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dgitlin@partners.org

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REXULTI® (brexpiprazole) tablets, for oral use

BRIEF SUMMARY OF PRESCRIBING INFORMATION (For complete details, please see *Full Prescribing Information and Medication Guide*.)

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.**
- **Antidepressants increase 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.**

INDICATIONS AND USAGE: REXULTI is indicated for adjunctive treatment of major depressive disorder (MDD) and treatment of schizophrenia.

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

WARNINGS AND PRECAUTIONS

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

Although the causes of death were varied, most of the deaths appeared to be either cardiovascular (e.g., heart failure, sudden death) or infectious (e.g., pneumonia) in nature. Observational studies suggest that, similar to atypical antipsychotic drugs, treatment with conventional antipsychotic drugs may increase mortality. The extent to which the findings of increased mortality in observational studies may be attributed to the antipsychotic drug as opposed to some characteristic(s) of the patients is not clear. REXULTI is not approved for the treatment of patients with dementia-related psychosis *[see Boxed Warning, Warnings and Precautions]*.

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 4,400 pediatric patients, the incidence of suicidal thoughts and behaviors in patients age 24 years and younger was greater in antidepressant-treated patients than in placebo-treated patients. The drug-placebo differences in the number of cases of suicidal thoughts and behaviors per 1000 patients treated are provided in Table 1.

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 1: 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
18-24	5 additional patients
	Decreases Compared to Placebo
25-64	1 fewer patient
≥65	6 fewer patients

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.

Cerebrovascular Adverse Reactions Including Stroke in Elderly Patients with Dementia-Related Psychosis In placebo-controlled trials with risperidone, aripiprazole, and olanzapine in elderly patients with dementia, there was a higher incidence of cerebrovascular adverse reactions (cerebrovascular accidents and transient ischemic attacks), including fatalities, compared to placebo-treated subjects. REXULTI is not approved for the treatment of patients with dementia-related psychosis *[see Boxed Warning, Warnings and Precautions]*.

Neuroleptic Malignant Syndrome (NMS) A potentially fatal symptom complex sometimes referred to as Neuroleptic Malignant Syndrome (NMS) has been reported in association with administration of antipsychotic drugs.

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.

The diagnostic evaluation of patients with this syndrome is complicated. In arriving at a diagnosis, it is important to exclude 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 antipsychotic drugs and other drugs not essential to concurrent 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 regimens for NMS.

If a patient requires antipsychotic drug treatment after recovery from NMS, the potential reintroduction of drug therapy should be carefully considered. The patient should be carefully monitored, since recurrences of NMS have 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 appears to be 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 are believed to increase as the duration of treatment and the total cumulative dose of antipsychotic drugs administered to the patient increase. However, the syndrome can develop, although much less commonly, after relatively brief treatment periods at low doses or may even arise after discontinuation of treatment.

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 appear to 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, 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.

Metabolic Changes Atypical antipsychotic drugs have been associated with metabolic changes that include hyperglycemia/diabetes mellitus, dyslipidemia, and body weight gain. While all of the drugs in the class have been shown to produce some metabolic changes, each drug has its own specific risk profile.

Hyperglycemia and Diabetes Mellitus

Hyperglycemia, in some cases extreme and associated with ketoacidosis or hyperosmolar coma or death, has been reported in patients treated with atypical antipsychotics. There have been reports of hyperglycemia in patients treated with REXULTI *[see Adverse Reactions]*.

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 reactions is not completely understood. However, epidemiological studies suggest an increased risk of hyperglycemia-related adverse reactions in patients treated with the atypical antipsychotics.

Patients with an established diagnosis of diabetes mellitus who are started on atypical antipsychotics should be monitored regularly for worsening of glucose control. 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. Any patient treated with atypical antipsychotics should 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 atypical antipsychotic drug.

Major Depressive Disorder

In the 6-week, placebo-controlled, fixed-dose clinical trials in 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 patients with normal baseline fasting glucose experienced a shift to high while taking REXULTI+Antidepressant (ADT); 25% of subjects with borderline fasting glucose experienced shifts to high. Combined, 9% of subjects with normal or borderline fasting glucose experienced shifts to high fasting glucose during the long-term depression studies.

Schizophrenia

In the 6-week, placebo-controlled, fixed-dose clinical trials in 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 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, 10% of subjects with normal or borderline fasting glucose experienced shifts to high fasting glucose during the long-term schizophrenia studies.

Dyslipidemia
Undesirable alterations in lipids have been observed in patients treated with atypical antipsychotics.
Major Depressive Disorder
In the 6-week, placebo-controlled, fixed-dose clinical trials in patients with MDD, changes in fasting total cholesterol, LDL cholesterol, and HDL cholesterol were similar in REXULTI- and placebo-treated patients. Table 2 shows the proportions of patients with changes in fasting triglycerides.

Table 2: Change in Fasting Triglycerides in the 6-Week, Placebo-Controlled, Fixed-Dose MDD Trials

Proportion of Patients with Shifts Baseline to Post-Baseline				
	Placebo	**1 mg/day**	**2 mg/day**	**3 mg/day**
Triglycerides 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 subjects who had a measurement at baseline and at least one post-baseline result. n=the number of subjects 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 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 subjects with normal or borderline fasting triglycerides experienced shifts to very high fasting triglycerides during the long-term depression studies.
Schizophrenia
In the 6-week, placebo-controlled, fixed-dose clinical trials in patients with schizophrenia, 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 Schizophrenia Trials

Proportion of Patients with Shifts Baseline to Post-Baseline				
	Placebo	**1 mg/day**	**2 mg/day**	**4 mg/day**
Triglycerides 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 subjects who had a measurement at baseline and at least one post-baseline result. n=the number of subjects with shift.

In the long-term, open-label schizophrenia studies, shifts in baseline fasting cholesterol from normal to high were reported in 6% (total cholesterol) and 2% (LDL cholesterol), and normal to low 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 subjects with normal or borderline fasting triglycerides experienced shifts to very high fasting triglycerides during the long-term schizophrenia studies.
Weight Gain
Weight gain has been observed in patients treated with atypical antipsychotics. Clinical monitoring of weight is recommended.
Major Depressive Disorder
Table 4 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 4: Increases in Body Weight in the 6-Week, Placebo-Controlled, Fixed-Dose MDD Trials

	Placebo n=407	**1 mg/day n=225**	**2 mg/day n=187**	**3 mg/day 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% (8/407)*	5% (11/225)*	5% (9/187)*	2% (5/228)*

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

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

	Placebo n=362	**1 mg/day n=120**	**2 mg/day n=362**	**4 mg/day 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% (15/362)*	10% (12/120)*	11% (38/362)*	10% (37/362)*

*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 a shift ≥7%.

In the long-term, open-label schizophrenia studies, 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.
Leukopenia, Neutropenia, and Agranulocytosis In clinical trial and/or post-marketing experience, leukopenia and neutropenia have been reported temporally related to atypical antipsychotic agents. Agranulocytosis has also been reported.
Possible risk factors for leukopenia/neutropenia include pre-existing low white blood cell count (WBC)/absolute neutrophil count (ANC) and history of drug-induced leukopenia/neutropenia. In patients with a history of a clinically significant low WBC/ANC or drug-induced leukopenia/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 severe neutropenia (absolute neutrophil count <1000/mm^3) and follow their WBC until recovery.
Orthostatic Hypotension and Syncope In the short-term, placebo-controlled clinical studies of REXULTI+ADT in patients with MDD, the incidence of orthostatic hypotension-related adverse reactions in REXULTI+ADT-treated patients compared to placebo+ADT patients included: dizziness (2% vs. 2%) and orthostatic hypotension (0.1% vs. 0%). In the short-term, placebo-controlled clinical studies of REXULTI in patients with schizophrenia, the incidence of orthostatic hypotension-related adverse reactions in REXULTI-treated compared to placebo patients included: dizziness (2% versus 2%), orthostatic hypotension (0.4% versus 0.2%), and syncope (0.1% versus 0%).
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.
Seizures As with other antipsychotic drugs, REXULTI should be used cautiously in patients with a history of seizures or with conditions that potentially lower the seizure threshold. Conditions that lower the seizure threshold may be more prevalent in patients 65 years or older.
Body Temperature Dysregulation 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 that 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.
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 pneumonia.
Potential for Cognitive and Motor Impairment In the short-term, placebo-controlled clinical trials in patients with MDD, somnolence (including sedation and hypersomnia) was reported in 4% of REXULTI+ADT-treated patients compared to 1% of placebo+ADT patients.
In the short-term, placebo-controlled clinical trials in patients with schizophrenia, somnolence (including sedation and hypersomnia) was reported in 5% of REXULTI-treated patients compared to 3% of placebo-treated patients.
As with other antipsychotics that have the potential to impair judgment, thinking or motor skills, patients should be cautioned about operating hazardous machinery including motor vehicles until they are certain that REXULTI therapy does not affect them adversely.

ADVERSE REACTIONS
The following adverse reactions are discussed in more detail in other sections of the labeling in the *Full Prescribing Information*:
- Increased Mortality in Elderly Patients with Dementia-Related Psychosis *[see Boxed Warning, Warnings and Precautions]*
- Suicidal Thoughts and Behaviors in Adolescents and Young Adults *[see Boxed Warning, Warnings and Precautions]*

- Cerebrovascular Adverse Reactions Including Stroke in Elderly Patients with Dementia-Related Psychosis *[see Warnings and Precautions]*
- Neuroleptic Malignant Syndrome (NMS) *[see Warnings and Precautions]*
- Tardive Dyskinesia *[see Warnings and Precautions]*
- Metabolic Changes *[see Warnings and Precautions]*
- Leukopenia, Neutropenia, and Agranulocytosis *[see Warnings and Precautions]*
- Orthostatic Hypotension and Syncope *[see Warnings and Precautions]*
- Seizures *[see Warnings and Precautions]*
- Body Temperature Dysregulation *[see Warnings and Precautions]*
- Dysphagia *[see Warnings and Precautions]*
- Potential for Cognitive and Motor Impairment *[see Warnings and Precautions]*

Clinical Trials Experience

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

Major Depressive Disorder

The safety of REXULTI was evaluated 1,054 patients (18 to 65 years of age) diagnosed with MDD who participated in two 6-week, placebo-controlled, fixed-dose clinical trials in patients with major depressive disorder in which REXULTI was administered at doses of 1 mg to 3 mg daily as adjunctive treatment to continued antidepressant therapy; patients in the placebo group continued to receive antidepressant therapy *[see Clinical Studies]*.

Adverse Reactions Reported as Reasons for Discontinuation of Treatment

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

Common Adverse Reactions

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

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

	Placebo (N=411)	REXULTI			
		1 mg/day (N=226)	2 mg/day (N=188)	3 mg/day (N=229)	ALL REXULTI (N=643)
Gastrointestinal Disorders					
Constipation	1%	3%	2%	1%	2%
General Disorders and Administration Site Conditions					
Fatigue	2%	3%	2%	5%	3%
Infections and Infestations					
Nasopharyngitis	2%	7%	1%	3%	4%
Investigations					
Weight Increased	2%	7%	8%	6%	7%
Blood Cortisol Decreased	1%	4%	0%	3%	2%
Metabolism and Nutrition					
Increased Appetite	2%	3%	3%	2%	3%
Nervous System Disorders					
Akathisia	2%	4%	7%	14%	9%
Headache	6%	9%	4%	6%	7%
Somnolence	0.5%	4%	4%	6%	5%
Tremor	2%	4%	2%	5%	4%
Dizziness	1%	1%	5%	2%	3%
Psychiatric Disorders					
Anxiety	1%	2%	4%	4%	3%
Restlessness	0%	2%	3%	4%	3%

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

Dose-Related Adverse Reactions in the MDD trials

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

Schizophrenia

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

Common Adverse Reactions

Adverse reactions associated with REXULTI (incidence of 2% or greater and REXULTI incidence greater than placebo) during short-term (up to 6 weeks) trials in patients with schizophrenia are shown in Table 7.

Table 7: Adverse Reactions in Pooled 6-Week, Placebo-Controlled, Fixed-Dose Schizophrenia Trials (Studies 3 and 4)*

	Placebo (N=368)	REXULTI			
		1 mg/day (N=120)	2 mg/day (N=368)	4 mg/day (N=364)	ALL REXULTI (N=852)
Gastrointestinal Disorders					
Dyspepsia	2%	6%	2%	3%	3%
Diarrhea	2%	1%	3%	3%	3%
Investigations					
Weight Increased	2%	3%	4%	4%	4%
Blood Creatine Phosphokinase Increased	1%	4%	2%	2%	2%
Nervous System Disorders					
Akathisia	5%	4%	5%	7%	6%
Tremor	1%	2%	2%	3%	3%
Sedation	1%	2%	2%	3%	2%

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

Extrapyramidal Symptoms

Major Depressive Disorder

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

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

Dystonia

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

Other Adverse Reactions Observed During the Premarketing Evaluation of REXULTI

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

Eye Disorders: Vision Blurred
Gastrointestinal Disorders: Nausea, Dry Mouth, Salivary Hypersecretion, Abdominal Pain, Flatulence
Infections and Infestations: Urinary Tract Infection
Investigations: Blood Prolactin Increased
Musculoskeletal and Connective Tissue Disorders: Myalgia
Psychiatric Disorders: Abnormal Dreams, Insomnia
S*kin and Subcutaneous Tissue Disorders:* Hyperhidrosis

DRUG INTERACTIONS

Drugs Having Clinically Important Interactions with REXULTI

Table 8: 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 Dosage and Administration]*.
Intervention:	With concomitant use of REXULTI with a strong CYP3A4 inhibitor, reduce the REXULTI dosage *[see Dosage and Administration]*.

Examples:	itraconazole, clarithromycin, ketoconazole
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 Dosage and Administration]*.
Intervention:	With concomitant use of REXULTI with a strong CYP2D6 inhibitor, reduce the REXULTI dosage *[see Dosage and Administration]*.
Examples:	paroxetine, fluoxetine, quinidine
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 Dosage and Administration]*.
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]*.
Examples:	1) itraconazole + quinidine 2) fluconazole + paroxetine 3) itraconazole + duloxetine 4) fluconazole + duloxetine
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 Dosage and Administration]*.
Intervention:	With concomitant use of REXULTI with a strong CYP3A4 inducer, increase the REXULTI dosage *[see Dosage and Administration]*.
Examples:	rifampin, St. John's wort

*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.

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.

USE IN SPECIFIC POPULATIONS

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 2-4% and 15-20%, 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 withdraw al 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.

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.

Pediatric Use Safety and effectiveness in pediatric patients have not been established. Antidepressants increased the risk of suicidal thoughts and behaviors in pediatric patients *[see Boxed Warning, Warnings and Precautions]*.

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

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

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

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 3–8% of Black/African Americans cannot metabolize CYP2D6 substrates and are classified as poor metabolizers (PM) *[see Dosage and Administration, Clinical Pharmacology]*.

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

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

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

DRUG ABUSE AND DEPENDENCE

Controlled Substance REXULTI is not a controlled substance.

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

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.

OVERDOSAGE

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

Charcoal

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

Hemodialysis

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

PATIENT COUNSELING INFORMATION

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

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

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

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IMPORTANT SAFETY INFORMATION (continued from back cover)

Metabolic Changes: Atypical antipsychotic drugs have been associated with metabolic changes including hyperglycemia/diabetes mellitus, dyslipidemia, and weight gain. Clinical monitoring is recommended.

Leukopenia, Neutropenia, and Agranulocytosis: Leukopenia, neutropenia, and agranulocytosis have been reported with antipsychotic use. Perform complete blood count (CBC) in patients with a pre-existing low white blood cell count (WBC) or a history of leukopenia or neutropenia. Consider discontinuing REXULTI if a clinically significant decline in WBC count occurs in the absence of other causative factors.

Orthostatic Hypotension and Syncope: REXULTI should be used with caution in patients with known cardiovascular disease, cerebrovascular disease, or conditions which would predispose them to hypotension.

Seizures: Use cautiously in patients with a history of seizures or with conditions that lower the seizure threshold.

Body Temperature Dysregulation: Appropriate care is advised for patients who may exercise strenuously, be exposed to extreme heat, receive concomitant medication with anticholinergic activity, or be subject to dehydration.

Dysphagia: Esophageal dysmotility and aspiration have been associated with antipsychotic drug use. REXULTI should be used with caution in patients at risk for aspiration pneumonia.

Potential for Cognitive and Motor Impairment: REXULTI may have the potential to impair judgment, thinking, or motor skills. Patients should not drive or operate hazardous machinery until they are certain REXULTI does not affect them adversely.

Alcohol: Advise patients to avoid alcohol while taking REXULTI.

Concomitant Medication: Administer half the dose of REXULTI with strong CYP2D6 or CYP3A4 inhibitors. Administer a quarter of the dose with strong/moderate CYP2D6 inhibitors or known CYP2D6 poor metabolizers taken with strong/moderate CYP3A4 inhibitors. Double the dose with strong CYP3A4 inducers over 1 to 2 weeks.

Most commonly observed adverse reactions: Adult patients with schizophrenia: (≥4% incidence and at least twice the rate of placebo for REXULTI vs. placebo, respectively): weight increased (4% vs. 2%).

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

Pregnancy: 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. REXULTI should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Lactation: It is not known if REXULTI is excreted in human breast milk. Discontinue the drug or nursing, taking into account the importance of the drug to the mother.

Please see BRIEF SUMMARY of FULL PRESCRIBING INFORMATION, including **Boxed WARNING**, on the preceding pages.

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

References

1. REXULTI [Prescribing Information]. Otsuka Pharmaceutical Co., Tokyo, Japan. **2.** Correll CU, Skuban A, Ouyang J, et al. Efficacy and safety of brexpiprazole for the treatment of acute schizophrenia: a 6-week randomized, double-blind, placebo-controlled trial [published online April 16, 2015]. *Am J Psychiatry*. 2015. doi:10.1176/appi.ajp.2015.14101275. **3.** Kane JM, Skuban A, Ouyang J, et al. A multicenter, randomized, double-blind, controlled phase 3 trial of fixed-dose brexpiprazole for the treatment of adults with acute schizophrenia. *Schizophr Res*. 2015;164(1-3):127-135.

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Efficacy in two 6-week clinical trials based on mean reduction in PANSS total score[1]

- Study 3: 2 mg/day and 4 mg/day statistically significant reduction vs placebo
- Study 4: 4 mg/day statistically significant reduction vs placebo

Safety profile—evaluated across two 6-week clinical trials[1]

- Most common adverse event occurring in ≥4% of patients across all doses and twice the rate of placebo was weight increase (4% and 2%, respectively)[1]

The efficacy and safety of REXULTI in adults with schizophrenia was demonstrated in two 6-week, placebo-controlled, fixed-dose clinical trials in subjects who met the DSM-IV-TR criteria for schizophrenia and would benefit from hospitalization for an acute exacerbation of schizophrenia.[1-3] The primary endpoint was change from baseline to Week 6 in PANSS total score.[1]

PANSS, Positive and Negative Syndrome Scale, is an instrument for measuring positive and negative symptoms, as well as general psychopathology, in schizophrenia.

INDICATION AND IMPORTANT SAFETY INFORMATION for REXULTI® (brexpiprazole)

INDICATION

REXULTI is indicated for the treatment of schizophrenia in adults.

REXULTI is available in 4 mg tablets, as well as other dosage strengths.

IMPORTANT SAFETY INFORMATION

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 compared to placebo. REXULTI® is not approved for the treatment of patients with dementia-related psychosis.

Contraindication: Known hypersensitivity reaction to REXULTI or any of its components. Reactions have included: rash, facial swelling, urticaria and anaphylaxis.

Cerebrovascular Adverse Events, Including Stroke: In placebo-controlled trials with risperidone, aripiprazole, and olanzapine in elderly patients with dementia, there was a higher incidence of cerebrovascular adverse reactions (stroke, TIA), including fatalities, compared to placebo-treated patients.

Neuroleptic Malignant Syndrome (NMS): A potentially fatal complex sometimes referred to as NMS has been associated with the administration of antipsychotic drugs. Manage with immediate discontinuation of antipsychotic drugs and other drugs not essential to concurrent therapy, intensive symptomatic treatment and medical monitoring.

Tardive Dyskinesia (TD): REXULTI should be prescribed in a manner most likely to minimize the occurrence of TD. If signs and symptoms of TD appear, drug discontinuation should be considered.

Please see IMPORTANT SAFETY INFORMATION continued on inside back cover, and BRIEF SUMMARY of FULL PRESCRIBING INFORMATION, including **Boxed WARNING**, on the preceding pages.