Rexulti® (Brexpiprazole) tablets 0.25mg, 0.5mg, 1mg, 2mg, 3mg and 4mg
FULL PRESCRIBING INFORMATION

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

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

1 INDICATIONS AND USAGE

Adults

Schizophrenia
Treatment of exacerbation and maintenance of schizophrenia for adults*[see Clinical Studies (14.1)]*.

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. REXULTI should be used for the shortest period of time that is clinically indicated. 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 [*see Clinical Studies (14.2)*].
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 (5.6), (5.7), (5.8)*]. 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.

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.

2 DOSAGE AND ADMINISTRATION

2.1 Treatment of Schizophrenia

The recommended starting dosage for REXULTI is 1 mg once daily on Days 1 to 4, taken orally with or without food *[see Clinical Pharmacology (12.3)]*.

The recommended target REXULTI dosage is 2 mg to 4 mg once daily. Titrate to 2 mg once daily on Day 5 through Day 7, then to 4 mg on Day 8 based on the patient's clinical response and tolerability. The maximum recommended daily dosage is 4 mg.

2.2 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 Studies (14.2)*]. 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 Studies (14.2)*].

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.

2.3 Switching from Other Antipsychotics

Switching from other antipsychotics to brexpiprazole: When switching from other antipsychotics to brexpiprazole gradual cross-titration should be considered, with gradual discontinuation of the previous treatment while brexpiprazole treatment is initiated.

Switching to other antipsychotics from brexpiprazole: When switching to other antipsychotics from brexpiprazole, no gradual cross-titration is needed, the new antipsychotics should be initiated in its lowest dose while brexpiprazole is discontinued. It should be considered that plasma concentration of brexpiprazole will decline gradually and will be completely washed out in 1 to 2 weeks.

2.4 Dosage Adjustments for 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 *[see Use in Specific Populations (8.7), Clinical Pharmacology (12.3)]*.

2.5 Dosage Adjustments for Renal Impairment

For patients with moderate, severe or end-stage renal impairment, the maximum recommended dosage is 3 mg once daily for patients with schizophrenia and 1.25 mg once daily for patients with MDD. *[see Use in Specific Populations (8.8), Clinical Pharmacology (12.3)]*

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

Dosage adjustments are recommended in patients who are known cytochrome P450 (CYP) 2D6 poor metabolizers and in patients taking concomitant CYP3A4 inhibitors or CYP2D6 inhibitors or strong CYP3A4 inducers (see Table 1). If the coadministered drug is discontinued, adjust the REXULTI dosage to its original level. If the coadministered CYP3A4 inducer is discontinued, reduce the REXULTI dosage to the original level over 1 to 2 weeks *[see Drug Interactions (7.1), Clinical Pharmacology (12.3)]*.

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

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

*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.

3 DOSAGE FORMS AND STRENGTHS

REXULTI tablets are available in 6 strengths (see Table 2).

Table 2: REXULTI Tablet Strengths and Identifying Features

Tablet Strength	Tablet Color/Shape	Tablet Markings
0.25 mg	Light brown; Round	“BRX” and “0.25”
0.5 mg	Light orange; Round	“BRX” and “0.5”
1 mg	Light yellow; Round	“BRX” and “1”
2 mg	Light green; Round	“BRX” and “2”
3 mg	Light purple; Round	“BRX” and “3”
4 mg	White; Round	“BRX” and “4”

4 CONTRAINDICATIONS

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

5 WARNINGS AND PRECAUTIONS

5.1 Increased Mortality in Elderly Patients with Dementia-Related Psychosis

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

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

5.2 Suicidal Thoughts and Behaviors

The possibility of a suicide attempt is inherent in psychotic illnesses and major depressive disorder (MDD). Close supervision and appropriate clinical management of high-risk patients should accompany drug therapy.

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

In placebo-controlled trials in elderly subjects with dementia, patients randomized to risperidone, aripiprazole, and olanzapine had a higher incidence of cerebrovascular adverse reactions (stroke and transient ischemic attack), including fatal stroke. REXULTI is not approved for the treatment of patients with dementia-related psychosis *[see Boxed Warning, Warnings and Precautions (5.1)]*.

5.4 QT Prolongation

QT prolongation can develop in patients treated with antipsychotics. In clinical trials, only a few, non-serious, QT prolongations have been reported with brexpiprazole. Caution should be exercised when brexpiprazole is prescribed in patients with known cardiovascular disease, family history of QT prolongation, electrolyte imbalance or in concomitant use with other medicinal products thought to prolong the QT interval.

5.5 Venous Thromboembolism

Cases of venous thromboembolism (VTE) have been reported with antipsychotics. Since patients treated with antipsychotics often present with acquired risk factors for VTE, all possible risk factors for VTE should be identified before and during treatment with brexpiprazole and preventive measures undertaken.

5.6 Neuroleptic Malignant Syndrome (NMS)

A potentially fatal symptom complex sometimes referred to as Neuroleptic Malignant Syndrome (NMS) has been reported in association with administration of antipsychotic drugs, including REXULTI. Clinical manifestations of NMS are hyperpyrexia, muscle rigidity, altered mental status and evidence of autonomic instability (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.

5.7 Tardive Dyskinesia

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

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

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

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

If signs and symptoms of tardive dyskinesia appear in a patient on REXULTI, dose reduction or drug discontinuation should be considered. These symptoms can temporally deteriorate or can even arise after discontinuation of treatment. However, some patients may require treatment with REXULTI despite the presence of the syndrome.

5.8 Metabolic Changes

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

Hyperglycemia and Diabetes Mellitus

Hyperglycemia, in some cases extreme and associated with ketoacidosis or hyperosmolar coma or death, has been reported in patients treated with atypical antipsychotics. There have been reports of hyperglycemia in patients treated with REXULTI *[see Adverse Reactions (6.1)]*. Assess fasting plasma glucose before or soon after initiation of antipsychotic medication, and monitor periodically during long-term treatment.

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.

Patients with diabetes mellitus or with risk factors for diabetes mellitus should be monitored regularly for worsening of glucose control.

Adjunctive Treatment in Major Depressive Disorder (MDD)

In the 6-week Trials 331-10-228, 331-10-227 and 331-13-214, 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 331-12-282, 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.

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.

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***	6% (15/253)*	10% (7/72)*	8% (19/232)*	10% (22/226)*

(< 150 mg/dL to ≥ 200 and < 500 mg/dL)				
Normal/Borderline to Very High (< 200 mg/dL to ≥ 500mg/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), 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 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 331-10-228, 331-10-227, 331-13-214 and 331-12-282, 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 4 shows the proportions of subjects with changes in fasting triglycerides in Trials 331-10-228, 331-10-227, 331-13-214 and 331-12-282.

Table 4: Change in Fasting Triglycerides in Trials 331-10-228, 331-10-227, 331-13-214 and 331-12-282 (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 to 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 to 3 mg/day group is from flexible-dose 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.

Weight Gain

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

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.

Adjunctive Treatment in Major Depressive Disorder (MDD)

Table 6 shows weight gain data at last visit and percentage of adult subjects with ≥7% increase in body weight at any visit from Trials 331-10-228, 331-10-227,331-13-214 and 331-12-282.

Table 6: Changes in Weight (kg) – Trials 331-10-228, 331-10-227, 331-13-214 (up to 6 weeks)

	Brexpiprazole (mg/day)+ADT				
	1 mg/day N=225	**2 mg/day N=379**	**3 mg/day N=228**	**2 to 3 mg/day[1]**	**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
Brex 2 to 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 week (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.

5.9 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. Patients with a prior history of impulse-control disorders may be at increased risk and should be monitored carefully. 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.

5.10 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.

5.11 Orthostatic Hypotension and Syncope

Atypical antipsychotics cause orthostatic hypotension and syncope. Adverse reactions related to orthostatic hypotension can include dizziness, lightheadedness and tachycardia. Generally, the risk is greatest during initial dose titration and when increasing the dose. 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 patients compared to placebo patients included: dizziness (2% versus 2%), orthostatic hypotension (0.4% versus 0.2%), and syncope (0.1% versus 0%).

Orthostatic vital signs should be monitored in patients who are vulnerable to hypotension, (e.g., elderly patients, patients with dehydration, hypovolemia, concomitant treatment with antihypertensive medication), patients with

known cardiovascular disease (history of myocardial infarction, ischemic heart disease, heart failure, or conduction abnormalities), and patients with cerebrovascular disease. In such patients, consider using a lower starting dose and slower titration, and monitor orthostatic vital signs. REXULTI has not been evaluated in patients with a recent history of myocardial infarction or unstable cardiovascular disease. Such patients were excluded from pre-marketing clinical trials.

5.12 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.

5.13 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.

5.14 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.

5.15 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.

5.16 Potential for Cognitive and Motor Impairment

REXULTI, like other antipsychotics, has minor to moderate influence on ability to drive and use machines, impair judgment, or thinking due to potential nervous system effects, such as sedation and dizziness that are common adverse drug reactions. In 6-week, 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.

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

5.17 Lactose

REXULTI film-coated tablets contain lactose. Patients with rare hereditary problems of galactose intolerance, total lactase deficiency or glucose-galactose malabsorption should not take this medicinal product.

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 *[see Warnings and Precautions (5.2)]*
- Cerebrovascular Adverse Reactions Including Stroke in Elderly Patients with Dementia-Related Psychosis *[see Warnings and Precautions (5.3)]*
- QT prolongation *[see Warnings and Precautions (5.4)]*
- Venous thromboembolism *[see Warnings and Precautions (5.5)]*
- Neuroleptic Malignant Syndrome (NMS) *[see Warnings and Precautions (5.6)]*
- Tardive Dyskinesia *[see Warnings and Precautions (5.7)]*
- Metabolic Changes *[see Warnings and Precautions (5.8)]*
- Pathological Gambling and Other Compulsive Behaviors *[see Warnings and Precautions (5.9)]*
- Leukopenia, Neutropenia, and Agranulocytosis *[see Warnings and Precautions (5.10)]*
- Orthostatic Hypotension and Syncope *[see Warnings and Precautions (5.11)]*
- Falls *[see Warnings and Precautions (5.12)]*
- Seizures *[see Warnings and Precautions (5.13)]*
- Body Temperature Dysregulation *[see Warnings and Precautions (5.14)]*
- Dysphagia *[see Warnings and Precautions (5.15)]*
- Potential for Cognitive and Motor Impairment *[see Warnings and Precautions (5.16)]*

6.1 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.

Schizophrenia

The safety of REXULTI was evaluated in 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 (14.1)]*.

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 1 and 2)*

	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

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.

In total 1032 patients were treated with REXULTI in the 6-week trials. In Trials 331-10-228, 331-10-227 and 331-13-214, 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 331-12-282, 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 331-12-282 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 8.

Table 8: TEAEs with Incidence of 2% or More in Any Brexpiprazole Dose Group (1 to 3 mg) and Greater than Placebo Group in Trials 331-10-228, 331-10-227, 331-13-214 and 331-12-282 (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 to 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%

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 to 3 mg/day[1] (N=197) %	ALL (N=1032) %	
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 to 3 mg/day group is from flexible-dose trial 7 (Trial 331-12-282)

Extrapyramidal Symptoms

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%).

Adjunctive Treatment in Major Depressive Disorder (MDD)

In Trial 331-10-228, 331-10-227, and 331-13-214 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 331-12-282, 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 to 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 9.

Table 9: Incidence of EPS-related TEAEs in Short-term Fixed-dose Trial 331-10-228, 331-10-227, 331-13-214 and Short-term Flexible dose Trial 331-12-282 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 to 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 to 3 mg/day group is from flexible-dose Trial 331-12-282

In Trials 331-10-228, 331-10-227, 331-13-214 and 331-12-282, 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 10.

Table 10: Change in EPS Compared to Placebo in MDD Trials 331-10-228, 331-10-227, 331-13-214 and 331-12-282

	Proportion of Subjects with Shifts (worsening) from Baseline				
	Brexpiprazole (mg/day)+ADT				
	1 mg	2 mg	3 mg	2 to 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 to 3 mg/day group is from flexible-dose Trial 331-12-282

Table 11 presents the reported incidence of concomitant medications used to treat EPS-related TEAEs, including akathisia during Trials 331-10-228, 331-10-227, 331-13-214 and 331-12-282

Table 11: Incidence of Reported Concomitant Use to Treat EPS-related TEAEs for Short- term Controlled MDD Adjunctive Trials 331-10-228, 331-10-227, 331-13-214 and 331-12-282

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 to 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 to 3 mg/day group is from flexible-dose Trial 331-12-282

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 are shown below. The following listing does not include adverse reactions: 1) already listed in previous tables or elsewhere in the labeling, 2) for which a drug cause was remote, 3) which were so general as to be uninformative, 4) which were not considered to have clinically significant implications, or 5) which occurred at a rate equal to or less than placebo.

Eye Disorders: Vision Blurred

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

Infections and Infestations: Urinary Tract Infection

Investigations: Blood Prolactin Increased

Musculoskeletal and Connective Tissue Disorders: Myalgia

Psychiatric Disorders: Abnormal Dreams, Insomnia

Skin and Subcutaneous Tissue Disorders: Hyperhidrosis

6.2 Postmarketing Experience

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

Nervous System disorders: Neuroleptic Malignant Syndrome

7 DRUG INTERACTIONS

7.1 Drugs Having Clinically Important Interactions with REXULTI

Table 12: 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 (2.6)]*
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 Clinical Pharmacology (12.3)]*
Intervention:	With concomitant use of REXULTI with a strong CYP2D6 inhibitor, reduce the REXULTI dosage *[see Dosage and Administration (2.6)]*
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 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 (2.6)]*
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 Clinical Pharmacology (12.3)]*
Intervention:	With concomitant use of REXULTI with a strong CYP3A4 inducer, increase the REXULTI dosage *[see Dosage and Administration (2.6)]*
Examples:	rifampin, St. John's wort

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

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. Use of REXULTI in pregnancy or in women of childbearing potential requires the benefits of treatment be weighed against the possible risks to mother and child.

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

Safety and effectiveness in pediatric patients have not been established.

8.5 Geriatric Use

Clinical studies of the efficacy of REXULTI did not include any patients aged 65 or older to determine whether they respond differently from younger patients. The safety and efficacy of brexpiprazole in the treatment of schizophrenia in patients aged 65 years and older have not been established. It is not possible to advise on a minimum effective/safe dose in this population.

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

8.6 CYP2D6 Poor Metabolizers

Dosage adjustment is recommended in known CYP2D6 poor metabolizers, because these patients have higher brexpiprazole concentrations than normal metabolizers of CYP2D6. Approximately 8% of Caucasians and 3% to 8% of Black/African Americans cannot metabolize CYP2D6 substrates and are classified as poor metabolizers (PM) *[see Dosage and Administration (2.6), Clinical Pharmacology (12.3)]*.

8.7 Hepatic Impairment

Reduce the maximum recommended dosage in patients with moderate to severe hepatic impairment (Child-Pugh score ≥ 7). Patients with moderate to severe hepatic impairment (Child-Pugh score ≥ 7) generally had higher

exposure to brexpiprazole than patients with normal hepatic function *[see Clinical Pharmacology (12.3)]*. Greater exposure may increase the risk of REXULTI-associated adverse reactions *[see Dosage and Administration (2.4)]*.

8.8 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 *[see Clinical Pharmacology (12.3)]*. Greater exposure may increase the risk of REXULTI-associated adverse reactions *[see Dosage and Administration (2.5)]*.

8.9 Other Specific Populations

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

9 DRUG ABUSE AND DEPENDENCE

9.1 Controlled Substance

REXULTI is not a controlled substance.

9.2 Abuse

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

9.3 Dependence

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

10 OVERDOSAGE

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

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

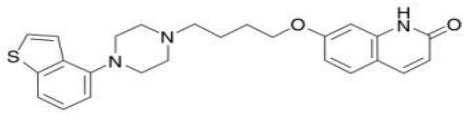
Oral activated charcoal and sorbitol (50 g/240 mL), administered one hour after ingesting oral brexpiprazole, decreased brexpiprazole Cmax and area under the curve (AUC) by approximately 5% to 23% and 31% to 39% respectively; however, there is insufficient information available on the therapeutic potential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

Hemodialysis

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

11 DESCRIPTION

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



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

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

The mechanism of action of brexpiprazole in the treatment of schizophrenia is unknown. However, the efficacy of brexpiprazole may be mediated through a combination of partial agonist activity at serotonin 5-HT_{1A} and dopamine D_2 receptors, and antagonist activity at serotonin 5-HT_{2A} receptors.

12.2 Pharmacodynamics

Brexpiprazole has affinity (expressed as K_i) for multiple monoaminergic receptors including serotonin 5-HT_{1A} (0.12 nM), 5-HT_{2A} (0.47 nM), 5-HT_{2B} (1.9 nM), 5-HT_7 (3.7 nM), dopamine D_2 (0.30 nM), D_3 (1.1 nM), and noradrenergic α_{1A} (3.8 nM), α_{1B} (0.17 nM), α_{1D} (2.6 nM), and α_{2C} (0.59 nM) receptors. Brexpiprazole acts as a partial agonist at the 5-HT_{1A}, D_2, and D_3 receptors and as an antagonist at 5-HT_{2A}, 5-HT_{2B}, 5-HT_7, α_{1A}, α_{1B}, α_{1D}, and α_{2C} receptors. Brexpiprazole also exhibits affinity for histamine H_1 receptor (19 nM) and for muscarinic M_1 receptor (67% inhibition at 10 µM).

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.

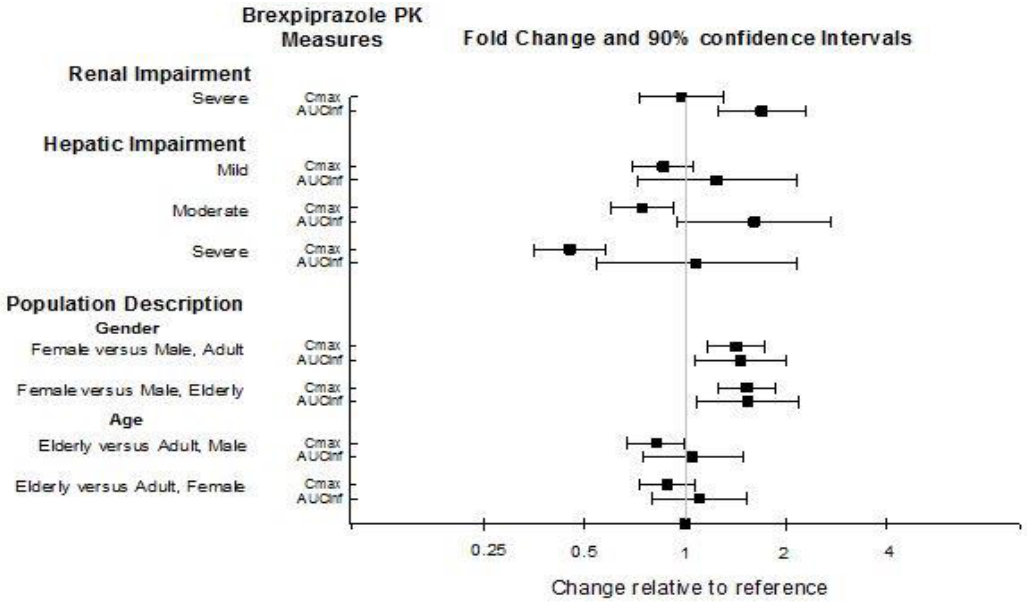
Excretion

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 administration 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

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

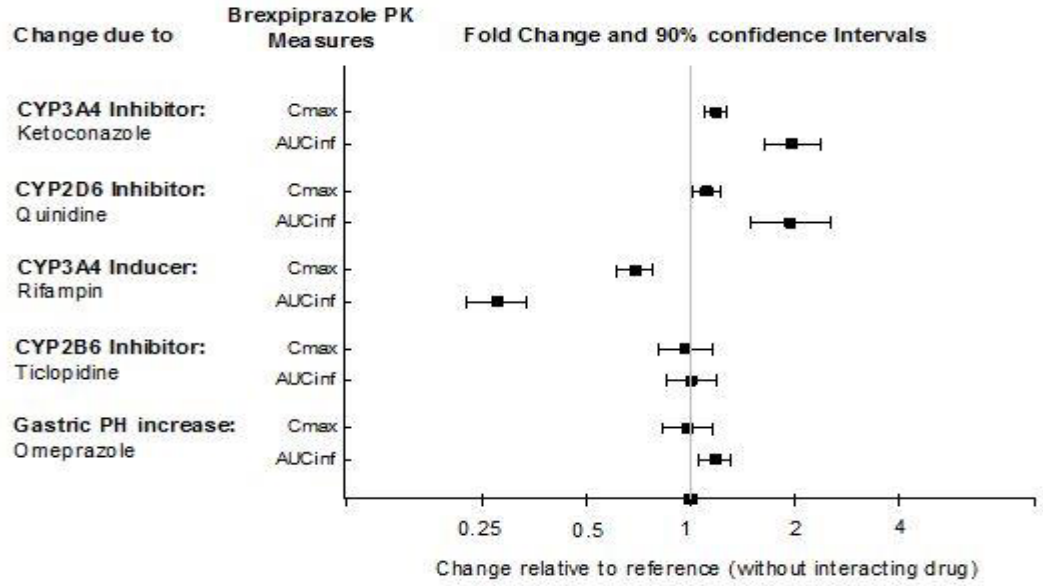
Figure 1: Effects of Intrinsic Factors on Brexpiprazole Pharmacokinetics



Drug Interaction Studies

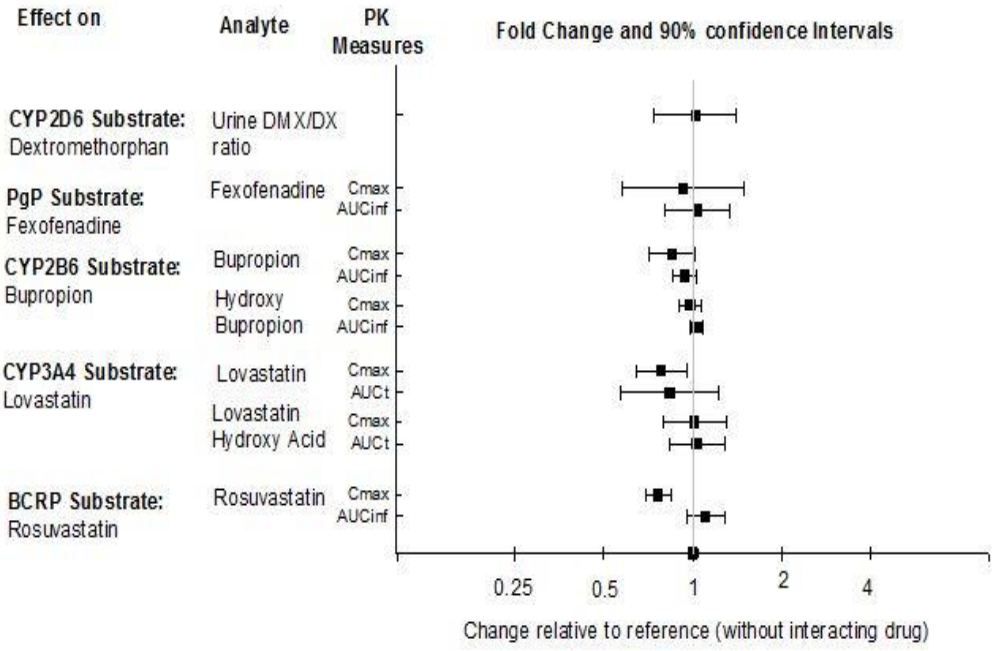
Effects of other drugs on the exposures of brexpiprazole are summarized in Figure 2. Based on simulation, a 5.1-fold increase in AUC values at steady-state is expected when extensive metabolizers of CYP2D6 are administered with both strong CYP2D6 and CYP3A4 inhibitors. A 4.8-fold increase in mean AUC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

Figure 2: The Effects of Other Drugs on Brexpiprazole Pharmacokinetics



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

Figure 3: The Effects 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 SD 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 Schizophrenia

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

In both studies, Study 231 (hereafter “Study 1”) and Study 230 (hereafter “Study 2”), patients were randomized to REXULTI 2 or 4 mg once per day or placebo. Patients in the REXULTI groups initiated treatment at 1 mg once

daily on Days 1 to 4. The REXULTI dosage was increased to 2 mg on Days 5 to 7. The dosage was then either maintained at 2 mg once daily or increased to 4 mg once daily, depending on treatment assignment, for the 5 remaining weeks.

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

In Study 1, REXULTI at both 2 mg/day and 4 mg/day was superior to placebo on the PANSS total score. In Study 2, REXULTI 4 mg/day was superior to placebo on the PANSS total score (Table 13). Figure 4 shows the time course of response based on the primary efficacy measure (change from baseline in PANSS total score) in Study 1.

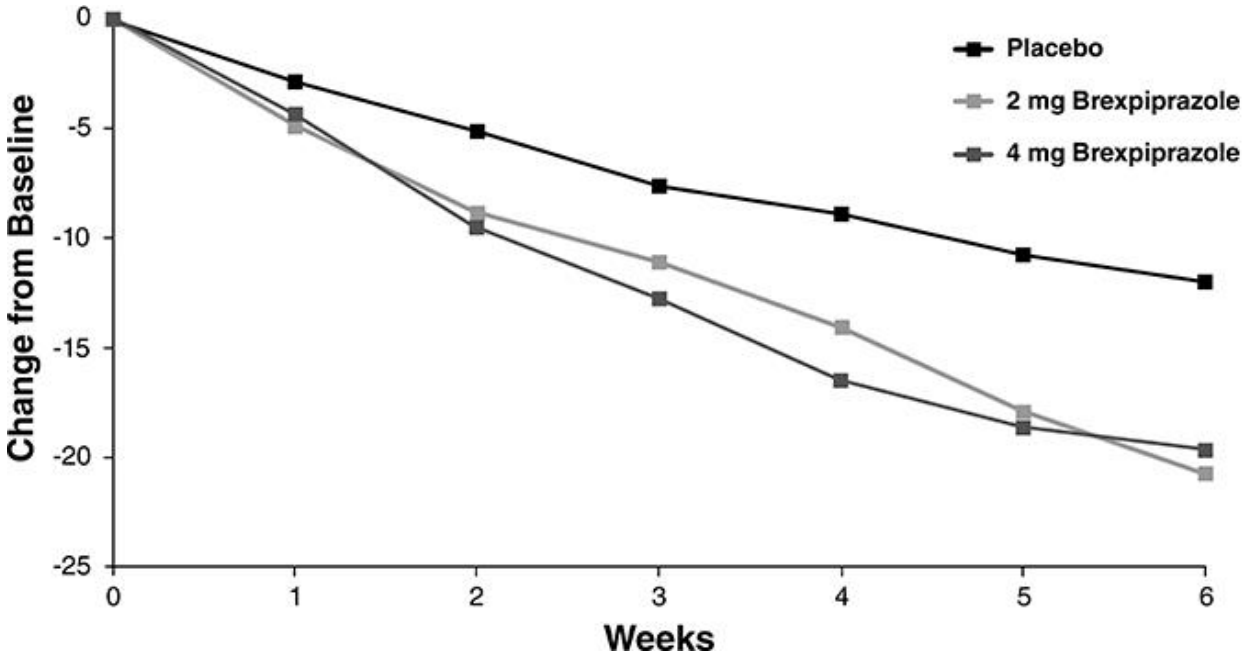
Examination of population subgroups based on age, gender and race did not suggest differential responsiveness.

Table 13: Summary of Efficacy Results for Studies in Schizophrenia

Study	Treatment Group	N	Primary Efficacy Measure: PANSS		
			Mean Baseline Score (SD)	LS Mean Change from Baseline (SE)	Placebo-subtracted Difference[a] (95% CI)
1	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)	--
2	REXULTI (2 mg/day)	179	96.3 (12.9)	-16.6 (1.5)	-3.1 (-7.2, 1.1)
	REXULTI (4 mg/day)*	181	95.0 (12.4)	-20.0 (1.5)	-6.5 (-10.6, -2.4)
	Placebo	180	94.6 (12.8)	-13.5 (1.5)	--

SD: standard deviation; SE: standard error; LS Mean: least-squares mean; CI: unadjusted confidence interval.
* Dosages statistically significantly superior to placebo.
a Difference (drug minus placebo) in least-squares mean change from baseline.

Figure 4: Change from Baseline in PANSS Total Score by Study Visit (Week) in Patients with Schizophrenia in Study 1

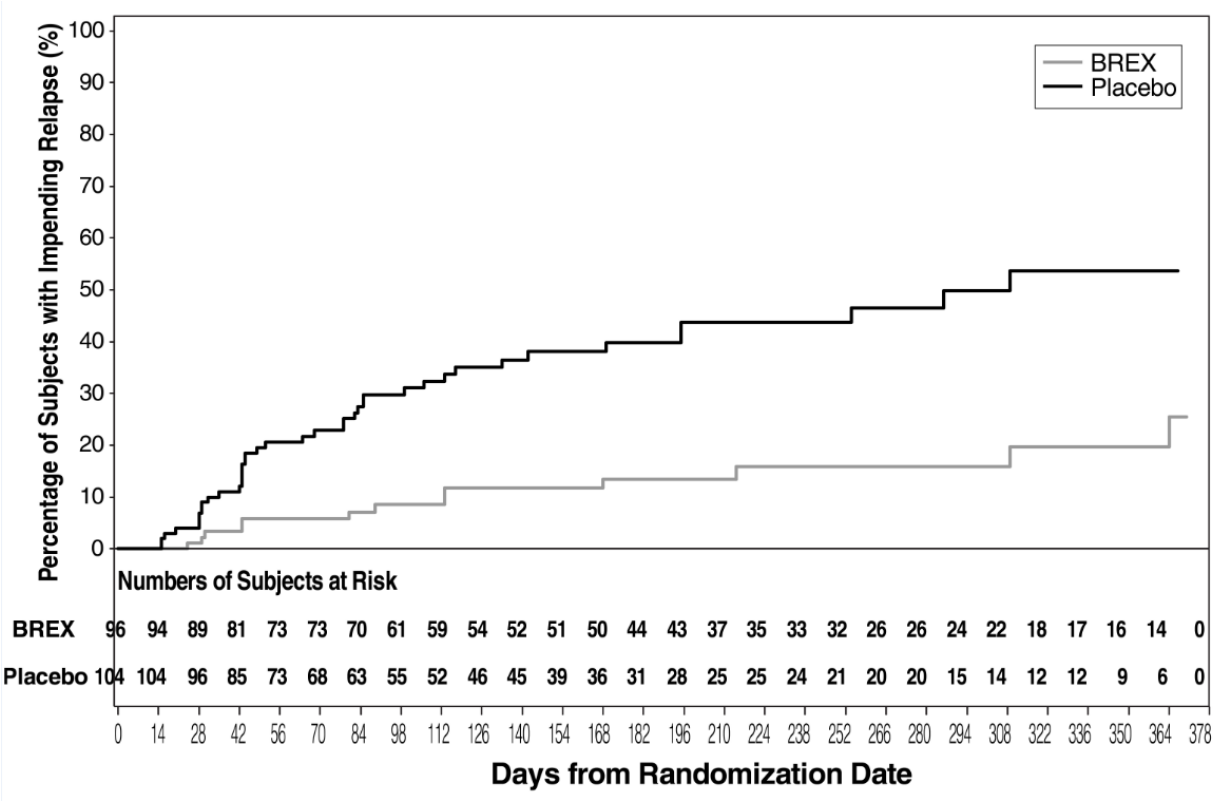


The safety and efficacy of REXULTI as maintenance treatment in adults with schizophrenia aged 18 to 65 years were demonstrated in the maintenance phase of a randomized withdrawal trial (Study 331-10-232, hereafter "Study 3"). Patients were stabilized for at least 12 weeks on 1 to 4 mg/day of REXULTI (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 3 was time from randomization to impending relapse during the double-blind phase, defined as: 1) CGI-Improvement score of ≥ 5 (minimally worse) and an increase to a score > 4 on PANSS conceptual disorganization, hallucinatory behavior, suspiciousness, or unusual thought content items, with either a ≥ 2 increase on a specific item or ≥ 4 point increase on the combined four PANSS items, 2) hospitalization due to worsening of psychotic symptoms, 3) current suicidal behavior, or 4) violent/aggressive behavior.

A pre-specified interim analysis demonstrated a statistically significantly longer time to relapse in patients randomized to the REXULTI group compared to placebo-treated patients. The trial was subsequently terminated early because maintenance of efficacy had been demonstrated. The Kaplan-Meier curves of the cumulative proportion of patients with relapse during the double-blind treatment phase for REXULTI and placebo groups are shown in Figure 5. The key secondary endpoint, the proportion of subjects who met the criteria for impending relapse, was statistically significantly lower in REXULTI-treated patients compared with placebo group.

Figure 5: Kaplan Meier Estimation of Percent Impending Relapse in Study 3



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

14.2 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) in Table 14.

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 to 3 prior antidepressant therapy(ies) in the current episode and an inadequate response during the 8 to 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 331-10-228 and 331-10-227 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) > 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 331-10-228 and 331-10-227 to the following: < 50% improvement from baseline on the HAMD-17 and a HAMD-17 score > 14 at Week 8; and, CGI-I > 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 331-13-214 and 331-12-282. With the exception of approximately 6% of patients in Studies 331-10-228 and 331-10-227, 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 331-10-228, 331-10-227 and 331-13-214) 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 331-10-227) or increased to 2 mg/day (Studies 331-10-228 and 331-13-214), from Week 3 onwards. Dosages were maintained at the assigned doses for the 4 remaining weeks. In the flexible dose study (Study 331-12-282), 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 331-12-282 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 14: 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	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		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		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	Phase A (8 to 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 to 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 to 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% to 84%) reported an inadequate response to one prior antidepressant treatment, before receiving 8 to 10 weeks of prospective antidepressant treatment during the trials. Following 8 to 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 331-10-228, 331-13-214 and 331-12-282 there was greater improvement in the mean MADRS Total Score with REXULTI (2 mg/day or 2 to 3 mg/day) + ADT compared to placebo + ADT ($p < 0.05$). No additional benefit was demonstrated at doses greater than 2 mg/day (Table 15). In Study 331-12-282 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 15: Summary of the Primary Efficacy Results (MADRS) of REXULTI in Trials 331-10-228, 331-10-227, 331-13-214 and 331-13-214 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 331-10-228[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 331-10-227[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 331-13-214						
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 331-13-282						
2 to 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 331-10-227, the brexpiprazole vs placebo treatment difference was statistically significant only if the larger of the two p-values was <0.05 or the smaller pvalue was <0.025.

[b]LSMD was the difference between LS mean of brexpiprazole and placebo.
[c]Results for the primary analysis populations for Studies 331-10-228 and 331-10-227 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 331-10-228, the mean SDS score showed greater improvement with REXULTI (2 mg/day) + ADT than with placebo + ADT ($p<0.05$).

16 HOW SUPPLIED/STORAGE AND HANDLING

16.1 How Supplied

REXULTI (brexpiprazole) tablets have markings on one side, and are available in the following strengths and package configurations (see Table 16):

Table 16: Package Configuration for REXULTI Tablets

Tablet Strength	Tablet Color/Shape	Tablet Markings	Pack Size	Reg Number
0.25 mg	light brown; round	"BRX" and "0.25"	Box 1 blister @ 10 tablets	DKI2009700917A1
0.5 mg	light orange; round	"BRX" and "0.5"	Box 1 blister @ 10 tablets	DKI2009700917B1
1 mg	light yellow; round	"BRX" and "1"	Box 1 blister @ 10 tablets	DKI2009700917C1
2 mg	light green; round	"BRX" and "2"	Box 1 blister @ 10 tablets	DKI2009700917D1
3 mg	light purple; round	"BRX" and "3"	Box 1 blister @ 10 tablets	DKI2009700917E1
4 mg	white; round	"BRX" and "4"	Box 1 blister @ 10 tablets	DKI2009700917F1

16.2 Storage

Store below 30ºC.

Keep out of the reach of children.

17 PATIENT COUNSELING INFORMATION

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 and adjustment *[see Dosage and Administration (2.1), (2.2), (2.3), (2.4), (2.5), (2.6)]*.
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 health care

provider or report to the emergency room if they experience signs or symptoms of NMS *[see Warnings and Precautions (5.6)]*.

Tardive Dyskinesia

Counsel patients on the signs and symptoms of tardive dyskinesia and to contact their health care provider if these abnormal movements occur *[see Warnings and Precautions (5.7)]*.

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 (5.8)]*.

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 (5.9)]*.

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 (5.10)]*.

Orthostatic Hypotension and Syncope

Educate patients about the risk of orthostatic hypotension and syncope especially early in treatment, and also at times of re-initiating treatment or increases in dosage *[see Warnings and Precautions (5.11)]*.

Heat Exposure and Dehydration

Counsel patients regarding appropriate care in avoiding overheating and dehydration *[see Warnings and Precautions (5.14)]*.

Interference with Cognitive and Motor Performance

Caution patients about performing activities requiring mental alertness, such as operating hazardous machinery or operating a motor vehicle, until they are reasonably certain that REXULTI therapy does not adversely affect their ability to engage in such activities *[see Warnings and Precautions (5.16)]*.

Concomitant Medications

Advise patients to inform their health care 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)]*.

HARUS DENGAN RESEP DOKTER

Otsuka

Manufactured by:
Korea Otsuka Pharmaceutical Co., Ltd.
27, Jeyakgongdan 3-gil,
Hyangnam-eup, Hwaseong-si,
Gyeonggi-do, 18622, Korea

Under license from:
Otsuka Pharmaceutical Co., Japan

Imported and repacked by:
PT Otsuka Indonesia
Jl. Sumber Waras No 25,
Lawang, Malang 65216, Indonesia

INFORMASI PRODUK UNTUK PASIEN

REXULTI
Brexpiprazole

Nama Produk : **REXULTI**

Bentuk sediaan : Tablet Salut Selaput 0.25 mg
Tablet Salut Selaput 0.5 mg
Tablet Salut Selaput 1 mg
Tablet Salut Selaput 2 mg
Tablet Salut Selaput 3 mg
Tablet Salut Selaput 4 mg

Pemerian **:** REXULTI 0,25 mg : coklat terang, bulat, dengan tanda "BRX" dan "0.25" pada salah satu sisi.
REXULTI 0.5 mg : oranye terang, bulat, dengan tanda "BRX" dan "0.5" pada salah satu sisi.
REXULTI 1 mg : kuning terang, bulat, dengan tanda "BRX" dan "1" pada salah satu sisi.
REXULTI 2 mg : hijau terang, bulat, dengan tanda "BRX" dan "2" pada salah satu sisi.
REXULTI 3 mg : ungu terang, bulat, dengan tanda "BRX" dan "3" pada salah satu sisi.
REXULTI 4 mg : putih, bulat, dengan tanda "BRX" dan " 4" pada salah satu sisi.

Apa yang terkandung dalam REXULTI ?
Zat aktif : brexpiprazole
Zat tambahan: lactose monohydrate, corn starch, microcrystalline cellulose, hydroxypropyl cellulose, low-substituted hydroxypropyl cellulose, magnesium stearate, hypromellose, dan talk. Zat pewarna mencakup titanium dioxide, iron oxide dan ferrosferric oxide.

Kekuatan : 0.25 mg , 0.5 mg , 1 mg , 2 mg , 3 mg dan 4 mg.

Untuk apa REXULTI digunakan ?
REXULTI adalah obat dengan resep dokter yang digunakan untuk pengobatan:
- Eksaserbasi dan pemeliharaan Skizofrenia (gangguan kejiwaan) pada pasien dewasa.
- *Major Depressive Disorder (MDD)*: REXULTI digunakan dengan obat antidepresan, saat dokter anda menetapkan bahwa antidepresan saja tidak cukup untuk mengobati depresi anda.

Belum diketahui apakah penggunaan REXULTI aman dan efektif pada orang-orang berusia di bawah umur 18 tahun.

Bagaimana saya meminum REXULTI ?

- Minum REXULTI sesuai saran dokter. Jangan merubah dosis atau menghentikan Rexulti atas inisiatif sendiri.
- REXULTI dapat diminum dalam keadaan perut kosong atau bersama makanan.
- Jangan sampai lupa minum obat REXULTI. Jika anda lupa minum obat, segera minum obat saat teringat. Jika sudah saatnya waktu untuk minum obat selanjutnya, maka abaikan minum obat yang terlupa dan minum obat pada waktunya. Jangan minum obat dua kali dosis REXULTI pada waktu yang sama. Jika anda tidak yakin terhadap dosis yang anda minum, silahkan mengubungi dokter anda.
- Jika anda minum obat REXULTI terlalu banyak, segera hubungi dokter atau ruang gawat darurat rumah sakit terdekat.

Untuk Skizofrenia, obat Anda biasanya akan diberikan dalam dosis yang ditingkatkan sebagai berikut:

- Untuk 4 hari pertama minum 1 mg tablet salut selaput per hari,
- Dari hari ke 5 hingga ke 7 minum 2 mg tablet salut selaput sekali sehari,
- Mulai hari ke 8 minum satu tablet dengan kekuatan yang diresepkan oleh dokter Anda setiap hari,
- Dokter Anda mungkin meresepkan dosis yang lebih rendah atau lebih tinggi hingga maksimum 4 mg sekali sehari.

Untuk *Major Depressive Disorder (MDD)*, obat anda biasanya akan diberikan sebagai berikut:

- Dosis awal adalah 0,5 atau 1 mg sekali sehari,
- Dosis umumnya adalah 2 mg sekali sehari.

Jika anda memiliki masalah ginjal dan hati, dokter Anda akan melakukan penyesuaian dosis obat ini.

Siapa yang tidak boleh menerima REXULTI ?

Jangan meminum REXULTI jika anda memiliki riwayat alergi pada brexpiprazole atau kandungan lain pada REXULTI .

Lihat komposisi Rexulti pada “Apa yang terkandung didalam REXULTI ?”.

Apa informasi penting yang harus saya ketahui tentang REXULTI ?

REXULTI dapat menyebabkan reaksi efek samping yang serius termasuk :

- **Peningkatan risiko kematian pada pasien lanjut usia dengan kondisi psikosis yang berkaitan dengan demensia.** Obat REXULTI dapat meningkatkan risiko kematian pada pasien lanjut usia yang sudah tidak berhubungan dengan kenyataan (psikosis) karena bingung dan hilangnya daya ingat (demensia). REXULTI tidak disetujui untuk pengobatan pasien psikosis yang berkaitan dengan demensia.
- **Risiko keinginan/tindakan bunuh diri.** Obat antidepresan, depresi dan gangguan kejiwaan serius, dapat menyebabkan keinginan/tindakan bunuh diri. REXULTI tidak disetujui untuk pengobatan pasien yang berumur kurang dari 18 tahun.
  - **Depresi dan penyakit kejiwaan serius lainnya adalah penyebab yang paling utama dari keinginan atau tindakan bunuh diri. Beberapa orang berisiko sangat tinggi untuk memiliki keinginan atau tindakan bunuh diri.** Hal ini termasuk orang yang memiliki (atau memiliki riwayat keluarga) penyakit bipolar (atau disebut juga penyakit depresi manik) atau keinginan atau tindakan bunuh diri.
  - **Bagaimana saya dapat mengawasi dan mencoba mencegah keinginan dan tindakan bunuh diri pada diri saya atau anggota keluarga saya ?**

- Beri perhatian penuh pada setiap perubahan, terutama perubahan tiba-tiba pada suasana hati, tingkah laku, pikiran atau perasaan. Terutama pada saat pengobatan antidepressan dimulai atau ketika dosis diubah.
- Segera hubungi dokter bila terjadi perubahan tiba - tiba atau perubahan suasana hati, tingkah laku, pikiran atau perasaan.
- Simpan semua berkas kunjungan ke dokter. Bila perlu hubungi dokter di luar jadwal kunjungan, terutama jika terlihat ada perubahan gejala.

Segera hubungi dokter jika anda atau anggota keluarga anda mempunyai gejala-gejala yang disebutkan di atas, terutama jika gejala tersebut baru, memburuk, atau membuat anda khawatir.

Apa lagi yang harus saya ketahui mengenai obat antidepresan?

- **Jangan pernah berhenti meminum obat antidepresan tanpa bertanya dahulu ke dokter anda.** Menghentikan obat antidepresan secara mendadak dapat menyebabkan gejala lainnya.
- **Antidepresan adalah obat yang digunakan untuk mengobati depresi atau penyakit lainnya.** Ini penting untuk mendiskusikan semua risiko pengobatan depresi dan juga risiko tidak mengobatinya. Pasien dan keluarganya atau pengasuhnya seharusnya mendiskusikan semua pilihan pengobatan dengan dokter, tidak hanya penggunaan antidepresan.
- **Obat antidepresan memiliki efek samping lainnya.** Bicarakan pada dokter mengenai kemungkinan efek samping obat yang diresepkan untuk anda atau anggota keluarga anda.
- **Obat antidepresan dapat berinteraksi dengan obat lainnya.** Ketahui semua obat yang anda atau anggota keluarga anda minum. Simpan daftar semua obat (termasuk obat resep, obat bukan resep, vitamin dan suplemen herbal) untuk ditunjukan ke dokter. Jangan memulai pengobatan baru tanpa mengecek terlebih dahulu dengan dokter anda.

Apa yang harus saya informasikan pada dokter sebelum meminum REXULTI ?

Sebelum meminum REXULTI, beritahukan dokter bila anda :

- Menderita diabetes atau memiliki faktor risiko diabetes (mis. Obesitas, atau orang lain dalam keluarga anda menderita diabetes). Dokter anda perlu memeriksa kadar gula darah anda secara teratur karena dapat ditingkatkan dengan obat ini. Tanda-tanda kadar gula darah tinggi adalah haus yang berlebihan, buang air kecil dalam jumlah besar, nafsu makan meningkat dan merasa lemah.
- Kadar tinggi kolesterol, trigliserida, LDL-kolesterol, atau kadar rendah HDL kolesterol.
- Mempunyai riwayat kejang.
- Tekanan darah tinggi atau tekanan darah rendah.
- Masalah jantung atau stroke.
- Jumlah sel darah putih yang rendah.
- Hamil atau sedang merencanakan kehamilan. Tidak diketahui apakah REXULTI dapat menyebabkan kondisi yang merugikan pada bayi yang dikandung. Penggunaan REXULTI pada akhir semester kelahiran dapat menyebabkan gangguan gerakan otot, gejala penghentian obat atau keduanya pada kelahiran.
    - Jika anda akan hamil selama menggunakan REXULTI, bicarakan pada dokter anda.

- Menyusui atau sedang merencanakan menyusui. Belum diketahui apakah REXULTI dapat diekresi melalui ASI. Anda dan dokter anda harus memutuskan apakah anda akan meminum REXULTI atau menyusui.
- Mengalami kombinasi demam, berkeringat, pernapasan lebih cepat, kekakuan otot dan rasa kantuk (mungkin merupakan tanda-tanda *Neuroleptic Malignant Syndrome* (NMS)).
- Memiliki pikiran atau perasaan tentang melukai diri sendiri atau bunuh diri. Pikiran dan perilaku bunuh diri lebih mungkin terjadi pada awal perawatan.
- Mengalami kesulitan menelan.
- Keluarga / pengasuh Anda mengamati bahwa Anda mempunyai keinginan untuk berperilaku dengan cara yang tidak biasa. Anda tidak dapat menahan dorongan untuk melakukan kegiatan tertentu yang dapat membahayakan diri sendiri atau orang lain. Gangguan kontrol impuls dapat mencakup perilaku seperti kecanduan judi, makan atau pengeluaran yang berlebihan, dorongan seks tinggi yang tidak normal atau kesibukan dengan peningkatan pikiran atau perasaan seksual. Dokter Anda mungkin perlu menyesuaikan atau menghentikan dosis Anda.
- Mengalami demensia (kehilangan ingatan dan kemampuan mental lainnya) terutama jika Anda berusia lanjut.
- Memiliki masalah dengan gerakan Anda yang disebut gejala ekstrapiramidal (EPS) di masa lalu. Ini mungkin termasuk gerakan tersentak, kejang, gelisah atau gerakan lambat.
- Mengalami peningkatan kadar hormon prolaktin, atau memiliki tumor di kelenjar pituitari Anda.

Beritahu dokter anda tentang semua obat yang akhir akhir ini/sedang diminum, termasuk semua obat resep dokter, obat tanpa resep dokter, vitamin dan supplemen herbal.

REXULTI dan obat lainnya dapat saling berpengaruh satu sama lain yang mengakibatkan efek samping yang serius. REXULTI dapat mempengaruhi mekanisme kerja obat lain dan juga sebaliknya.

Dokter anda dapat menjelaskan pada anda jika REXULTI aman diminum bersama obat anda yang lain. **Jangan** memulai atau mengakhiri obat lain selama penggunaan REXULTI tanpa memberi tahu dokter anda terlebih dahulu.
Kenali obat yang anda minum. Simpan daftar obat anda untuk diperlihatkan pada dokter dan apoteker ketika anda mendapat obat baru.

Apakah obat ini dapat digunakan selama kehamilan dan menyusui ?

Anda dan dokter anda harus memutuskan jika akan meminum REXULTI selama kehamilan dan menyusui bayi. Tidak diketahui apakah REXULTI dapat menyebabkan kondisi yang merugikan pada bayi yang dikandung. Penggunaan REXULTI pada akhir semester kelahiran dapat menyebabkan gangguan gerakan otot, gejala penghentian obat atau keduanya pada bayi yang baru lahir. Belum diketahui apakah REXULTI dapat dieksresi melalui ASI.

Apa yang harus saya hindari selama menggunakan REXULTI ?

- **Jangan** mengendarai mobil, mengoperasikan mesin berat atau aktifitas lain yang membahayakan sampai anda tahu bagaimana REXULTI mempengaruhi anda. REXULTI mungkin menyebabkan anda mengantuk.
- Hindari mengalami dehidrasi atau terlalu panas selama menggunakan REXULTI.
  - **Jangan** terlalu banyak olahraga.
  - Pada cuaca panas, jika memungkinkan berada di tempat sejuk.

- Hindari matahari. **Jangan** menggunakan terlalu banyak pakaian atau pakaian yang tebal.
- Minum air putih yang banyak.

Apakah efek samping yang mungkin terjadi pada penggunaan REXULTI ?

Lihat "Apa informasi penting yang harus saya ketahui tentang REXULTI ?"

REXULTI mungkin dapat menyebabkan efek samping yang serius, termasuk:

- **Stroke pada pasien lanjut usia (masalah pada serebrovaskular) yang dapat menyebabkan kematian.**

- ***Neuroleptic Malignant Syndrome* (NMS):** Segera hubungi dokter anda jika **mengalami beberapa atau semua** gejala-gejala berikut ini : demam tinggi, kaku otot, kebingungan, berkeringat, perubahan denyut nadi, detak jantung, dan tekanan darah. Ini adalah gejala yang jarang tetapi serius yang dapat menyebabkan kematian. Segera hubungi dokter jika mengalami gejala-gejala tersebut.

- **Gerakan badan tidak terkontrol (*Tardive dyskinesia*) :** REXULTI dapat menyebabkan gerakan yang tidak terkontrol pada wajah, lidah atau anggota tubuh lainnya. *Tardive dyskinesia* mungkin tidak segera sembuh, walaupun anda segera menghentikan penggunaan REXULTI. *Tardive dyskinesia* dapat juga muncul pada saat anda berhenti menggunakan REXULTI.

- **Masalah pada metabolisme seperti :**
  - **Kadar gula darah tinggi (hiperglikemia).** Peningkatan kadar gula dapat terjadi pada beberapa orang yang meminum REXULTI. Peningkatan kadar gula darah secara ekstrim dapat menyebabkan koma atau kematian. Jika anda memiliki diabetes atau faktor risiko diabetes (seperti berat badan berlebih atau mempunyai anggota keluarga diabetes), dokter anda harus memeriksa kadar gula darah anda sebelum anda memulai pengobatan dengan REXULTI dan selama pengobatan.

    Hubungi dokter anda jika anda mengalami gejala karena tingginya kadar gula darah selama menggunakan REXULTI:
    - Merasa sangat haus
    - Merasa sakit pada lambung
    - Sering kencing lebih dari biasanya
    - Merasa sangat lapar
    - Merasa lemas atau lelah
    - Merasa bingung, atau nafas berbau buah

  - **Peningkatan kadar lemak (kolesterol dan trigliserida) dalam darah**
  - **Peningkatan berat badan:** anda dan dokter anda harus memeriksa berat badan secara teratur.

- **Keinginan yang tidak biasa.** Beberapa orang yang meminum Rexulti memiliki keinginan yang tidak biasa, seperti berjudi, dorongan makan yang tidak terkontrol, dorongan untuk berbelanja, dan keinginan seksual. Jika anda atau anggota keluarga anda menyadari bahwa anda memiliki keinginan atau tingkah laku yang tidak biasa, hubungi kepada dokter anda.

- **Jumlah sel darah putih yang rendah**

- **Penurunan tekanan darah (hipotensi ortostatik).** Anda mungkin akan merasa pusing atau merasa akan pingsan ketika bangkit terlalu cepat dari posisi duduk atau berbaring.

- **Kejang**

- **Masalah kontrol suhu badan di mana anda merasa terlalu hangat.** Lihat**"Apa yang harus saya hindari selama menggunakan REXULTI ?"**

- **Kesulitan menelan yang menyebabkan makanan atau cairan masuk ke paru paru.**

Efek samping REXULTI yang paling sering terjadi termasuk peningkatan berat badan dan batin yang gelisah seperti perasaan ingin bergerak.

Ini semua bukan keseluruhan efek samping REXULTI. Untuk informasi tambahan, tanyakan dokter anda atau apoteker.

Bagaimana menyimpan obat ini ?
Rexulti disimpan pada suhu di bawah 30°C.
Jauhkan REXULTI dan obat lainnya dari jangkauan anak-anak.

Nomor Izin Edar
Rexulti 0,25 mg , No Reg DKI2009700917A1
Rexulti 0,5 mg , No Reg DKI2009700917B1
Rexulti 1 mg , No Reg DKI2009700917C1
Rexulti 2 mg , No Reg DKI2009700917D1
Rexulti 3 mg , No Reg DKI2009700917E1
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HARUS DENGAN RESEP DOKTER

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