementia. REXULTI and other antipsychotic drugs should be used cautiously in patients at risk for aspiration pneumonia.

Use in Patients with Hepatic Impairment
For patients with moderate to severe hepatic impairment (Child-Pugh score ≥7), the maximum recommended dosage is 1.25 mg once daily for patients with MDD, and 3 mg once daily for patients with schizophrenia (see DOSAGE AND ADMINISTRATION, Dosing Considerations; ACTION AND CLINICAL PHARMACOLOGY, Pharmacokinetics, Special Populations and Conditions).

Use in Patients with Renal Impairment
For patients with moderate, severe or end-stage renal impairment (creatinine clearance CL_{cr}<60 mL/minute), the maximum recommended dosage is 1.25 mg once daily for patients with MDD, and 3 mg once daily for patients with schizophrenia (see DOSAGE AND ADMINISTRATION, Dosing Considerations; ACTION AND CLINICAL PHARMACOLOGY, Pharmacokinetics, Special Populations and Conditions).

CYP2D6 Poor Metabolizers
Dosage adjustments are recommended in patients who are known cytochrome P450 (CYP) 2D6 poor metabolizers (see DOSAGE AND ADMINISTRATION, Dosing Considerations; ACTION AND CLINICAL PHARMACOLOGY, Pharmacokinetics, Special Populations and Conditions).

Lactose
REXULTI tablets contain lactose. This should be considered when prescribing to patients with rare hereditary problems of galactose intolerance, lactase deficiency or glucose-galactose malabsorption.

ADVERSE REACTIONS

Adverse Drug Reaction Overview

Clinical Trial Adverse Drug Reactions

Because clinical trials are conducted under very specific conditions the adverse reaction rates observed in the clinical trials may not reflect the rates observed in practice and should not be compared to the rates in the clinical trials of another drug. Adverse drug reaction information from clinical trials is useful for identifying drug-related adverse events and for approximating rates.

Short-term and long-term, Placebo-controlled Trials of Adult Patients with Schizophrenia

The following findings are based on two 6-week, placebo-controlled, fixed-dose clinical trials, and one long-term 52-week double blind placebo controlled randomized-withdrawal trial for schizophrenia in which REXULTI was administered at daily doses between 1 mg and 4 mg. These are referred to as Trials 1, 2 and 3 respectively. In Trials 1 and 2, 852 patients received REXULTI at fixed daily doses of 1, 2 or 4 mg and 368 patients received placebo. In Trial 3, following an open-label stabilization period of up to 36 weeks, 97 patients received REXULTI at flexible daily doses between 1 and 4 mg and 104 patients received placebo in the double-blind randomized withdrawal period; the mean daily REXULTI dose was 3.6 mg at the last visit in the study. This trial was terminated after efficacy was demonstrated in an interim analysis, and only 23 patients (11%), 14 in the REXULTI group and 9 in the placebo group, completed the 52-weeks of the double-blind, controlled period.

Safety data is also available for 1265 patients who participated in uncontrolled, open-label studies and received REXULTI daily doses from 1 mg to 4 mg; 604 patients completed at least 26 weeks and 372 completed at least 52 weeks in the open-label studies.

Most Common Adverse Events: There are no common adverse events that meet the criteria incidence of ≥5% and at least twice the rate of placebo in the Trials 1 and 2, the 6-week, placebo-controlled, fixed-dose trials, or Trial 3, during the double-blind randomized-withdrawal period.

Adverse Events Reported as Reasons for Discontinuation of Treatment: A total of 7.8% (67/852) REXULTI-treated subjects and 14.7% (54/368) of placebo-treated subjects discontinued due to adverse events. There were no adverse events associated with discontinuation in subjects treated with REXULTI that were at least 2% and at least twice the placebo rate.

Treatment emergent adverse events (TEAEs) associated with REXULTI (incidence of 2% or greater and REXULTI incidence greater than placebo) that occurred during acute therapy (up to 6-weeks in subjects with schizophrenia) are shown in Table 1.

Table 1: TEAEs with Incidence of 2% or More in Any Brex Group and Greater Than Placebo Group in Trials 1 and 2 (6-Week, Placebo-Controlled, Fixed-Dose Trials in Schizophrenia)

System Organ Class MedDRA Preferred Term	Brexpiprazole (mg/day)				Placebo (N=368) %
	1 mg (N=120) %	2 mg (N=368) %	4 mg (N=364) %	ALL (N=852) %	
Gastrointestinal disorders					
Diarrhoea	1%	3%	3%	3%	2%
Dyspepsia	6%	2%	3%	3%	2%
Dry mouth	1%	2%	2%	2%	1%
Abdominal pain upper	0%	1%	2%	1%	1%
Investigations					
Weight increased	3%	4%	4%	4%	2%
Blood creatine phosphokinase increased	4%	2%	2%	2%	1%
Musculoskeletal and connective tissue disorders					
Back pain	1%	2%	3%	2%	2%
Pain in extremity	3%	2%	2%	2%	1%
Myalgia	2%	1%	1%	1%	1%
Nervous system disorders					
Akathisia	4%	5%	7%	6%	5%
Tremor	2%	2%	3%	3%	1%
Sedation	2%	2%	3%	2%	1%
Dizziness	2%	1%	3%	2%	1%
Psychiatric disorders					
Restlessness	0%	1%	2%	1%	1%
Skin and Subcutaneous tissue disorders					
Rash	3%	2%	1%	2%	<1%

In the longer-term randomized-withdrawal Trial 3, the general treatment-emergent adverse event profile for the initial 12 to 36-week single-blind REXULTI treatment phase of this study was comparable to the one characterised in the 6-week, placebo-controlled, fixed-dose studies 1 and 2 described above. In the double-blind, randomized withdrawal phase of the study, there was only one potentially drug related adverse event that occurred at a rate greater than 2% and double that of placebo (tremor 3%). No additional safety concerns were noted, however, the exposure in the

double-blind phase was limited (97 in REXULTI and 104 in placebo, about 40% overall completed at least 6 months, and 11% overall completed the 52 weeks).

Short-term Placebo-Controlled Clinical Trials in Adult Patients Receiving REXULTI as Adjunctive Treatment in Major Depressive Disorder (MDD)

The following findings are based on four phase 3, 6-week, placebo-controlled trials (331-10-228, 331-10-227, 331-13-214, 331-12-282), three of which were fixed-dose and one which was flexible-dose with an active reference. These are referred to as Trials 4, 5, 6 and 7 respectively.

In total 1032 patients were treated with REXULTI in the 6-week trials. In Trials 4, 5 and 6, 835 patients received REXULTI at fixed daily doses of 1, 2 or 3 mg and 613 patients received placebo, added to their current antidepressant therapy (ADT). In Trial 7, 197 patients received REXULTI at flexible daily doses of 2 to 3 mg + ADT, 100 patients received an active reference + ADT, and 206 patients received placebo + ADT. In Trial 7 the mean daily REXULTI dose was 2.2 mg at the last visit in the study.

Safety data are also available for 2240 patients who participated in uncontrolled, open-label studies and received REXULTI daily doses from 1 mg to 3 mg with ADT; 1304 patients completed at least 26 weeks and 1002 completed at least 52 weeks in the open-label studies.

Most Common Adverse Events: The most common adverse events (incidence of ≥ 5% in the REXULTI +ADT group and at least twice the rate of placebo + ADT) during short-term and long-term studies were akathisia and weight increased.

Adverse Events Reported as Reasons for Discontinuation of Treatment: In the 6-week studies a total of 2.4% (37/1520) REXULTI+ADT-treated subjects and 0.7% (8/1132) of placebo+ADT-treated subjects discontinued due to adverse events. There were no adverse event associated with discontinuation in subjects treated with REXULTI+ADT that were at least 2% and at least twice the placebo + ADT rate.

Treatment emergent adverse events associated with the use of REXULTI+ADT (incidence of 2% or greater and REXULTI+ADT incidence greater than adjunctive placebo+ADT) that occurred during acute therapy (6-weeks in patients with MDD) in fixed- and flexible-dose trials are shown in Table 2.

Table 2: TEAEs with Incidence of 2% or More in Any Brexpiprazole Dose Group (1 to 3 mg) and Greater than Placebo Group in Trials 4, 5, 6 and 7 (6-Week, Placebo-Controlled, Fixed Dose and Flexible Dose Trials in Adjunctive Treatment in MDD)

System Organ Class MedDRA Preferred Term	Brexpiprazole (mg/day)+ADT					Placebo+ADT (N=819) %
	1 mg (N=226) %	2 mg (N=380) %	3 mg (N=229) %	2-3 mg/day[1] (N=197) %	ALL (N=1032) %	
Subjects with any TEAE	55%	60%	63%	51%	58%	49%
Eye disorders						
Vision blurred	1%	2%	2%	1%	2%	0%
Gastrointestinal Disorders						
Constipation	3%	3%	1%	1%	2%	1%
Dry mouth	1%	3%	1%	1%	2%	1%
Flatulence	2%	1%	1%	1%	1%	1%
Diarrhea	4%	3%	2%	0%	2%	3%
General Disorders and Administration Site Conditions						
Fatigue	3%	2%	5%	2%	3%	1%
Asthenia	0%	<1%	0%	2%	1%	<1%
Infections and Infestations						
Nasopharyngitis	7%	3%	3%	5%	4%	3%
Investigations						
Weight Increased	7%	7%	6%	4%	6%	2%
Blood cortisol decreased	4%	0%	3%	0%	1%	1%
Blood prolactin increased	<1%	1%	3%	0%	1%	0%
Metabolism and Nutrition Disorders						
Increased Appetite	3%	4%	2%	3%	3%	2%
Musculoskeletal and Connective Tissue disorders						
Back Pain	1%	2%	0%	1%	1%	2%
Nervous System Disorders						
Akathisia	4%	8%	14%	6%	8%	3%
Headache	9%	4%	6%	6%	6%	6%
Somnolence	4%	5%	6%	6%	5%	1%
Tremor	4%	2%	5%	1%	3%	1%
Dizziness	1%	4%	2%	4%	3%	1%
Psychiatric Disorders						
Restlessness	2%	6%	4%	3%	4%	1%
Insomnia	2%	3%	3%	3%	3%	2%
Anxiety	2%	3%	4%	1%	2%	1%
Irritability	1%	1%	<1%	2%	1%	1%

Legend: ADT=antidepressant

[1]Brex 2-3 mg/day group is from flexible-dose trial 7 (Trial 331-12-282)

Selected Adverse Events

Extrapyramidal Symptoms

Schizophrenia

In Trials 1 and 2, the incidence of reported EPS-related events, excluding akathisia events, was 5.1% versus 3.5% for placebo-treated subjects. The incidence of akathisia events for REXULTI-treated subjects was 5.4% versus 4.9% for placebo-treated subjects. Akathisia was reported more often during Weeks 1 through 3 and was mild to moderate in severity. The incidence of EPS-related TEAEs is presented in Table 3.

Table 3: Incidence of EPS-related TEAEs in Short-term Controlled Schizophrenia Trials 1 and 2

EPS Class Adverse Event MedDRA Preferred Term	Brexpiprazole (mg/day)				Placebo N = 368 %
	1 mg N = 120 %	2 mg N = 368 %	4 mg N = 364 %	ALL N = 852 %	
Subjects with any adverse event	7%	10%	14%	11%	8%
Total Akathisia Events[a]	5%	5%	7%	6%	5%
Total Dyskinetic Events[b]	0%	<1%	<1%	<1%	<1%
Total Dystonic Events[c]	2%	1%	2%	2%	2%
Total Parkinsonian Events[d]	2%	4%	6%	4%	2%
Total Residual Events[e]	0%	0%	<1%	<1%	0%

[a] Total Akathisia events includes adverse event terms: akathisia, psychomotor hyperactivity
[b] Total Dyskinetic events includes adverse events: dyskinesia, tardive dyskinesia
[c] Total Dystonic events includes adverse event terms: dystonia, muscle rigidity, muscle spasms
[d] Total Parkinsonian events includes adverse event terms: bradykinesia, extrapyramidal disorder, parkinsonism, tremor
[e] Total Residual events includes adverse event terms: muscle twitching

In Trials 1 and 2, data was objectively collected on the Simpson Angus Rating Score (SAS) for extrapyramidal symptoms (EPS), the Barnes Akathisia Global Score (BARS) for akathisia and the Abnormal Involuntary Movement Score (AIMS) for dyskinesia. The incidence of EPS change is presented in Table 4.

Table 4: Change in EPS Compared to Placebo in Schizophrenia Trials 1 and 2

Proportion of Subjects with Shifts (worsening) from Baseline				
	Brexpiprazole (mg/day)			
	1 mg	**2 mg**	**4 mg**	**Placebo**
AIMS[a] Total Score	1% (1/120)*	3% (12/361)*	4% (13/362)*	4% (13/361)*
BARS[b] Global Score	1% (1/119)*	1% (2/361)*	2% (9/362)*	1% (5/362)*
SAS[c] Total Score	6% (7/119)*	6% (21/356)*	8% (28/357)*	5% (19/356)*

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

[a] Abnormal Involuntary Movement Scale - %shifts from ≤1 at baseline to any post-baseline value ≥2

[b] Barnes Akathisia Rating Scale- %shifts from ≤2 at baseline to any post-baseline value >2

[c] Simpson Angus Scale- %shifts from ≤3 at baseline to any post-baseline value >3

Table 5 presents the reported incidence of concomitant medications used to treat EPS-related TEAEs, including akathisia.

Table 5: Incidence of Reported Concomitant Use to Treat EPS-related TEAEs for Short-term Controlled Schizophrenia Trials 1 and 2

Drug Class **Medication Preferred Name**	**Brexpiprazole (mg/day)**			**Placebo** **N = 368** **n (%)**
	1 mg **N = 120** **n (%)**	**2 mg** **N = 368** **n (%)**	**4 mg** **N = 364** **n (%)**	
Total using 1 or more medications	5 (4.2)	23 (6.3)	34 (9.3)	19 (5.2)
Anti-Parkinson Drugs	4 (3.3)	18 (4.9)	26 (7.1)	15 (4.1)
Beta Blocking Agents	1 (0.8)	8 (2.2)	11 (3.0)	6 (1.6)

Adjunctive Treatment in Major Depressive Disorder (MDD)

In Trials 4, 5 and 6, the incidence of reported EPS-related events, excluding akathisia events, was 5.3% versus 2.4% for placebo-treated subjects. The incidence of akathisia events for REXULTI-treated subjects was dose-dependent. In most cases, akathisia was assessed as mild or moderate in severity. Discontinuations due to akathisia were reported only for REXULTI-treated subjects (0.3% for REXULTI 2 mg/day + ADT, 2.2% for REXULTI 3 mg/day + ADT).

In Trial 7, the incidence of reported EPS-related events, excluding akathisia events, was 2.5% versus 0.5% for placebo-treated subjects. The incidence of akathisia events for REXULTI-treated subjects was 6.1% (2-3 mg) in the REXULTI +ADT group versus 1.9% in the placebo+ADT group. In most cases, akathisia was assessed as mild or moderate in severity.

The incidence of EPS-related TEAEs in the short-term fixed-dose and flexible dose trials is presented in Table 6.

Table 6: Incidence of EPS-related TEAEs in Short-term Fixed-dose Trials 4, 5, and 6 and Short-term Flexible dose Trial 7 in Adjunctive Treatment in MDD

EPS Category	Brexpiprazole (mg/day)+ADT					Placebo+ADT N = 819 %
	1 mg N = 226 %	2 mg N = 380 %	3 mg N = 229 %	2-3 mg[1] N = 197 %	ALL N = 1032 %	
Subjects with any adverse event	10%	13%	18%	9%	13%	5%
Total Akathisia Events[a]	4%	8%	14%	6%	8%	3%
Total Dyskinesia Events[b]	<1%	0%	0%	0%	<1%	0%
Total Dystonic Events[c]	1%	1%	2%	2%	1%	1%
Total Parkinsonian Events[d]	5%	4%	6%	1%	4%	2%
Total Residual Events[e]	<1%	1%	0%	0%	1%	0%

Legend: ADT=antidepressant
[a] Total Akathisia events includes adverse event terms: akathisia
[b]Total Dyskinetic events includes adverse events: dyskinesia
[c] Total Dystonic events includes adverse event terms: dystonia, muscle contractions involuntary, muscle rigidity, muscle spasms
[d] Total Parkinsonian events includes adverse event terms: cogwheel rigidity, extrapyramidal disorder, hypertonia, hypokinesia, parkinsonian gait, parkinsonian rest tremor, parkinsonism, tremor
[e] Total Residual events includes adverse event terms: muscle twitching
[1]Brex 2-3 mg/day group is from flexible-dose trial 7 (Trial 331-12-282)

In Trials 4, 5, 6 and 7, data was objectively collected on the Simpson Angus Rating Score (SAS) for extrapyramidal symptoms (EPS), the Barnes Akathisia Global Score (BARS) for akathisia and the Abnormal Involuntary Movement Score (AIMS) for dyskinesia. The incidence of EPS change is presented in Table 7.

Table 7: Change in EPS Compared to Placebo in MDD Trials 4, 5, 6 and 7

	Proportion of Subjects with Shifts (worsening) from Baseline				
	Brexpiprazole (mg/day)+ADT				
	1 mg	**2 mg**	**3 mg**	**2-3 mg[1]**	**Placebo+ADT**
AIMS[a] Total Score	3% (6/222)*	3% (11/367)*	3% (6/220)*	0% (0/191)*	1% (6/806)*
BARS[b] Global Score	1% (3/220)*	6% (23/373)*	6% (12/220)*	4% (7/191)*	2% (14/810)*
SAS[c] Total Score	1% (3/221)*	4% (16/372)*	5% (10/220)*	0% (0/191)*	2% (16/811)*

Legend: ADT=antidepressant

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

[a] Abnormal Involuntary Movement Scale - %shifts from ≤1 at baseline to any post-baseline value ≥2

[b] Barnes Akathisia Rating Scale- %shifts from ≤2 at baseline to any post-baseline value >2

[c] Simpson Angus Scale- %shifts from ≤3 at baseline to any post-baseline value >3

[1]Brex 2-3 mg/day group is from flexible-dose trial 7 (Trial 331-12-282)

Table 8 presents the reported incidence of concomitant medications used to treat EPS-related TEAEs, including akathisia during Trials 4, 5, 6 and 7.

Table 8: Incidence of Reported Concomitant Use to Treat EPS-related TEAEs for Short-term Controlled MDD Adjunctive Trials 4, 5, 6 and 7

Drug Class Medication Preferred Name	**Brexpiprazole (mg/day)+ADT**				**Placebo+ADT N = 819 n (%)**
	1 mg N = 226 n (%)	**2 mg N = 380 n (%)**	**3 mg N = 229 n (%)**	**2-3 mg[1] N = 197 n (%)**	
Total using 1 or more medications	2 (0.9)	15 (3.9)	16 (7.0)	7 (3.6)	7 (0.9)
Anti-Parkinson Drugs	2 (0.9)	2 (0.5)	9 (3.9)	1 (0.5)	2 (0.2)
Beta Blocking Agents	0 (0.0)	12 (3.2)	7 (3.1)	6 (3.0)	5 (0.6)
Psycholeptics	0 (0.0)	3 (0.8)	5 (2.2)	0 (0)	0 (0.0)

Legend: ADT=antidepressant

[1]Brex 2-3 mg/day group is from flexible-dose trial 7 (Trial 331-12-282)

Weight Gain

Schizophrenia

Table 9 shows weight gain data at last visit and percentage of adult subjects with ≥7% increase in body weight at any visit from Trials 1 and 2.

Table 9: Changes in Weight (kg) - Trials 1 and 2 (up to 6 weeks)

	Brexpiprazole (mg/day)			
	1 mg/day N=120	**2 mg/day N=362**	**4 mg/day N=362**	**Placebo N=362**
	Mean Change from Baseline (kg) at Last Visit			
All Subjects	+1.0	+1.2	+1.2	+0.2
	Proportion of Subjects with a ≥7% Increase in Body Weight (kg) at Any Visit			
	N=120	**N=368**	**N=364**	**N=368**
≥7% Increase	10.0% (12/120)	10.5% (38/362)	10.2% (37/362)	4.1% (15/362)

The percentage of subjects in the 6-week Trials 1 and 2 with an increase of ≥7% in body weight was 10.5% and 10.2% in the REXULTI 2 and 4 mg/day group respectively, compared with 4.1% in the placebo group.

During the longer-term randomized-withdrawal Trial 3 the proportion of subjects with a ≥7% *increase* in body weight at any visit was 5.2% (5/96) in the REXULTI-treated group compared to 1.0% (1/104) in the placebo group. The proportion of subjects with a ≥7% *decrease* in body weight at any visit was 9.3% (9/96) in the REXULTI-treated group compared to 15.3% (16/104) in the placebo group. In the stabilization phase of this trial, the proportion of subjects with a ≥7% *increase* in body weight at any visit was 11.3% (52/462) and with a ≥7% *decrease* in body weight at any visit was 3.9% (18/462).

In the long-term, open-label schizophrenia studies, the mean change in body weight from baseline to last visit was 1.0 kg (N=1468). The proportion of subjects with a ≥7% increase in body weight at any visit was 17.9% (226/1257) and with a ≥7% decrease in body weight at any visit was 8.2% (104/1257). Weight gain led to discontinuation of study medication in 0.4% (5/1265) of subjects.

Adjunctive Treatment in Major Depressive Disorder (MDD)

Table 10 shows weight gain data at last visit and percentage of adult subjects with ≥7% increase in body weight at any visit from Trials 4, 5, 6 and 7.

Table 10: Changes in Weight (kg) - Trials 4, 5, 6 and 7 (up to 6 weeks)

	Brexpiprazole (mg/day)+ADT				
	1 mg/day N=225	**2 mg/day N=379**	**3 mg/day N=228**	**2-3 mg/day[1] N=193**	**Placebo+ADT N=819**
	Mean Change from Baseline (kg) at Last Visit				
All Subjects	+1.3	+1.6	+1.6	+1.1	+0.3
	Proportion of Subjects with a ≥7% Increase in Body Weight (kg) at Any Visit				
	N=225	**N=379**	**N=229**	**N=193**	**N=609**
≥7% Increase	4.9% (11/225)	4.5% (17/379)	2.2% (5/228)	5.7% (11/193)	1.8% (15/814)

Legend: ADT=antidepressant
[1]Brex 2-3 mg/day group is from flexible-dose trial 7 (Trial 331-12-282)

In the long-term open label studies the proportion of subjects with a ≥7% increase in body weight at last visit (LOCF) was 22.1% (494/2232) and with a ≥7% decrease in body weight was 3.2% (72/2232). At 52 weeks (completers), the proportion of subject with a ≥7% increase in body weight at was 28.2 % (286/1013) and with a ≥7% decrease in body weight was 3.7% (37/1013). Weight gain led to discontinuation of study medication in 3.8% (84/2240) of subjects.

Constipation

Patients should be advised of the risk of severe constipation during REXULTI treatment, and they should tell their doctor if constipation occurs or worsens, since they may need medical intervention.

Less Common Clinical Trial Adverse Drug Reactions (<2%)

Other adverse reactions (<2% frequency in REXULTI-treated patients and greater than placebo) reported in the short-term, placebo-controlled trials in subjects with schizophrenia and MDD (N=2926) and in the long-term placebo-controlled trials in subjects with schizophrenia (N=97), 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.

Blood and Lymphatic System Disorders:
Infrequent: Anemia
Cardiovascular Disorders:
Infrequent: Vision Blurred, Sinus Bradycardia, Atrioventricular Block First Degree, Palpitations
Endocrine Disorders:
Infrequent: Hyperprolactinemia
Eye Disorders:
Infrequent: Lacrimation increased, Blepharospasm

Gastrointestinal Disorders:

Infrequent: Salivary Hypersecretion, Dental Caries, Abdominal Distension, Gastroesophageal Reflux Disease, Toothache

General Disorders & Administration Site Conditions:

Infrequent: Asthenia, Pyrexia, Chest Pain

Infections and Infestations:

Frequent: Upper Respiratory Tract Infection

Infrequent: Bronchitis, Conjunctivitis, Urinary Tract Infection

Investigations:

Infrequent: Hepatic Enzyme Increased, Blood Triglycerides Increased, Aspartate Aminotransferase Increased

Musculoskeletal and Connective Tissue Disorders:

Infrequent: Musculoskeletal Pain, Musculoskeletal Stiffness, Rhabdomyolysis

Nervous System Disorders:

Infrequent: Psychomotor Activity, Extrapyramidal Disorder

Psychiatric Disorders:

Infrequent: Abnormal Dreams, Bruxism, Tension

Respiratory, Thoracic and Mediastinal Disorders:

Infrequent: Cough, Dyspnea

Skin and Subcutaneous Tissue Disorders:

Infrequent: Night Sweats

Vascular Disorders:

Infrequent: Hypertension, Orthostatic Hypotension, Hypotension, Flushing

Abnormal Hematologic and Clinical Chemistry Findings

Fasting Glucose

Schizophrenia

In the 6-week Trials 1 and 2, the proportion of patients with changes in fasting glucose to post-baseline high (≥126 mg/dL) results were comparable between REXULTI and placebo treated subjects.

In the longer-term randomized-withdrawal Trial 3, 7% of patients with normal baseline fasting glucose (N=388) had changes to high fasting glucose during the single-blind REXULTI treatment in the Stabilization phase. During the double-blind phase, from the patients with normal baseline fasting glucose, 4.5% in the REXULTI group (3/66) and 0% in the placebo group (0/62) had changes to high fasting glucose.

In the long-term, open-label schizophrenia studies, 7% of patients with normal baseline fasting glucose experienced a shift from normal to high while taking REXULTI, 17% of subjects with borderline fasting glucose experienced shifts from borderline to high. Combined, 9% of subjects with normal or borderline fasting glucose experienced shifts to high fasting glucose during the long-term schizophrenia studies.

Adjunctive Treatment in Major Depressive Disorder (MDD)

In the 6-week Trials 4, 5 and 6, the proportion of patients with changes in fasting glucose from normal values at baseline (ie, < 100 mg/dL) to post-baseline high (≥126 mg/dL) results were comparable between REXULTI+ADT and placebo+ADT treated subjects. In Trial 7, the percentage of patients with a shift in fasting glucose from a normal value (ie, < 100 mg/dL) at baseline to a high value (ie, ≥ 126 mg/dL) was 0.8% in the flexible-dose REXULTI + ADT group compared to 0% in the placebo + ADT group. Mean changes from baseline to last visit in the REXULTI + ADT groups were similar to the placebo + ADT group for HbA1c.

In the long-term, open-label MDD studies, 5.2% of patients with normal baseline fasting glucose experienced a shift from normal to high while taking REXULTI + ADT, 24.4% of subjects with borderline fasting glucose experienced shifts from borderline to high. Combined, 9.1% of subjects with normal or borderline fasting glucose experienced shifts to high fasting glucose during the long-term MDD studies.

Fasting Lipids

Schizophrenia

In Trials 1 and 2, the proportion of patients with clinically significant changes from baseline in fasting total cholesterol, LDL cholesterol, and HDL cholesterol were similar in REXULTI- and placebo-treated subjects. Table 11 shows the proportions of subjects with changes in fasting triglycerides.

Table 11: Change in Fasting Triglycerides in Trials 1 and 2 (up to 6 weeks)

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

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

In the longer-term randomized-withdrawal Trial 3, 22% of patients with normal baseline fasting triglycerides (N=394) had changes to high or very high fasting triglycerides during single-blind REXULTI treatment in the Stabilization phase. During the double-blind phase, from the patients with normal baseline fasting triglycerides, 7% in the REXULTI group (4/57) and 0% in the placebo group (0/60) had changes to high fasting triglycerides.

In the long-term open-label studies, shifts in baseline fasting cholesterol from normal to high were reported in 6% (total cholesterol), 3% (LDL cholesterol), and shifts in baseline from normal to low were reported in 20% (HDL cholesterol) of patients taking REXULTI. Of patients with normal baseline triglycerides, 14% experienced shifts to high, and 0.3% experienced shifts to very high triglycerides. Combined, 0.5% of subjects with normal or borderline fasting triglycerides experienced shifts to very high fasting triglycerides during the long-term schizophrenia studies.

Adjunctive Treatment in Major Depressive Disorder (MDD)

In Trials 4, 5, 6, and 7, the proportion of patients with clinically significant changes from baseline in fasting total cholesterol, LDL cholesterol, and HDL cholesterol were similar in REXULTI+ADT- and placebo+ADT-treated subjects. Table 12 shows the proportions of subjects with changes in fasting triglycerides in Trials 4, 5, 6 and 7.

Table 12: Change in Fasting Triglycerides in Trials 4, 5, 6 and 7 (up to 6 weeks)

	Proportion of Subjects with Shifts Baseline to Post-Baseline				
	Brexpiprazole (mg/day)+ADT				
	1 mg/day	**2 mg/day**	**3 mg/day**	**2-3 mg/day[1]**	**Placebo+ADT**
Triglycerides ***Normal to High*** (<150 mg/dL to ≥200 and <500 mg/dL)	5% (7/145)*	8% (19/226)*	9% (13/150)*	9% (11/120)*	5% (25/522)*
Normal/Borderline to Very High (<200 mg/dL to ≥500 mg/dL)	0% (0/177)*	0.4% (1/275)*	0% (0/179)*	0% (0/152)*	0% (0/618)*

Legend: ADT=antidepressant
* denotes n/N where N=the total number of subjects who had a measurement at baseline and at least one post-baseline result.
n=the number of subjects with shift.
[1]Brex 2-3 mg/day group is from flexible-dose trial 7 (Trial 331-12-282)

In the long-term open-label studies, shifts in baseline fasting cholesterol from normal to high were reported in 8.7% (total cholesterol), 3.2% (LDL cholesterol), and shifts in baseline from normal to low were reported in 13.3% (HDL cholesterol) of patients taking REXULTI + ADT. Of patients with normal baseline triglycerides, 17.3% experienced shifts to high, and 0.2% experienced shifts to very high triglycerides. Combined, 0.6% of subjects with normal or borderline fasting triglycerides experienced shifts to very high fasting triglycerides during the long-term MDD studies.

Prolactin

Schizophrenia

Table 13 shows the mean change from baseline in prolactin and the proportion of subjects with prolactin elevations.

Table 13: Changes in Prolactin (ng/mL) - Trials 1 and 2 (up to 6 weeks)

		Brexpiprazole (mg/day)			
		1 mg/day	**2 mg/day**	**4 mg/day**	**Placebo**
Mean Change from Baseline (ng/mL) at Last Visit					
All Male		N=73	N=220	N=208	N=206
		-2.16	-1.36	-0.47	-1.08
All Female		N=41	N=129	N=132	N=127
		-1.08	-1.31	-0.81	-5.57
Male with normal baseline		N=40	N=139	N=145	N=142
		+2.61	+2.52	+3.12	+1.36
Female with normal baseline		N=29	N=102	N=102	N=92
		+5.95	+7.00	+6.46	+2.55
Proportion of Subjects with new onset abnormal results at any time post-baseline					
All Male		N=73	N=221	N=208	N=207
	>1x ULN	10%	12%	17%	12%
	>2x ULN	3%	3%	0.5%	5%
	>3x ULN	0%	0%	2%	2%
All Female		N=41	N=129	N=132	N=127
	>1x ULN	7%	12%	17%	7%
	>2x ULN	7%	6%	3%	5%
	>3x ULN	2%	1%	1%	2%

In the longer-term randomized withdrawal Trial 3, the mean change from baseline at last visit in prolactin in females was -2.17 ng/mL in REXULTI-treated group compared with -4.25 ng/mL in the placebo group. In males, mean change from baseline at last visit in prolactin was -1.73 ng/mL in REXULTI-treated group compared with 1.38 ng/mL in the placebo group. For females with normal prolactin results at baseline, the mean changes to last visit were 4.04 ng/mL in the REXULTI-treated group and -5.95 ng/mL in the placebo group; for males with normal baseline, the mean changes to last visit were 0.05 ng/mL in the REXULTI-treated group and 2.61 ng/mL

in the placebo group. The proportion of subjects with prolactin elevations >1X ULN in females was 5.2% in the REXULTI-treated group compared with 2.6% in the placebo group. In males, the proportion of subjects with prolactin elevations > 1X ULN was 3.6% in the REXULTI-treated group compared with 4.9% in the placebo group. Similarly, prolactin elevations >3X ULN in females was 0.0% in the REXULTI-treated group compared with 5.2% in the placebo group. In males, prolactin elevations >3X ULN was 0.0% in the REXULTI-treated group compared with 3.2% in the placebo group.

In the long-term open-label schizophrenia trials, the mean change from baseline at last visit in prolactin in females was 2.78 ng/mL in REXULTI-treated group and 0.60 ng/mL in males. The proportion of subjects with prolactin elevations >1X ULN was 17.5% in females and 14.0% in males in the REXULTI-treated group, and prolactin elevations >3X ULN was 4.1% in females and 1.7% in males.

Adjunctive Treatment in Major Depressive Disorder (MDD)

Table 14 shows the mean change from baseline in prolactin and the proportion of subjects with prolactin elevations in Trials 4, 5, 6 and 7.

Table 14: Changes in Prolactin (ng/mL) - Trials 4, 5, 6 and 7 (up to 6 weeks)

	Brexpiprazole (mg/day)+ADT				
	1 mg/day	**2 mg/day**	**3 mg/day**	**2-3 mg/day[1]**	**Placebo+ADT**
	Mean Change from Baseline (ng/mL) at Last Visit				
All Male	N=68	N=100	N=72	N=68	N=235
	+0.98	+2.16	+2.14	+0.26	-0.01
All Female	N=154	N=262	N=152	N=122	N=559
	+3.99	+7.69	+10.28	+1.09	+0.06
Male with normal baseline	N=60	N=97	N=67	N=60	N=215
	+1.55	+2.13	+2.86	+1.37	+0.12
Female with normal baseline	N=153	N=254	N=150	N=115	N=543
	+4.13	+8.14	+10.52	+1.92	+0.67
	Proportion of Subjects with new onset abnormal results at any time post-baseline				
All Male	N=68	N=102	N=72	N=68	N=242
>1x ULN	18%	15%	22%	19%	9%
>2x ULN	0%	0%	1%	6%	3%
>3x ULN	0%	1%	1%	2%	<1%
All Female	N=155	N=270	N=155	N=123	N=571
>1x ULN	10%	17%	26%	11%	3%
>2x ULN	0%	1%	2%	1%	<1%
>3x ULN	0%	0%	0%	2%	1%

Legend: ADT=antidepressant
[1]Brex 2-3 mg/day group is from flexible-dose trial 7 (Trial 331-12-282)

In the long-term open-label MDD trials, the mean change from baseline at last visit in prolactin in females was 1.86 ng/mL in REXULTI+ ADT group and 0.50 ng/mL in males. The proportion of subjects with prolactin elevations >1X ULN was 15.4% in females and 13.5% in males in the REXULTI+ ADT group, and prolactin elevations >3X ULN was 0.5% in females and 0.9% in males.

Post-Market Adverse Drug Reactions

Immune system disorders: hypersensitivity reactions (including anaphylaxis, angioedema, facial swelling, rash and urticaria)

Neurological: seizure

Psychiatric disorders: suicidality (including completed suicide, attempted suicide, suicidal behavior and suicidal ideation).

Atypical antipsychotic drugs, such as REXULTI, have been associated with cases of sleep apnea, with or without concomitant weight gain. In patients who have a history of or are at risk for sleep apnea, REXULTI should be prescribed with caution.

Complex sleep-related behaviors such as somnambulism and sleep-related eating disorder have been associated with the use of atypical antipsychotic drugs.

DRUG INTERACTIONS

Overview

REXULTI is predominantly metabolized by cytochrome P450 (CYP)3A4 and CYP2D6.

REXULTI should be used with caution in combination with drugs known to prolong QTc interval or cause electrolyte disturbances (see WARNINGS AND PRECAUTIONS, Cardiovascular, QT Interval).

Drug-Drug Interactions

Potential for other drugs to affect REXULTI

Dosage adjustments are recommended in patients who are known CYP2D6 poor metabolizers and in patients taking concomitant CYP3A4 inhibitors or CYP2D6 inhibitors or strong CYP3A4 inducers (Table 15). If the co-administered drug is discontinued, adjust the REXULTI dosage to its original level. If the co-administered CYP3A4 inducer is discontinued, reduce the REXULTI dosage to the original level over 1 to 2 weeks (see DOSAGE AND ADMINISTRATION, Dosing Considerations).

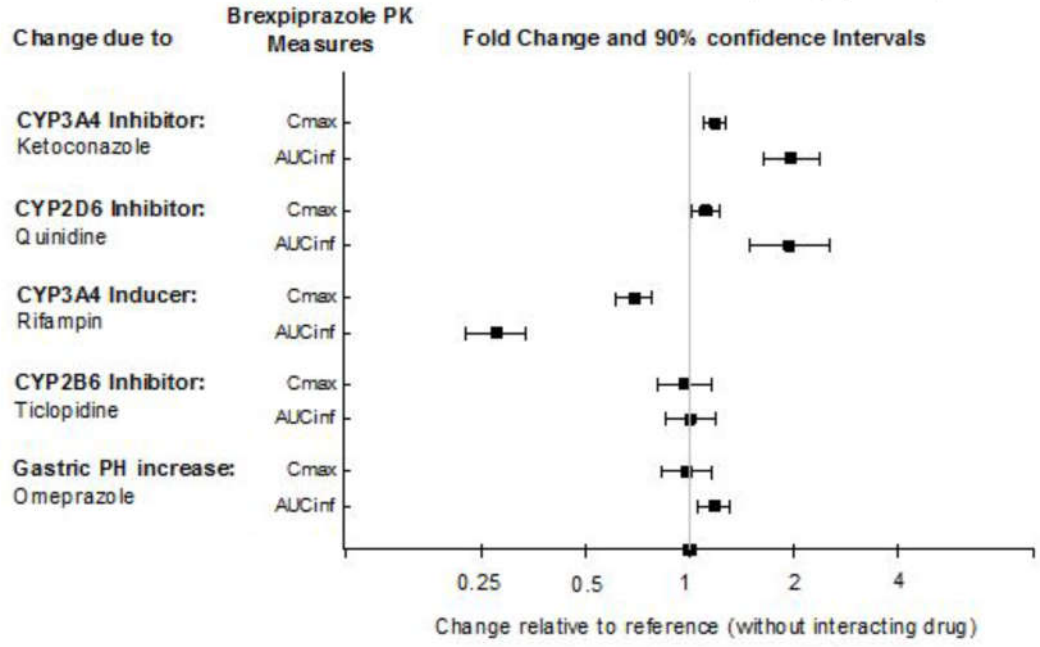
Table 15: Summary of Effect of Co-administered Drugs on Exposure to REXULTI (brexpiprazole) in Healthy Subjects

Co-administered Drug	Ref	Dose Schedule Clinical comment		Effect on REXULTI Pharmacokinetics		Recommendation
		Co-administered Drug	REXULTI	C_{max}	AUC	
Ketoconazole (strong CYP3A4 inhibitor*)	CT	200 mg BID for 7 days	single 2 mg dose	No change	Increased by 97%	Administer half of usual REXULTI dose
Quinidine (strong CYP2D6 inhibitor)	CT	324 mg OD for 7 days	single 2 mg dose	No change	Increased by 94%	Administer half of usual REXULTI dose
Ticlopidine (strong CYP2B6 inhibitor)	CT	250 mg BID for 7 days	single 2 mg dose	No change	No change	No REXULTI dose adjustment required
Rifampin (strong CYP3A4 inducer)	CT	600 mg BID for 12 days	single 4 mg dose	Decreased by 31%	Decreased by 73%	Double usual REXULTI dose over 1 to 2 weeks, adjust as required based on clinical response
Omeprazole (Gastric Acid pH Modifiers)	CT	40 mg OD for 5 days	single 4 mg dose	No change	No change	No REXULTI dose adjustment required

Legend: CT = Clinical Trial
*Mild and moderate CYP3A4 inhibitors (e.g. erythromycin, grapefruit juice) have not been studied

The effects of other drugs on the exposure of REXULTI are summarized in Figure 1.

Figure 1: The Effects of Other Drugs on REXULTI (brexpiprazole) Pharmacokinetics*



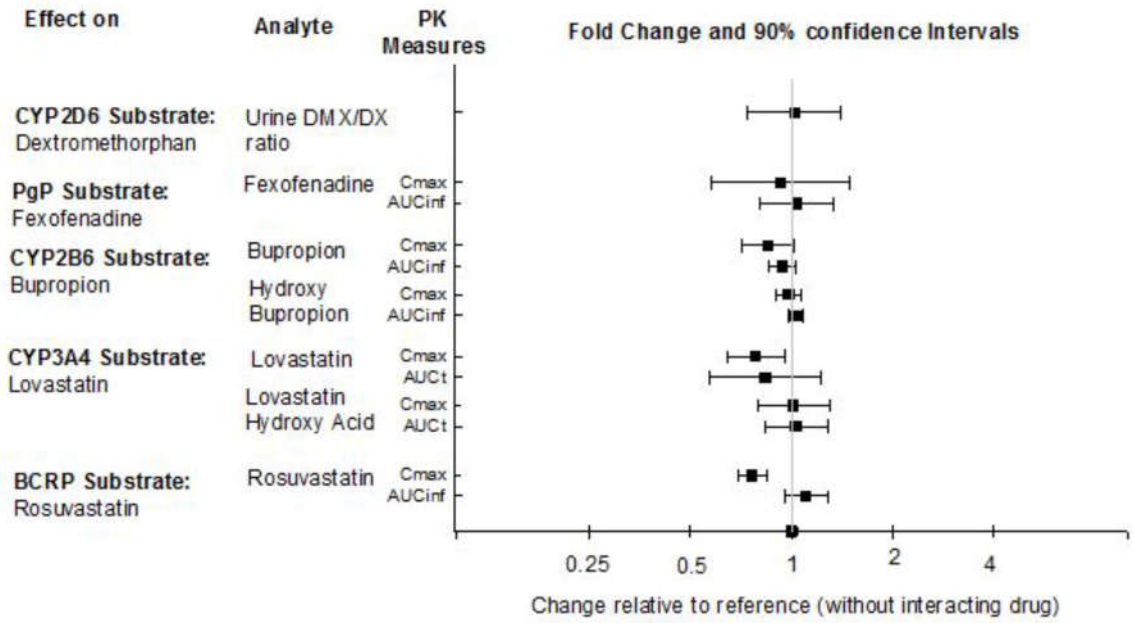
*see also impact for dosage recommendations in Table 15 above.

Potential for REXULTI to affect other drugs

Results of *in vitro* studies suggest that REXULTI is unlikely to cause clinically important pharmacokinetic interactions with drugs metabolized by cytochrome P450 enzymes. Clinical studies showed that oral brexpiprazole (2 mg/day, 5 days) had no effect on the metabolism of single doses of dextromethorphan (a CYP2D6 substrate), lovastatin (a CYP3A4 substrate) or bupropion (a CYP2B6 substrate). REXULTI did not affect absorption of single doses of drugs that are substrates of BCRP transporter (rosuvastatin) and PgP (P-glycoprotein) transporter (fexofenadine). No dosage adjustment of CYP2D6, CYP3A4, CYP2B6, BCRP and PgP substrates is required during concomitant administration with REXULTI.

The effects of REXULTI on the exposure of other drugs are summarized in Figure 2.

Figure 2: The Effects of REXULTI (brexpiprazole) on Pharmacokinetics of Other Drugs



Drug-Food Interactions

REXULTI may be administered with or without food.

Drug-Herb Interactions

Interactions with herbal products have not been established.

Drug-Laboratory Interactions

Interactions with laboratory tests have not been established.

Drug-Lifestyle Interactions

Alcohol/CNS Drugs
Given the primary CNS effects of brexpiprazole, as with most psychoactive medications, combination use of REXULTI with alcohol or other CNS drugs with overlapping undesirable effects such as sedation, should be avoided.

Smoking
Based on studies utilizing human liver enzymes *in vitro*, brexpiprazole is not a substrate for CYP1A2. No dosage adjustment is required based on smoking status.

DOSAGE AND ADMINISTRATION

Recommended dose and dose adjustment

Table 16: Dose and dose adjustment

Indication	Starting Dose	Recommended Target Dose	Maximum Dose
Schizophrenia	1 mg/day	2-4 mg/day	4 mg/day
Adjunctive Treatment in Major Depressive Disorder (MDD)	0.5 mg/day or 1 mg/day	2 mg/day	2 mg/day

Schizophrenia

The recommended starting dosage for REXULTI is 1 mg once daily on Days 1 to 4, taken orally with or without food.

The recommended target REXULTI dosage is 2 mg to 4 mg once daily. In short-term fixed-dose clinical trials, the dose was titrated to 2 mg once daily on Day 5 through Day 7, then to 4 mg on Day 8. The maximum recommended daily dosage is 4 mg. Periodically reassess to determine the continued need and appropriate dosage for treatment.

Patients should be treated with the lowest effective dose that provides optimal clinical response and tolerability.

Adjunctive Treatment in Major Depressive Disorder (MDD)

The dose range of 1 to 3 mg/day was evaluated as adjunctive treatment in clinical trials. No additional benefit was demonstrated at doses greater than 2 mg/day (see CLINICAL TRIALS, Adjunctive Treatment of Major Depressive Disorder). Periodically reassess to determine the continued need and appropriate dose for treatment.

The required length of adjunctive treatment with REXULTI is not known. When prescribed as an adjunct to antidepressants in the treatment of MDD, REXULTI should be used for the shortest period of time that is clinically indicated (see CLINICAL TRIALS, Adjunctive Treatment of Major Depressive Disorder).

The recommended starting dose for REXULTI as adjunctive treatment is 0.5 mg or 1 mg once daily, taken orally with or without food.

Titrate to 1 mg once daily, then up to the recommended 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 dose is 2 mg once daily.

Dosing Considerations

Hepatic Impairment: For patients with moderate to severe hepatic impairment (Child-Pugh score ≥7), the maximum recommended dosage is 3 mg once daily for patients with schizophrenia and 1.25 mg once daily for patients with MDD.

Renal Impairment: For patients with moderate, severe or end-stage renal impairment (creatinine clearance CL_{cr}<60 mL/minute), the maximum recommended dosage is 3 mg once daily for patients with schizophrenia and 1.25 mg once daily for patients with MDD.

CYP isozymes: 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 17). If the co-administered drug is discontinued, adjust the REXULTI dosage to its original level. If the co-administered CYP3A4 inducer is discontinued, reduce the REXULTI dosage to the original level over 1 to 2 weeks.

Table 17: 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	
Known 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 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.

Geriatrics: The safety and efficacy of REXULTI in patients 65 years of age or older have not been established. Caution should be used when treating geriatric patients (see WARNINGS AND PRECAUTIONS, Special Population, Geriatrics). REXULTI is not indicated in elderly patients with dementia (see WARNINGS AND PRECAUTIONS, Serious Warnings and Precaution Box and Special Populations).

Pediatrics: The safety and efficacy of REXULTI have not been established in patients less than 18 years of age. REXULTI is not indicated in pediatric patients and its use is not recommended in this population (see WARNINGS AND PRECAUTIONS, Special Populations, Pediatrics).

Missed Dose

If a dose is missed then it should be taken as soon as possible unless it is close to the next dose. Two doses should not be taken.

Administration
REXULTI may be given once daily, with or without food.

Switching from Other Antipsychotics
There are no systematically collected data to specifically address switching patients with schizophrenia or MDD from other antipsychotics to REXULTI or concerning concomitant administration with other antipsychotics. While immediate discontinuation of the previous antipsychotic treatment may be acceptable for some patients with schizophrenia or MDD, more gradual discontinuation may be most appropriate for others. In all cases, the period of overlapping antipsychotic administration should be minimized.

OVERDOSAGE
There is limited clinical trial experience regarding human overdosage with REXULTI. ECG monitoring is recommended in the event of overdose.

For management of a suspected drug overdose, contact your regional Poison Control Centre.

ACTION AND CLINICAL PHARMACOLOGY

Mechanism of Action

The mechanism of action of brexpiprazole is unknown. The efficacy of brexpiprazole may be mediated through a combination of partial agonist activity at serotonergic 5-HT_{1A} and at dopaminergic D_2 receptors with antagonist activity at serotonergic 5-HT_{2A} receptors. The clinical relevance of these receptor interactions with brexpiprazole is unknown.

Pharmacodynamics

Brexpiprazole has high affinity (expressed as Ki values) for serotonin $5HT_{1A}$ (0.12 nM), $5HT_{2A}$ (0.47 nM), $5HT_{2B}$ (1.88 nM), dopamine D_2 (0.3 nM), D_3 (1.14 nM), and noradrenergic α_{1A} (3.78 nM), α_{1B} (0.17 nM), α_{1D} (2.60 nM), and α_{2C} (0.59 nM) receptors.

Brexpiprazole exhibits a moderate affinity for dopamine D_4 (6.3 nM), serotonin 5-HT_{7A} (9.48 nM), noradrenergic α_{2A} (15 nM), α_{2B} (17 nM) and histamine H_1 (19 nM) receptors; and weak affinity for the serotonin 5-HT_{1B} (32 nM) and 5-HT_{2C} (33 nM) receptors (see DETAILED PHARMACOLOGY).

Brexpiprazole acts as a partial agonist at the 5-HT_{1A}, D_2, and D_3 receptors and as an antagonist at $5HT_{2A}$, $5HT_{2B}$, $5HT_7$, α_{1A}, α_{1B}, α_{1D}, and α_{2C} receptors.

Cardiac Electrophysiology: In a multicenter, randomized, double-blind, placebo- and positive-controlled, parallel group, multiple dose ECG assessment study, subjects with schizophrenia or schizoaffective disorder received treatment with brexpiprazole at a therapeutic dose of 4 mg/day or a supratherapeutic dose of 12 mg/day for 11 days. On day 11, the maximum placebo-adjusted mean change from baseline in the QTcI interval was 8.3 ms (90% CI 3.7, 12.9) at 6 h post-dosing

in the brexpiprazole 4 mg/day group (N=62) and 3.1 ms (90% CI -1.7, 8.0) at 4 h post-dosing in the brexpiprazole 12 mg/day group (N=53). No exposure-response relationship was apparent.

Sub-group analyses suggested that the QTc prolongation was larger in female subjects than in males. In the brexpiprazole 4 mg/day group, the maximum placebo-adjusted mean change from baseline in the QTcI interval was 5.2 ms (90% CI 1.5, 8.9) in males (N=48) and 15.0 ms (90% CI 7.7, 22.3) in females (N=14) at 6 h post-dosing. In the brexpiprazole 12 mg/day group, the maximum placebo-adjusted mean change from baseline in the QTcI interval was 2.9 ms (90% CI -1.2, 6.9) in males (N=40) at 12 h post-dosing and 10.4 ms (90% CI 2.7, 18.2) in females (N=13) at 24 h post-dosing. Limitations of the gender sub-group analyses included diminished statistical power.

The brexpiprazole 4 mg/day treatment had no effect on heart rate; however, the brexpiprazole 12 mg/day treatment was associated with an increase in heart rate, with a maximum mean difference from placebo of 4.8 bpm (90% CI 1.9, 7.7) at 2 h.

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 10-12 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.

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

In vivo brexpirazole 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.

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 brexpiprazole oral tablet after once daily administration is 19.8 (±11.4) mL/h/kg. After multiple once daily administration of brexpiprazole, the terminal elimination half-life of brexpiprazole and its major metabolite, DM-3411, is 91.4 hours and 85.7 hours, respectively.

Special Populations and Conditions

Pediatrics: The safety and efficacy of REXULTI in patients under the age of 18 years have not been established.

The pharmacokinetics, safety and tolerability of brexpiprazole 0.5 – 4 mg per day oral doses were assessed in 43 adolescent subjects (aged 13 to 17 years, weight range 43.4 - 116.2 kg) with a diagnosis of schizophrenia, bipolar disorder, or other related psychiatric disorders in an open-label, dose-escalation trial (Trial 8). The brexpiprazole exposure, in terms of AUC and C_{max}, seemed slightly higher and apparent clearance seemed slightly lower in adolescent subjects compared with adult subjects.

The pharmacokinetics, safety and tolerability of brexpiprazole single oral doses of 0.75 and 1.5 mg in 12 subjects 6 to < 10 years old (weight range 20.1 - 40.0 kg) and single oral doses of 1.5 and 3 mg in 12 subjects 10 to < 13 years old (weight range 28.0 - 61.0 kg) with a diagnosis of CNS disorders were assessed in a sequential cohort, nonrandomized crossover trial (Trial 9). Children 6 to < 10 years old appeared to have slightly higher brexpiprazole exposure and lower brexpiprazole apparent clearance as compared to children 10 to < 13 years old.

The pharmacokinetic profile in pediatric patients and the comparison with adults should be considered preliminary. REXULTI is not indicated for use in patients below the age of 18 (see INDICATIONS AND CLINICAL USE, Pediatrics; WARNINGS AND PRECAUTIONS, Special Populations, Pediatrics).

Geriatrics: Clinical studies of the efficacy of REXULTI did not include a meaningful number of subjects aged 65 or older to determine whether they respond differently from younger subjects. 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.

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 Serious Warnings and Precautions box).

CYP2D6 poor metabolism status: Based on the results of the population PK analysis CYP2D6 poor metabolizer subjects exhibited 47% higher exposure (AUCτ) to brexpiprazole compared with CYP2D6 extensive metabolizer subjects (see DOSAGE AND ADMINISTRATION,

Dosing Considerations).

Age/Gender: After single dose administration of brexpiprazole (2 mg), elderly subjects (older than 65 years old) exhibited similar brexpiprazole systemic exposure (C_{max} and AUC) in comparison to the adult subjects (18-45 years old) and female subjects exhibited approximately 40-50% higher brexpiprazole systemic exposure (C_{max} and AUC) in comparison to the male subjects. Population pharmacokinetic evaluation identified age and female sex as statistically significant covariates affecting brexpiprazole PK while the effects were not considered clinically relevant. No dosage adjustment is required in subjects based on age or gender (see WARNINGS AND PRECAUTIONS, Special Populations, Geriatrics).

Race: Although no specific pharmacokinetic study was conducted to investigate the effects of race on the disposition of brexpiprazole, population pharmacokinetic evaluation revealed no evidence of clinically significant race-related differences in the pharmacokinetics of brexpiprazole. No dosage adjustment is required in patients based on race.

Hepatic Insufficiency: In subjects with varying degrees of hepatic impairment (Child-Pugh Classes A, B, and C; N=22), the AUC of oral brexpiprazole (2 mg single dose), compared to matched healthy subjects, increased 24% in mild hepatic impairment, increased 60% in moderate hepatic impairment, and 8% in severe hepatic impairment. Specific dosing considerations are recommended for patients with moderate to severe hepatic impairment (see DOSAGE AND ADMINISTRATION, Dosing Considerations, Hepatic Impairment).

Renal Insufficiency: In subjects with severe renal impairment (CL_{cr} <30 mL/min; N=10), AUC of oral brexpiprazole (2 mg single dose) compared to matched healthy subjects was increased by 68% while its C_{max} was not changed. Specific dosing considerations are recommended for patients with moderate, severe or end stage renal impairment (see DOSAGE AND ADMINISTRATION, Dosing Considerations, Renal Impairment).

STORAGE AND STABILITY

Store REXULTI tablets between 15°- 30°C (59°-86°F).

SPECIAL HANDLING INSTRUCTIONS

Keep out of reach of children.

DOSAGE FORMS, COMPOSITION AND PACKAGING

REXULTI is available in bottles of 30 tablets and blister packs of 30 tablets.
REXULTI is available in the following tablet strengths:

Table 18: REXULTI Tablet Presentations

Tablet Strength	Tablet Color/Shape	Tablet Markings (Debossed with "BRX" and tablet strength on one side)
0.25 mg	Light brown, film-coated Round; shallow convex; bevel-edged	"BRX" and "0.25"
0.5 mg	Light orange, film-coated Round; shallow convex; bevel-edged	"BRX" and "0.5"
1 mg	Light yellow, film-coated Round; shallow convex; bevel-edged	"BRX" and "1"
2 mg	Light green, film-coated Round; shallow convex; bevel-edged	"BRX" and "2"
3 mg	Light purple, film-coated Round; shallow convex; bevel-edged	"BRX" and "3"
4 mg	White, film-coated Round; shallow convex; bevel-edged	"BRX" and "4"

REXULTI contains the following inactive ingredients; lactose monohydrate, corn starch, microcrystalline cellulose, hydroxypropyl cellulose, low-substituted hydroxypropyl cellulose, magnesium stearate, hypromellose, and talc.

Colourants: titanium dioxide, ferric oxide yellow (0.25 mg, 0.5 mg, 1 mg, 2 mg), ferric oxide red (0.25 mg, 0.5 mg, 3 mg), and ferrosoferric oxide (0.25 mg, 2 mg, 3 mg).

PART II: SCIENTIFIC INFORMATION

PHARMACEUTICAL INFORMATION

Drug Substance

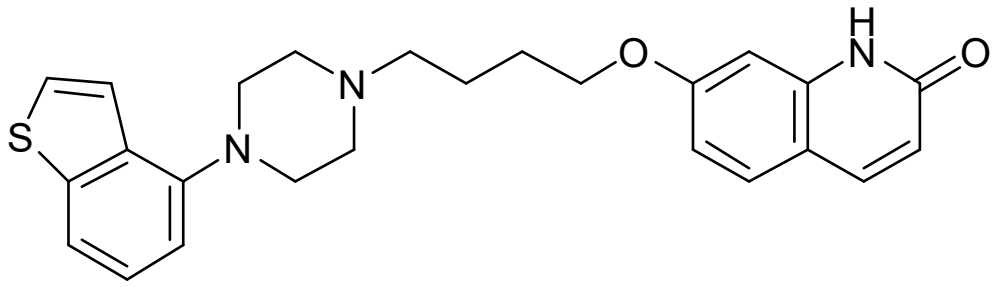
Proper name: brexpiprazole

Chemical name: 7-{4-[4-(1-Benzothiophen-4-yl)piperazin-1-yl]butoxy}quinolin-2(1*H*)-one

Molecular formula: $C_{25}H_{27}N_3O_2S$

Molecular mass: 433.57g/mol.

Structural formula:



Physicochemical properties: Brexpiprazole is nonhygroscopic, with white to off white crystals or crystalline powders, and a melting point of 183°C (decomposition). Brexpiprazole is a weakly basic compound with a pKa of 7.8. It is practically insoluble in water, and the solubility of the drug substance at pH 2 is 0.56 mg/mL, at pH 4 is 0.13 mg/mL, and at pH 6 is 0.0020 mg/mL.

CLINICAL TRIALS

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 and one longer-term randomized withdrawal trial in subjects who met DSM-IV-TR criteria for schizophrenia and were experiencing an acute exacerbation of psychotic symptoms. The efficacy was also evaluated in a 6-week, randomized, double-blind, placebo-controlled and active-reference flexible dose clinical trial.

In two fixed dose trials, Trial 231 (hereafter "Trial 1") and Trial 230 (hereafter "Trial 2"), subjects were randomized to REXULTI 2 or 4 mg once per day or placebo. Subjects 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). The key secondary endpoint of both trials was the change from baseline to Week 6 in Clinical Global Impression Severity of Illness Scale (CGI-S) total score, a validated clinician-related scale that measures the subject's current illness state and overall clinical state on a 1 (normal, not at all ill) to 7-point (extremely ill) scale.

In Trial 1, REXULTI was superior to placebo (N=178) at both 2 mg/day (n=180) and 4 mg/day (N=178) doses for the primary endpoint (PANSS total score) and key secondary endpoint (CGI-S total score).

In Trial 2, REXULTI at 4 mg/day group (N=181) was superior to placebo (N=180) for the primary endpoint (PANSS total score), but not at the 2 mg/day dose (N=179).

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

In the 6-week flexible-dose study (Study 14644A), REXULTI at doses between 2 and 4 mg/day (N=150) was not superior to placebo (N=159) for the primary endpoint, the mean changes in PANSS total score at Week 6; however, the active reference (N=150) confirmed the assay sensitivity of the study.

The longer term Trial 3 was a randomized-withdrawal, double-blind, placebo-controlled trial to assess the efficacy of REXULTI (1 - 4 mg/day) in adults with schizophrenia experiencing an exacerbation of psychotic symptoms at study entry, who met criteria for stability for at least 12 weeks during single-blind treatment with REXULTI (flexible doses 1- 4 mg/day), and were then randomized to continue on their REXULTI dose or to switch to placebo, for up to 52 weeks. The

primary endpoint was the time to exacerbation of psychotic symptoms/impending relapse; the key secondary endpoint was the percentage of subjects with exacerbation of psychotic symptoms/impending relapse.

A pre-specified interim analysis, conducted after 50% of the events planned in the calculation of power, demonstrated a statistically significantly longer time to relapse in subjects randomized to the REXULTI group compared to placebo-treated subjects and the trial was subsequently terminated early because of demonstrated efficacy. The final analysis demonstrated a statistically significantly longer time to relapse in subjects randomized to the REXULTI group (N=96) compared to placebo-treated subjects (N=104). Time to impending relapse was statistically significantly delayed with REXULTI compared with placebo in both the interim and final analyses ($p = 0.0008$ and $p < 0.0001$, respectively; log-rank test). For the final analysis, the hazard ratio from the Cox proportional hazard model for the placebo to REXULTI comparison was 3.420 (95% CI: 1.825, 6.411); thus, subjects in the placebo group had a 3.4-fold greater risk of experiencing impending relapse than the subjects in the REXULTI group.

The key secondary endpoint, the proportion of subjects who met the criteria for impending relapse, was statistically significantly lower in REXULTI-treated subjects compared with placebo group (13.5% vs. 38.5%, $p<0.0001$).

Short-term Adjunctive Treatment in Major Depressive Disorder (MDD)

The efficacy of REXULTI, as an adjunctive treatment to antidepressant therapy for major depressive disorder (MDD), was evaluated in four phase 3, 6-week, double-blind, placebo-controlled trials: three fixed-dose trials (331-10-228, 331-10-227, 331-13-214) and one flexible-dose trial with an active reference (331-12-282). These trials are referred to as Trials 4, 5, 6 and 7, respectively, in Table 19.

The adult patients in these trials fulfilled the DSM-IV-TR criteria for MDD, with or without symptoms of anxiety, and demonstrated an inadequate response (patient reported) to 1-3 prior antidepressant therapy(ies) in the current episode and an inadequate response during the 8-10 weeks of prospective antidepressant treatment (escitalopram, fluoxetine, paroxetine controlled-release, sertraline, duloxetine or venlafaxine extended-release) during the trials. Inadequate response to prospective antidepressant treatment in Studies 4 and 5 was initially defined as < 50% improvement from baseline on the Hamilton Depression scale (HAMD-17), a HAMD-17 score > 14, and a Clinical Global Impression (CGI-I) $\geq$ 3 at Week 8. To ensure that randomized patients had an inadequate response throughout the prospective antidepressant treatment phase, this definition was amended during Studies 4 and 5 to the following: < 50% improvement from baseline on the HAMD-17 and a HAMD-17 score > 14 at Week 8; and, CGI-I $\geq$ 3 and < 50% improvement from baseline on the Montgomery-Asberg Depression Rating Scale (MADRS) Total Score at Weeks 2, 4, 6 and 8 (and Week 10, as applicable). This definition of inadequate response to prospective antidepressant treatment was also applied in Studies 6 and 7. With the exception of approximately 6% of patients in Studies 4 and 5, all patients who were randomized in the short-term clinical trials fulfilled the revised definition of inadequate response to prospective antidepressant treatment.

Patients remained on the same antidepressant treatment throughout the entire duration of each study. All patients randomized to REXULTI in the fixed dose studies (Studies 4, 5 and 6) initiated treatment at 0.5 mg/day during Week 1. The REXULTI dose was increased to 1 mg/day during Week 2 in all dose groups and, based on the assigned treatment, the dose was either maintained at 1 mg/day or increased to 3 mg/day (Study 5) or increased to 2 mg/day (Studies 4 and 6), from Week 3 onwards. Dosages were maintained at the assigned doses for the 4 remaining weeks. In the flexible dose study (Study 7), patients randomized to REXULTI initiated treatment at 1 mg/day during Week 1, and the dose was increased to the target dose of 2 mg/day during Week 2. Patients remained at 2 mg/day in Study 7 unless there was a decision to increase the dose to 3 mg/day.

The primary efficacy endpoint in all studies was mean change from baseline (randomization) to Week 6 on the Montgomery Asberg Depression Rating Scale (MADRS) Total Score, a 10-item clinician-rated scale that assesses the degree of depressive symptomatology (apparent sadness, reported sadness, inner tension, reduced sleep, reduced appetite, concentration difficulties, lassitude, inability to feel, pessimistic thoughts, and suicidal thoughts). Each item is scored from 0 (normal/symptom not present) to 6 (most severe symptoms) and the range for the total score is 0 to 60.

The key secondary instrument was the Sheehan Disability Scale (SDS), a 3-item self-rated instrument used to assess three domains of functioning (work/school, social life, and family life) with each item scored from 0 (no disruption at all) to 10 (extreme disruption).

Table 19: Clinical Studies Supporting Efficacy of REXULTI in the Adjunctive Treatment in Major Depressive Disorder

Study	Trial design[a]	Oral Dosage	Number of Subjects (N)[b] Gender [Male/Female (M/F)][b]	Age (yrs) Mean (SD)[b]
331-10-228 (Trial 4)	Phase A (8 weeks): Single-blind placebo +ADT Phase B (6 weeks): Double-blind, placebo-controlled + ADT	2 mg/day Brex+ADT	N=187 (58M/129F)	44.1 (11.6)
		Placebo+ADT	N=191 (54M/137F)	45.2 (11.3)
331-10-227 (Trial 5)		1 mg/day Brex+ADT	N=225 (67M/158F)	45.7 (11.6)
		3 mg/day Brex+ADT	N=226 (71M/155F)	44.6 (11.2)
		Placebo+ADT	N=218 (75M/143F)	46.6 (11.1)
331-13-214 (Trial 6)		2 mg/day Brex+ADT	N=191 (45M/146F)	43.2 (12.6)
		Placebo+ADT	N=202 (58M/144F)	42.7 (12.5)
331-12-282 (Trial 7)	Phase A (8-10 weeks): Double-blind placebo +ADT Phase B (6 weeks): Double-blind, placebo-controlled and active-referenced + ADT	2 to 3 mg/day Brex+ADT	N=191 (68M/123F)	43.8 (11.5)
		Placebo+ADT	N=205 (56M/149F)	41.8 (11.7)

Brex=brexpiprazole; ADT=antidepressant; SD=standard deviation

[a]These were 14-16-week trials which required a retrospective failure to 1 to 3 courses of ADT treatment during the current depressive episode and consisted of an 8-10-week, single- or double-blind placebo + ADT (Phase A), followed by a 6-week double blind, randomization phase.

[b]Demographic characteristics based on randomized subjects (Phase B) who took at least one dose of study medication during Phase B and who had MADRS Total Score values at the randomization visit and at least one post-randomization visit.

Study Results

For the randomized patients, the mean duration of the current major depressive episode ranged between approximately 12 and 18 months and the majority of patients (approximately 79% - 84%) reported an inadequate response to one prior antidepressant treatment, before receiving 8-10 weeks of prospective antidepressant treatment during the trials. Following 8-10 weeks of prospective antidepressant treatment, the mean MADRS Total Score at randomization ranged between 25 and 27. Mean SDS score at randomization was between 5.6 and 6.3.

In Trials 4, 6 and 7 there was greater improvement in the mean MADRS Total Score with REXULTI (2 mg/day or 2-3 mg/day) + ADT compared to placebo + ADT ($p < 0.05$). No additional benefit was demonstrated at doses greater than 2 mg/day (Table 20). In Study 7, the majority of patients treated with REXULTI received 2 mg/day and the mean daily REXULTI dose at endpoint was 2.2 mg/day.

Table 20: Summary of the Primary Efficacy Results (MADRS) of REXULTI in Trials 4, 5, 6, and 7 for the Adjunctive Treatment in Major Depressive Disorder

Trial Treatment Group	N	Baseline End of Phase A	Mean Change End of Phase B	Treatment Comparison vs Placebo		
		Mean (SD)	LS Mean (SE)[a]	LSMD[b]	95% CI[a]	P-value[a]
Trial 4[c]						
2 mg Brex+ADT	187	26.61 (5.79)	-8.27 (0.61)	-3.12	(-4.70, -1.54)	0.0001
Placebo+ADT	191	27.14 (5.60)	-5.15 (0.63)	-	-	-
Trial 5[c]						
1 mg Brex+ADT	225	26.69 (5.61)	-7.65 (0.50)	-1.19	(-2.58, 0.20)	0.0925
3 mg Brex+ADT	226	26.31 (5.24)	-7.98 (0.51)	-1.52	(-2.92, -0.13)	0.0327
Placebo+ADT	218	26.23 (5.27)	-6.45 (0.51)	-	-	-
Trial 6						
2 mg Brex+ADT	191	27.05 (5.67)	-10.4 (0.63)	-2.30	(-3.97, -0.62)	0.0074
Placebo+ADT	202	26.20 (6.20)	-8.07 (0.61)	-	-	-
Trial 7						
2-3 mg Brex+ADT	191	25.28 (5.02)	-6.04 (0.43)	-1.48	(-2.56, -0.39)	0.0078
Placebo+ADT	205	25.39 (5.19)	-4.57 (0.41)	-	-	-

Legend: ADT=antidepressant

NOTE: Baseline equals Week 8 or Week 10 measurement prior to randomization.

[a]MMRM with model terms treatment, site, visit, treatment-by-visit, and baseline-by-visit interaction as covariates, where baseline is MADRS Total Score at end of Phase A (Week 8). An unstructured covariance was used. To control Type 1 error for testing two doses in Study 5, the brexpiprazole vs placebo treatment difference was statistically significant only if the larger of the two p-values was $\leq$0.05 or the smaller p-value was $\leq$0.025.

[b]LSMD was the difference between LS mean of brexpiprazole and placebo.

[c]Results for the primary analysis populations for Studies 4 and 5 are presented and include approximately 6% of patients who were randomized prior to the revised definition of inadequate response, which required an inadequate response throughout the 8-week duration of prospective antidepressant treatment.

In Trial 4, the mean SDS score showed greater improvement with REXULTI (2 mg/day) + ADT than with placebo + ADT ($p<0.05$).

DETAILED PHARMACOLOGY

Brexpiprazole has a broad receptor binding profile with high affinity (K_i < 5 nM) for multiple monoaminergic receptors including serotonin 5-HT_{1A}, 5-HT_{2A}, 5-HT_{2B}, dopamine D_2, D_3, and noradrenergic α_{1A}, α_{1B}, α_{1D}, and α_{2C} receptors. Brexpiprazole exhibits a moderate affinity for dopamine D_4, serotonin 5-HT_{7A}, noradrenergic α_{2A}, α_{2B} and histamine H_1 receptors; and weak affinity for the serotonin 5-HT_{1B} and 5-HT_{2C} receptors. Although affinity constants have not been determined, brexpiprazole (at 10 μM) showed occupancy at the muscarinic M1 receptor (64%), dopamine transporter (90%) and serotonin transporter (65%).

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. Dose response occupancy and brain/plasma exposure relationship were determined *in vivo* or *ex vivo* for D_2/D_3, 5-HT_{2A}, 5-HT_{1A}, and

5-HT_7 receptors as well as the serotonin transporter in preclinical studies. These results are consistent with the relative binding affinities and indicate that brexpiprazole has activity at several targets in the central nervous system at therapeutic plasma exposures.

Brexpiprazole was shown *in vitro* to inhibit both norepinephrine and serotonin uptake into synaptosome preparations from rat brain tissue. Brexpiprazole also inhibited monoamine oxidase B (MAO-B) enzyme activity in rat liver extracts.

Central Nervous System Safety Pharmacology: In safety pharmacology studies, brexpiprazole had a depression effect on the CNS that was related to the exaggerated pharmacological effect of the compound. Brexpiprazole caused a decreased body temperature in repeat-dose toxicity studies at doses ≥30 mg/kg in rats, monkeys and dogs (see TOXICOLOGY).

Cardiovascular Safety Pharmacology: Significant decrease in blood pressure and prolongation of QT interval and QTc were noted in the conscious telemetry dog trial, and on Day 1 of administration at doses ≥3 mg/kg in the repeat-dose toxicity studies with monkeys and in the juvenile toxicity study with dogs (15- and 24-fold the MRHD on a mg/m^2 basis, respectively). In conscious telemetry dogs (N=4), brexpiprazole was administered at sequential oral doses of 0 (vehicle), 1, 3, 10, and 30 mg/kg at intervals of 7-8 days. Brexpiprazole at 10 mg/kg and 30 mg/kg caused statistically significant increases in the QTc interval and the QRS duration compared to the vehicle control group.

In anesthetised dogs (N=4) under phenylephrine-induced hypertensive state, intravenous infusions of brexpiprazole were associated with statistically significant decreases in systolic and diastolic blood pressure at 0.3 mg/kg and 3 mg/kg and decrease in heart rate at 3 mg/kg. The effect of brexpiprazole on blood pressure may be due to a blockade of α_1- adrenoceptors in peripheral blood vessels, which is consistent with the pharmacological profile for this compound.

In Chinese hamster ovary cells CHO-K1 expressing the alpha subunit of the human IKr potassium channel, brexpiprazole caused a statistically significant and concentration-dependent suppression of hERG currents over a 0.01 to 1 µM concentration range, with a IC_{50} of 0.117 µM (51 ng/mL).

TOXICOLOGY

Acute Toxicity

In single-dose oral (gavage) toxicity studies, the minimum oral lethal dose was >1000 and 300 mg/kg, respectively for male and female Sprague Dawley (SD) rats, and > 100 mg/kg for both male and female cynomolgus monkeys. At doses of 1000 and 300 mg/kg, clinical signs observed in male and female rats included hypoactivity, closed eyes or incomplete eyelid closure, fixed stare, lacrimation, abnormal posture, and hypothermia. In monkey, clinical signs included drowsiness, partially closed eyes, crouching or prone positions, tremors of the limbs, decrease in movement, and decrease in body temperature.

Repeat Dose Toxicity
In a repeat-dose toxicity study conducted in rats at oral doses of 0, 3, 10, 30 and 100 mg/kg/day for 26 weeks duration, the no observed adverse effect level (NOAEL) was 3 mg/kg (7-fold MRHD on a mg/m^2 basis). Clinical signs observed at 30 and 100 mg/kg included CNS depression, hypoactivity, hypothermia, gynecomastia, galactorrhea, and increases in blood levels of aspartate aminotransferase and gamma globulin, as well as decrease in body weight and food consumption. Female rats increased in body weight at 3 mg/kg compared to the control group. Major histopathology finding corresponded to atrophy of the uterus, thymus and pituitary glands, and enlargement of adrenal glands at doses ≥10 mg/kg.

In repeat-dose toxicity studies conducted in Cynomolgus monkeys at oral doses of 0, 1, 3 and 30 mg/kg/day for 13 and 39 weeks duration, the NOAEL was 1 mg/kg (5-fold MRHD) for both sexes. At doses ≥3 mg/kg, animals exhibited CNS depression, decrease in blood pressure, decreases in leukocytes and reticulocytes, as well as increases in blood cholesterol and phospholipids. Major histopathology finding corresponded to death-related gastrointestinal bleeding and ulcers at 30 mg/kg.

Juvenile Repeat Dose Toxicity
In repeat-dose toxicity study conducted in juvenile rats at oral doses of 0, 3, 10 and 20 mg/kg/day for 8 weeks duration, the NOAEL was <3 mg/kg (7-fold MRHD on a mg/m^2 basis) in both sexes. At doses ≥10mg/kg, animals exhibited CNS depression, hypoactivity, as well as increases in blood globulins and phospholipids. Decrease in body weight, pubertal delays and gynecomastia were also noted at the end of the administration period compared with the control group. Female rats increased in body weight at 3 mg/kg. Major histopathology finding corresponded to atrophy of the pituitary glands, liver and kidney at doses ≥10 mg/kg. Following 2 weeks untreated recovery period, differences in fertility and reproductive performance between treatment groups were unremarkable.

In repeat-dose toxicity study conducted in juvenile Beagle dogs at oral doses of 0, 1, 3 and 30 mg/kg/day for 26 weeks duration, the NOAEL was <3 mg/kg (24-fold MRHD) in both sexes. At 30 mg/kg, animals exhibited CNS depression, hypoactivity, decreased respiration rates, lower blood pressure and decrease in reticulocytes, as well as, increases in blood cholesterol and phospholipids. Major histopathology finding corresponded to enlargement of adrenal glands and liver at 30 mg/kg. Toxicology findings were unremarkable after 8 weeks untreated recovery period, except for male pubertal delays noted in the 30 mg/kg group.

Carcinogenesis
The lifetime carcinogenic potential of brexpiprazole was evaluated in two year studies in mice and rats. In mice, brexpiprazole was administered orally (gavage) at doses of 0.75, 2 and 5 mg/kg/day (1 to 6-fold MRHD on a mg/m^2 basis. There was no increase in the incidence of tumors in males at any dose group. In female mice, there was an increased incidence of mammary gland adenocarcinoma and adenosquamous carcinoma, and pars distalis adenoma of the pituitary gland at all doses. In rats, brexpiprazole was administered orally (gavage) at doses of 1, 3 and 10 mg/kg/day in males or 3, 10 and 30 mg/kg/day in females (for males 2 to 24-fold and for females 7 to 73-fold the MRHD). Long-term administration of brexpiprazole to rats did not induce neoplastic lesions.

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 sexes in 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), *in vivo* in the micronucleus assay in rats, and the unscheduled DNA synthesis assay in rats. Brexpiprazole was mutagenic and clastogenic but occurred only at doses that induced cytotoxicity (20-30 µg/mL) in the *in vitro* forward gene mutation assay in mouse lymphoma cells and in the *in vitro* chromosomal aberration assay in Chinese hamster ovary cells. Based on a weight of evidence, brexpiprazole is not considered to present a genotoxic risk to humans at therapeutic doses and exposures.

Impairment of Fertility
In female rats treated with brexpiprazole at oral doses of 0, 0.3, 3 or 30 mg/kg/day prior to mating with untreated males and continuing through conception and implantation, the NOAEL in terms of reproductive performance and fertility was 0.3 mg/kg/day (0.7-fold MRHD). Prolonged diestrus and decreased fertility were observed at 3 mg/kg/day. At 30 mg/kg/day a prolongation of the mating phase was observed and significantly increased preimplantation losses were seen.

In male rats treated with brexpiprazole at oral doses of 0, 3, 10 or 100 mg/kg/day for 63 days prior to mating and during copulation (with untreated females), the NOAEL in terms of male fertility and toxicological effects was 10 mg/kg/day (24-fold MRHD).

Reproductive Toxicity
In a prenatal and postnatal developmental study in rats, pregnant dams receiving brexpiprazole at oral doses of 0, 3, 10 and 30 mg/kg/day from implantation until weaning of offspring, the NOAEL for maternal toxicity and newborn viability was 3 mg/kg/day (7-fold MRHD). Increase in the number of stillbirth and death in pups during lactation were observed at 10 and 30 mg/kg. Changes observed at 30 mg/kg/day included impaired nursing in dams, and low birth weight, impaired viability, suppressed body weight gain, delayed pinna unfolding and decreased number of corpora lutea in the offspring.

In a rabbit embryo-fetal development study, pregnant dams receiving brexpiprazole at oral doses of 0, 10, 30 and 150 mg/kg/day during gestation, the NOAEL for reproductive toxicity was 10 mg/kg/day (49-fold MRHD). At doses ≥30 mg/kg, an increase incidence in renal pelvic dilation and caudal vena cava abnormality was observed in fetuses. At 150 mg/kg/day, decreased body weight, retarded ossification, and increased incidences of visceral and skeletal malformations were observed.

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READ THIS FOR SAFE AND EFFECTIVE USE OF YOUR MEDICINE

PATIENT MEDICATION INFORMATION

REXULTI®
brexpiprazole tablets

Read this carefully before you start taking **REXULTI** and each time you get a refill. This leaflet is a summary and will not tell you everything about this drug. Talk to your healthcare professional about your medical condition and treatment and ask if there is any new information about **REXULTI.**

Serious Warnings and Precautions

Increased Risk of Death in Elderly People with Dementia. Medicines like REXULTI can raise the risk of death in elderly people who have dementia. REXULTI is not approved for use in patients with dementia.

What is REXULTI used for?
REXULTI is used in adults:

- for the treatment of schizophrenia;
- along with antidepressant medication for the treatment of major depressive disorder (MDD)

Schizophrenia is characterized by symptoms such as:
- hallucinations; hearing, seeing or sensing things that are not there,
- suspiciousness, mistaken beliefs,
- incoherent speech and behavior and emotional flatness.

People with schizophrenia may also feel depressed, guilty, anxious or tense.

Depression is a condition with symptoms such as:
- feeling sad
- loss of interest and enjoyment
- a change in appetite or weight
- difficulty concentrating or sleeping
- feeling tired
- headaches
- unexplained aches and pain

REXULTI is not a cure, but it can help manage symptoms in adult patients.

How does REXULTI work?
REXULTI belongs to a group of medicines called atypical antipsychotic drugs.
Antipsychotic drugs affect the chemicals (neurotransmitters) in the brain that allow nerve cells to talk to each other. Illnesses that affect the brain, like schizophrenia or depression, may be due to certain naturally occurring chemicals (called neurotransmitters) in the brain being out of balance. These imbalances may cause some of the symptoms you may be experiencing. Exactly how REXULTI works is unknown.

What are the ingredients in REXULTI?
Medicinal ingredient: brexpiprazole
Non-medicinal ingredients: corn starch, ferric oxide yellow (0.25 mg, 0.5 mg, 1 mg, 2 mg), ferric oxide red (0.25 mg, 0.5 mg, 3 mg), ferrosoferric oxide (0.25 mg, 2 mg, 3 mg), hydroxypropyl cellulose, low-substituted hydroxypropyl cellulose, hypromellose, lactose monohydrate, magnesium stearate, microcrystalline cellulose, talc, titanium dioxide.

REXULTI comes in the following dosage forms:
Film-coated tablets: 0.25 mg, 0.5 mg, 1 mg, 2 mg, 3 mg and 4 mg.

Do not use REXULTI if:
- you are allergic (hypersensitive) to REXULTI or to any ingredient in the tablets (see **What are the ingredients in REXULTI?**).

To help avoid side effects and ensure proper use, talk to your healthcare professional before you take REXULTI. Talk about any health conditions or problems you may have, including if you:
- have or have a family history of diabetes or high blood sugar.
- have high levels of cholesterol or fats (triglycerides) in your blood.
- have or have had seizures (convulsions).
- have or have had high blood pressure.
- have low blood pressure or get dizzy, especially upon standing, or have a history of fainting.
- have sleep apnea.
- have had a stroke.
- have heart problems including “long QT syndrome”.
- have a family history of “long QT syndrome” or sudden cardiac death at less than 50 years of age.
- have had problems with the way your heart beats or if you are taking medication that affects how your heart beats.
- have or have had liver or kidney problems.
- have or have had a low levels of white blood cells.
- are at risk for developing blood clots such as: a family history of blood clots, age over 65, smoking, obesity, recent major surgery (such as hip or knee replacement), being immobile due to air travel or other reason, take oral birth control ("The Pill").
- are dehydrated or suffer from excessive vomiting, diarrhea, or sweating.
- do strenuous exercise or work in a hot, sunny place.

- have a history of drug abuse or addiction.
- drink alcohol or use recreational drugs.
- have had problems tolerating the recommended doses of some drugs.
- have been told you are a "CYP2D6 poor metabolizer".
- have a tumour in your pituitary gland.
- have or have had involuntary, irregular muscle movements, especially in the face (tardive dyskinesia).
- have a problem with the movement of your gut (paralytic ileus), a narrowing or blockage of your gut or other serious gut problem.
- are elderly and have dementia (loss of memory and other abilities).
- have one of the following rare hereditary diseases because lactose is a non-medicinal ingredient in REXULTI:
    - Galactose intolerance
    - Lapp lactase deficiency
    - Glucose-galactose malabsorption
- are pregnant or plan to become pregnant. It is not known if REXULTI may harm your unborn baby. Using REXULTI in the last trimester of pregnancy may cause muscle movement problems, medicine withdrawal symptoms, or both of these in your newborn. If you become pregnant while taking REXULTI, contact your healthcare professional immediately.
- are breastfeeding or plan to breastfeed. It is not known if REXULTI passes into your breast milk. You and your healthcare professional should decide if you will take REXULTI or breastfeed.

Other warnings you should know about:

Thoughts of suicide and worsening of your depression or other mental illnesses:
You may sometimes have thoughts of harming or killing yourself if you are:
- depressed and/or
- have other mental illnesses

Since medicines like REXULTI take time to work, usually about two weeks but sometimes longer, these thoughts occur more often when you first start treatment.

If you have thoughts of harming or killing yourself at any time, contact your healthcare professional or go to a hospital **right away**. You may find it helpful to tell a relative or close friend that you are depressed or have other mental illnesses, and ask them to read this leaflet. You might ask them to tell you if they think your depression or mental illness is getting worse, or if they are worried about changes in your behaviour.

Impulse behaviours: The following behaviours may occur in some people who take REXULTI:
- hypersexuality (uncontrollable and/or inappropriate sexual behaviour)
- an urge to gamble, spend money, binge eat, other urges or the development of new or increased urge

Tell your doctor **right away** if you or those close to you notice these behaviours.

Effects in Newborns
Babies born to mothers taking REXULTI while they are pregnant can have serious health problems. Sometimes, the problems may get better on their own. Be prepared to get immediate medical help for your baby if they:

- have trouble breathing
- are overly sleepy
- have muscle stiffness or floppy muscles (like a rag doll)
- are shaking
- are having trouble feeding

Falls: The following symptoms have been reported with the use of antipsychotic drugs:

- Feeling sleepy,
- a fall in blood pressure when you stand up from sitting or lying down,
- vision or speech problems

This can lead to falls that may cause fractures or other fall-related injuries. Certain medications, diseases or conditions can make this worse.

Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS): A severe reaction to the medication has been reported with the use of antipsychotic drugs. Symptoms include:

- fever,
- severe rash,
- swollen lymph glands,
- flu-like feeling, yellow skin or eyes,
- shortness of breath,
- dry cough,
- chest pain or discomfort,
- feeling thirsty,
- urinating less often, less urine

Neuroleptic Malignant Syndrome (NMS): NMS is potentially a life-threatening condition that has been reported with the use of antipsychotic drugs. Symptoms include:

- severe muscle stiffness or inflexibility with high fever,
- rapid or irregular heartbeat,
- sweating,
- state of confusion or reduced consciousness

High levels of prolactin: If you have high levels of prolactin (measured with a blood test) and a condition called hypogonadism you may be at an increased risk of breaking a bone due to osteoporosis. This occurs in both men and women.

Driving and Using Machines
REXULTI may make you feel drowsy. Do not drive a car, operate machinery, or do other dangerous activities until you know how REXULTI affects you.

Low Blood Pressure
Some people may faint, or get lightheaded and dizzy, especially when getting up from a lying or sitting position. This is more likely to happen if you are elderly and also at the start of treatment or when you increase the dose. This will usually pass on its own but if it does not, tell your healthcare professional.

Dehydration and Overheating
It is important not to become too hot or dehydrated while you are taking 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.

Blood Tests: Your healthcare professional should take blood tests before starting REXULTI. Blood tests will include checking the number of infection-fighting white blood cells, cholesterol levels, blood fat levels and levels of the hormone prolactin. Your doctor should continue to monitor your blood for as long as you are being treated. While you are taking REXULTI your healthcare professional will also check your weight, blood sugar and blood pressure regularly.

Tell your healthcare professional about all the medicines you take, including any drugs, vitamins, minerals, natural supplements or alternative medicines.

The following may interact with REXULTI:

- Drugs used to treat HIV infection and AIDS, such as indinavir, lopinavir/ritonavir, nelfinavir, ritonavir and saquinavir.
- Antibiotics used to treat bacterial infections, such as erythromycin, clarithromycin, azithromycin, tacrolimus, moxifloxacin, levofloxacin, ciprofloxacin and rifampin.
- Pentamidine, an antimicrobial drug used to treat infections in people with weakened immune systems.
- Drugs used to treat malaria, such as quinine and chloroquine.
- Drugs used to treat fungal infections, such as amphotericin B, itraconazole, fluconazole, voriconazole and ketoconazole.
- Domperidone often used to increase production of breast milk.
- Drugs used to prevent nausea and vomiting, such as ondansetron.
- Chemotherapy drugs used to treat cancer, such as sunitinib, nilotinib, ceritinib, vandetanib, vorinostat and arsenic trioxide.
- Drugs used to treat breathing problems like asthma and COPD, such as salmeterol and formoterol.
- Antidepressant drugs such as bupropion, fluoxetine, citalopram, venlafaxine, amitriptyline, imipramine, maprotiline and paroxetine.
- Drugs used to treat heart problems such as quinidine, procainamide, disopyramide, amiodarone, sotalol, ibutilide, dronedarone, flecainide and propafenone.
- Anti-seizure drugs such as carbamazepine and phenytoin.
- Diuretics or “water pills”.

- Laxatives and enemas.
- Antacid drugs, such as proton pump inhibitors.
- Opioids such as methadone.
- Other antipsychotic drugs such as chlorpromazine, pimozide, haloperidol, droperidol, ziprasidone and risperidone.
- Drugs used to lower blood pressure.
- St John's wort, an herbal product used to treat depression.
- Alcohol. You should not drink alcohol with taking REXULTI.
- Grapefruit or grapefruit juice. Do not eat grapefruit or drink grapefruit juice while taking REXULTI.

How to take REXULTI:
- Take REXULTI exactly as your healthcare professional tells you to take it.
- Your healthcare professional has decided on the best dosage for you depending on your overall health and other medications you are taking. Your healthcare professional may change your dose depending on how you respond.
- Do not change your dose or stop taking REXULTI without speaking to your healthcare professional.
- REXULTI can be taken with or without food.

Usual adult dose:
Schizophrenia:
Usual starting dose: 1 mg once a day.

Usual dose: 2-4 mg once a day.

Major Depressive Disorder (MDD):
Usual starting dose: 0.5 mg or 1 mg once a day.

Usual dose: 2 mg once a day.

Overdose:

If you think you have taken too much REXULTI, contact your healthcare professional, hospital emergency department or regional Poison Control Centre immediately, even if there are no symptoms.

Missed Dose:
You should not miss a dose of REXULTI. If you miss a dose, take the missed dose as soon as you remember. If you are close to your next dose, just skip the missed dose and take your next dose at your regular time. Do not take 2 doses of REXULTI at the same time. If you are not sure about your dosing, call your healthcare professional.

What are possible side effects from using REXULTI?
These are not all the possible side effects you may feel when taking REXULTI. If you experience any side effects not listed here, contact your healthcare professional.

Common side effects may include:

- diarrhea, constipation
- indigestion, stomach pain
- dry mouth
- weight gain, increased appetite
- dizziness
- difficulty staying still or restlessness
- shakiness (tremor)
- back pain, muscle pain
- sleepiness, drowsiness, fatigue, weakness, sleep disturbances (insomnia)
- anxiety
- headache
- nasopharyngitis (common cold like symptoms)
- rash
- sleep apnea (a sleep disorder where your breathing is interrupted during sleep)
- sleep walking and eating while asleep (sleep-related eating disorders)

Serious side effects and what to do about them			
Symptom / effect	Talk to your healthcare professional		Stop taking drug and get immediate medical help
	Only if severe	In all cases	
UNCOMMON **Allergic Reaction:** rash, hives, swelling of the face, lips, tongue or throat, difficulty swallowing or breathing			√
Tardive Dyskinesia: muscle twitching or unusual movement of the face or tongue		√	
Stroke and Transient Ischemic Attacks: sudden weakness or numbness of the face, arms, or legs and speech or vision problems			√
Seizure: loss of consciousness with uncontrollable shaking			√
Blood Clots: swelling, pain and redness in an arm or leg that is warm to touch. You may develop sudden chest pain, difficulty breathing and heart palpitations.		√	
Increased Blood Sugar: frequent urination, thirst, and hunger	√		
Decreased White Blood Cells: infections, fatigue, fever, aches, pains, and flu-like symptoms		√	
Dysphagia: tightness of the throat, difficulty swallowing or breathing which may lead to choking		√	
Low Blood Pressure: dizziness, fainting, lightheadedness. May occur when you go from lying or sitting to standing up.	√		
Neuroleptic Malignant Syndrome: severe muscle stiffness or inflexibility with high fever, rapid or irregular heartbeat, sweating, state of confusion or reduced consciousness			√
Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS): fever, severe rash, swollen lymph glands, flu-like feeling, yellow skin or eyes, shortness of breath, dry cough, chest pain or discomfort, feeling thirsty, urinating less often, less urine			√
Priapism: long-lasting (greater than 4 hours in duration) and painful erection of the penis			√
New or worsening constipation		√	
Rhabdomyolysis: very dark ("tea coloured") urine, muscle tenderness and/or aching			√
UNKNOWN **Thoughts of death or suicide**		√	

If you have a troublesome symptom or side effect that is not listed here or becomes bad enough to interfere with your daily activities, talk to your healthcare professional.

Reporting Side Effects
You can help improve the safe use of health products for Canadians by reporting serious and unexpected side effects to Health Canada. Your report may help to identify new side effects and change the product safety information.
3 ways to report:

- Online at MedEffect (https://www.canada.ca/en/health-canada/services/drugs-health-products/medeffect-canada/adverse-reaction-reporting.html)
- By calling 1-866-234-2345 (toll-free);
- By completing a Consumer Side Effect Reporting Form and sending it by:
  - Fax to 1-866-678-6789 (toll-free), or
  - Mail to: Canada Vigilance Program
    Health Canada, Postal Locator 1908C
    Ottawa, ON
    K1A 0K9

    Postage paid labels and the Consumer Side Effect Reporting Form are available at MedEffect (https://www.canada.ca/en/health-canada/services/drugs-health-products/medeffect-canada/adverse-reaction-reporting.html)

NOTE: Contact your healthcare professional if you need information about how to manage your side effects. The Canada Vigilance Program does not provide medical advice.

Storage:
Store REXULTI at room temperature, between 15 and 30°C.

Keep out of reach and sight of children.

If you want more information about REXULTI:

- Talk to your healthcare professional.
- Find the full product monograph that is prepared for healthcare professionals and includes this Patient Medication Information by visiting the Health Canada website (www.healthcanada.gc.ca); the manufacturer's website www.otsukacanada.com, or by calling 1-877-341-9245.

This leaflet was prepared by Otsuka Pharmaceutical Co., Ltd.

Last Revised: September 29, 2020

Marketing Status in United States

Drug Databases (https://www.fda.gov/Drugs/InformationOnDrugs/)

Orange Book: Approved Drug Products with Therapeutic Equivalence Evaluations

Home (index.cfm?resetfields=1) | Back to Search Results

Product Details for NDA 205422

Collapse All

REXULTI (BREXPIPRAZOLE)
0.25MG
Marketing Status: Prescription

Active Ingredient: BREXPIPRAZOLE
Proprietary Name: REXULTI
Dosage Form; Route of Administration: TABLET; ORAL
Strength: 0.25MG
Reference Listed Drug: Yes
Reference Standard: No
TE Code: AB
Application Number: N205422
Product Number: 001
Approval Date: Jul 10, 2015
Applicant Holder Full Name: OTSUKA PHARMACEUTICAL CO LTD
Marketing Status: Prescription
Patent and Exclusivity Information (patent_info.cfm?Product_No=001&Appl_No=205422&Appl_type=N)

REXULTI (BREXPIPRAZOLE)
0.5MG
Marketing Status: Prescription

Active Ingredient: BREXPIPRAZOLE
Proprietary Name: REXULTI
Dosage Form; Route of Administration: TABLET; ORAL
Strength: 0.5MG
Reference Listed Drug: Yes

Reference Standard: No
TE Code: AB
Application Number: N205422
Product Number: 002
Approval Date: Jul 10, 2015
Applicant Holder Full Name: OTSUKA PHARMACEUTICAL CO LTD
Marketing Status: Prescription
Patent and Exclusivity Information (patent_info.cfm?Product_No=002&Appl_No=205422&Appl_type=N)

REXULTI (BREXPIPRAZOLE)
1MG
Marketing Status: Prescription

Active Ingredient: BREXPIPRAZOLE
Proprietary Name: REXULTI
Dosage Form; Route of Administration: TABLET; ORAL
Strength: 1MG
Reference Listed Drug: Yes
Reference Standard: No
TE Code: AB
Application Number: N205422
Product Number: 003
Approval Date: Jul 10, 2015
Applicant Holder Full Name: OTSUKA PHARMACEUTICAL CO LTD
Marketing Status: Prescription
Patent and Exclusivity Information (patent_info.cfm?Product_No=003&Appl_No=205422&Appl_type=N)

REXULTI (BREXPIPRAZOLE)
2MG
Marketing Status: Prescription

Active Ingredient: BREXPIPRAZOLE
Proprietary Name: REXULTI
Dosage Form; Route of Administration: TABLET; ORAL
Strength: 2MG
Reference Listed Drug: Yes
Reference Standard: Yes
TE Code: AB
Application Number: N205422
Product Number: 004
Approval Date: Jul 10, 2015
Applicant Holder Full Name: OTSUKA PHARMACEUTICAL CO LTD

Marketing Status: Prescription
Patent and Exclusivity Information (patent_info.cfm?Product_No=004&Appl_No=205422&Appl_type=N)

REXULTI (BREXPIPRAZOLE)
3MG
Marketing Status: Prescription

Active Ingredient: BREXPIPRAZOLE
Proprietary Name: REXULTI
Dosage Form; Route of Administration: TABLET; ORAL
Strength: 3MG
Reference Listed Drug: Yes
Reference Standard: No
TE Code: AB
Application Number: N205422
Product Number: 005
Approval Date: Jul 10, 2015
Applicant Holder Full Name: OTSUKA PHARMACEUTICAL CO LTD
Marketing Status: Prescription
Patent and Exclusivity Information (patent_info.cfm?Product_No=005&Appl_No=205422&Appl_type=N)

REXULTI (BREXPIPRAZOLE)
4MG
Marketing Status: Prescription

Active Ingredient: BREXPIPRAZOLE
Proprietary Name: REXULTI
Dosage Form; Route of Administration: TABLET; ORAL
Strength: 4MG
Reference Listed Drug: Yes
Reference Standard: No
TE Code: AB
Application Number: N205422
Product Number: 006
Approval Date: Jul 10, 2015
Applicant Holder Full Name: OTSUKA PHARMACEUTICAL CO LTD
Marketing Status: Prescription
Patent and Exclusivity Information (patent_info.cfm?Product_No=006&Appl_No=205422&Appl_type=N)