Package Leaflet

1 DESCRIPTION

Brexpiprazole is a serotonin-dopamine activity modulator that is available as brexpiprazole film-coated tablets.

1.1.1 Name of Medicinal Product

Rexulti 0.25 mg, 0.5 mg, 1 mg, 2 mg, 3 mg, and 4 mg film-coated tablets

1.2 Qualitative and Quantitative Composition

0.25 mg, 0.5 mg, 1 mg, 2 mg, 3 mg, and 4 mg film-coated tablets contain 0.25 mg, 0.5 mg, 1 mg, 2 mg, 3 mg, and 4 mg of brexpiprazole, respectively

1.3 Physicochemistry

1.3.1 Non Proprietary Name

Brexpiprazole

1.3.2 Chemical Name

7-{4-[4-(1-Benzothiophen-4-yl)piperazin-1-yl]butyloxy}quinolin-2(1H)-one

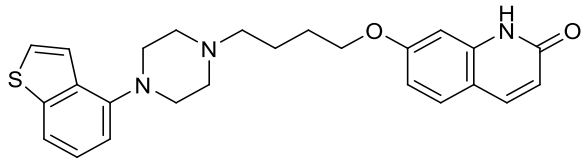
1.3.3 Molecular Formula

$C_{25}H_{27}N_3O_2S$

1.3.4 Molecular Weight

433.57

1.3.5 Structural Formula



1.3.6 Drug Substance Description

Brexpiprazole occurs as white to off-white crystals or crystalline powders.

1.4 Pharmaceutical Form

Table 1 REXULTI Film-coated Tablet			
Dose	**Shape**	**Color**	**Marking**
0.25 mg	round	light brown	“BRX” and “0.25”
0.5 mg	round	light orange	”BRX” and ”0.5”
1 mg	round	light yellow	”BRX” and “1”
2 mg	round	light green	”BRX” and “2”
3 mg	round	light purple	”BRX” and “3”
4 mg	round	white	”BRX” and “4”

2 THERAPEUTIC INDICATIONS

Brexpiprazole is indicated in adult patients for:

- Use as an adjunctive therapy to antidepressants for the treatment of major depressive disorder (MDD). Efficacy was demonstrated in 6-week trials in adults with MDD who had an inadequate response to antidepressant therapy during the current episode. The long-term efficacy of brexpiprazole as adjunctive treatment in MDD has not been established
- Treatment of schizophrenia
- Treatment of agitation associated with Alzheimer’s dementia (AAD)
- Limitations of Use: REXULTI is not indicated as an as needed (“prn”) treatment for agitation associated with dementia due to Alzheimer’s disease
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3 POSOLOGY AND METHOD OF ADMINISTRATION

For oral use once daily with or without food

3.1 Dosage and Method of Administration

Adjunctive Treatment of Major Depressive Disorder

The recommended starting dose for REXULTI as adjunctive treatment is 0.5 mg or 1 mg once daily. Dose titration to 1 mg/day and up to the target dose of 2 mg/day should occur at intervals of up to 1 week based on the patient’s clinical response and tolerability. Doses up to 3 mg/day have been studied in clinical

trials. The benefit of the 3 mg dose has not been clearly established. Periodically reassess to determine the continued need and appropriate dose for treatment.

The long-term efficacy of REXULTI as adjunctive treatment in MDD has not been established.

Schizophrenia

The recommended starting dose for REXULTI in the treatment of patients with schizophrenia is 1 mg once daily on days 1 to 4. The recommended target dose range 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.

Maintenance treatment: The recommended maintenance dose range is 2 mg/day to 4 mg/day. Periodically reassess to determine the continued need for maintenance treatment.

Treatment of Agitation Associated with Alzheimer's Dementia

The recommended starting dosage for REXULTI for the treatment of AAD is 0.5 mg taken orally once daily on Days 1 to 7. The dosage should be titrated on Days 8 through 14 to 1 mg, and on Day 15 to 2 mg. The recommended target dose range is 2 mg once daily. After at least 14 days at 2 mg once daily, the dose can be increased to the maximum recommended daily dose of 3 mg, if clinically warranted.

3.2 Dosing Precautions

Dosing Adjustment for Hepatic Impairment

For patients with moderate to severe hepatic impairment (Child-Pugh score ≥7), the maximum recommended dosage is 2 mg once daily for patients with MDD or AAD, and 3 mg once daily for patients with schizophrenia.

Dosing Adjustment for Renal Impairment

For patients with moderate, severe or end-stage renal impairment (creatinine clearance CLcr<60 mL/minute), the maximum recommended dosage is 2 mg once daily for patients with MDD or AAD and 3 mg once daily for patients with schizophrenia.

Table 2 Dosing Modifications for CYP2D6 Poor Metabolizers and for Concomitant Use with CYP Inhibitors/Inducers

Factors	Adjusted Dosage
CYP2D6 Poor Metabolizers	
Known CYP2D6 poor metabolizers	Administer half of the usual dose

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

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

** If the co-administered CYP3A4 inducer is discontinued, reduce the dosage to the original level over 1 to 2 weeks.

4 CONTRAINDICATIONS

Hypersensitivity to the active substance or to any of the excipients. Reactions have included rash, facial swelling, urticaria, and anaphylaxis.

5 WARNINGS AND PRECAUTIONS FOR USE

5.1 Warnings and Precautions

5.1.1 Product Specific Warnings and Precautions

Increased Mortality in Elderly Patients with Dementia-related Psychosis

Elderly patients with dementia-related psychosis treated with antipsychotic drugs are at an increased risk of death compared to placebo. Analyses of 17 placebo-controlled trials (modal duration of 10 weeks), in patients taking atypical antipsychotic drugs (including risperidone, aripiprazole, olanzapine, and quetiapine), 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 varied, most of the deaths appeared to be either cardiovascular (e.g., heart failure, sudden death) or infectious (e.g., pneumonia) in nature. Brexpiprazole is not approved for the treatment of patient with dementia-related psychosis without symptoms of agitation associated with Alzheimer’s dementia.

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

In placebo-controlled trials with risperidone, aripiprazole and olanzapine in elderly patients with dementia, related psychosis, there was a higher incidence of cerebrovascular adverse reactions (cerebrovascular accidents and transient ischemic attack, including fatal stroke. REXULTI is not approved for the treatment of patients with dementia-related psychosis without symptoms of agitation associated with Alzheimer's dementia.

Suicidal Risk

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.

Suicidal Thoughts and Behaviours in Children, Adolescents and Young Adults
In pooled analyses of placebo-controlled trials of antidepressant drugs (SSRIs and other antidepressant classes) that included approximately 77,000 adult patients, and over 4,400 paediatric patients, the incidence of suicidal thoughts and behaviours in patients age 24 years and younger was greater in antidepressant-treated patients than in placebo-treated patients. The drug-placebo differences in the number of cases of suicidal thoughts and behaviours per 1000 patients treated are provided in Table 3. No suicides occurred in any of the paediatric studies. There were suicides in the adult studies, but the number was not sufficient to reach any conclusion about antidepressant drug effect on suicide.

Table 3: Risk Differences of the Number of Patients with Suicidal Thoughts or Behaviours in the Pooled Placebo-Controlled Trials of Antidepressants in Paediatric and Adult Patients

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

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

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

Neuroleptic Malignant Syndrome (NMS)

A potentially fatal symptom complex, 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 creatine phosphokinase, myoglobinuria (rhabdomyolysis), and acute renal failure. If a patient develops signs and symptoms indicative of NMS, or presents with unexplained high fever without additional clinical manifestations of NMS, all antipsychotic drugs including REXULTI must be discontinued. If a patient requires antipsychotic drug treatment after recovery from NMS, the potential reintroduction of drug therapy should be carefully considered.

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.

There is no known treatment for established cases of tardive dyskinesia, although the syndrome 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 the syndrome is unknown.

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

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

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. Assessment of the relationship between atypical antipsychotics use and glucose abnormalities is complicated by the possibility of an increased background risk of diabetes mellitus in patients with schizophrenia and the increasing incidence of diabetes mellitus in the general population. Given these confounders, the relationship between atypical antipsychotic use and hyperglycaemia-related adverse events is not completely understood. However, epidemiological studies suggest an increased risk of treatment-emergent hyperglycaemia-related adverse events in patients treated with the atypical antipsychotics. Precise risk estimates for hyperglycaemia-related adverse events in patients treated with atypical antipsychotics are not available.

Patients with an established diagnosis of diabetes mellitus who are started on atypical antipsychotics should be monitored regularly for worsening of glucose control. Patients with risk factors for diabetes mellitus (e.g. obesity, family history of diabetes) who are starting treatment with atypical antipsychotics should undergo fasting blood glucose testing in the beginning of treatment and periodically during treatment. Any patient treated with atypical antipsychotics should be monitored for symptoms of hyperglycaemia including polydipsia, polyuria, polyphagia, and weakness. Patients who develop symptoms of hyperglycaemia during treatment with atypical antipsychotics should undergo fasting blood-glucose testing. In some cases, hyperglycaemia has resolved when the atypical antipsychotic was discontinued; however, some patients required continuation of anti-diabetic treatment despite discontinuation of the suspect drug.

Agitation Associated with Alzheimer's Dementia

In the 12-week placebo-controlled, fixed-dose studies in patients (51 to 90 years of age) with AAD, the proportions of patients with shifts in fasting glucose from normal (<100 mg/dL) to high (≥126 mg/dL) or impaired (≥100 and <126 mg/dL) to high were similar in patients treated with REXULTI (14%) and patients treated with placebo (16%).

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

There have been reports of hyperglycemia in patients treated with REXULTI. (see *7 Undesirable effects).*

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 (see *7 Undesirable effects).*

Agitation Associated with Alzheimer's Dementia

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

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Table 6 Change in Fasting Triglycerides in the 12-Week Placebo-Controlled, Fixed-Dose AAD Studies

Proportion of Patients with Shifts Baseline to Post-Baseline				
Triglycerides	Placebo	1 mg/day	2 mg/day	3 mg/day
Normal to High (<150 and 200 to <500 mg/dL)	6% (10/157)*	9% (9/99)*	13% (17/133)*	6% (6/94)*
Borderline to High (150 and <200mg/dL to 200 and <500 mg/dL)	12% (3/26)*	33% (2/6)*	28% (7/25)*	26% (6/23)*
Normal/Borderline to High (<200 mg/dL to 200 and <500 mg/dL)	7% (13/183)*	11% (11/105)*	15% (24/158)*	10% (12/117)*

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

n=the number of patients with shift

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

Weight Gain

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

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

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

For more details related to metabolic changes and weight gain see 7 *Undesirable effects*.

Prolactin

REXULTI can elevate prolactin levels. Elevations associated with REXULTI treatment are generally mild and may decline during administration, however, in some infrequent cases the effect may persist during administration.

Genitourinary

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

Venous thromboembolism

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

Immune
Hypersensitivity

Spontaneous post-market reports of serious hypersensitivity reactions, such as anaphylaxis, angioedema and facial swelling, rash and urticaria, have been reported with REXULTI.

Cardiovascular disorders

REXULTI has not been evaluated in patients with a history of myocardial infarction/ischaemic heart disease or clinically significant cardiovascular disease since such patients were excluded from clinical trials.

REXULTI should be used with caution in patients with known cardiovascular disease (history of myocardial infarction or ischaemic heart disease, heart failure, or conduction abnormalities), cerebrovascular disease, conditions which would predispose patients to hypotension (dehydration, hypovolemia, and treatment with antihypertensive medicinal products) or hypertension (including accelerated or malignant).

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.

Orthostatic Hypotension and Syncope

Atypical antipsychotics cause orthostatic hypotension and syncope. Generally, the risk is greatest during initial dose titration and when increasing the dose.

In two short-term, placebo-controlled clinical studies of REXULTI+ADT in patients with MDD Studies 1 (Study 228) and 2 (Study 227), the incidence of orthostatic hypotension-related adverse reactions in REXULTI+ADT-treated patients compared to placebo+ADT patients included: dizziness (2% vs. 2%) and orthostatic hypotension (0.1% vs. 0%). In two short-term, placebo-controlled clinical studies of REXULTI in patients with schizophrenia Studies 6 (Study 231) and 7 (Study 230) the incidence of orthostatic hypotension-related adverse reactions in REXULTI-treated patients compared to placebo patients included: dizziness (2% versus 2%), orthostatic hypotension (0.4% versus 0.2%), and syncope (0.1% versus 0%).

Orthostatic vital signs should be monitored in patients who are vulnerable to hypotension, (e.g., elderly patients, patients with dehydration, hypovolemia, concomitant treatment with antihypertensive medication), patients with known cardiovascular disease (history of myocardial infarction, ischemic heart disease, heart failure, or conduction abnormalities), and patients with cerebrovascular disease. REXULTI has not been evaluated in patients with a recent history of myocardial infarction or unstable cardiovascular disease. Such patients were excluded from pre-marketing clinical trials. In 12-week, placebo-controlled clinical studies of REXULTI in patients with AAD, the incidence of orthostatic hypotension-related adverse reactions in patients treated with REXULTI compared to patients treated with placebo included: dizziness (3% versus 3%), orthostatic hypotension (1% versus 1%), and syncope (0.2% versus 0.8%).

QT Interval

QT prolongation can develop in patients treated with antipsychotics. In clinical trials, only a few, nonserious, QT prolongations have been reported with REXULTI. Caution should be exercised when REXULTI 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.

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.

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.

Body Temperature Regulation

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.

Dysphagia

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

Pathological Gambling and Other Compulsive Behaviours

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 behaviours. Because patients may not recognize these behaviours as abnormal, it is important for prescribers to ask patients or their caregivers specifically about the development of new or intense gambling urges, compulsive sexual urges, compulsive shopping, binge or compulsive eating, or other urges while being treated with REXULTI. In some cases, although not all, urges were reported to have stopped when the dose was reduced, or the medication was discontinued. Compulsive behaviours 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.

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.

5.1.2 Potential for Cognitive and Motor Impairment

REXULTI, like other antipsychotics has the potential to impair judgment, thinking or motor skills. In two 6-week, placebo-controlled clinical trials in patients with MDD, somnolence (including sedation and hypersomnia) was reported in 4% for REXULTI+ADT-treated patients compared to 1% of placebo+ADT patients Studies 1 (Study 228) and 2 (Study 227).

In two 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 Studies 6 (Study 231) and 7 (Study 230).

In the 12-week placebo-controlled, fixed-dose clinical studies in patients (51 to 90 years of age) with AAD, somnolence (including sedation) was reported in 3% of patients treated with REXULTI compared to 1% of patients treated with placebo.

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

5.2 Special Population

Hepatic Impairment

Patients with moderate to severe hepatic impairment (Child-Pugh score ≥7) generally had higher exposure to brexpiprazole than patients with normal hepatic function; therefore, the maximum recommended dosage is 2 mg once daily for patients with MDD, and 3 mg once daily for patients with schizophrenia. In subjects with varying degrees of hepatic impairment (Child-Pugh Classes A, B, and C), the AUC of oral brexpiprazole (2 mg single dose), compared to matched healthy subjects, increased 24% in mild hepatic impairment, increased 60% in moderate hepatic impairment, and did not change in severe hepatic impairment

Renal Impairment

Patients with impaired renal function (CLcr<60 mL/minute) had higher exposure to brexpiprazole than patients with normal renal function; therefore, the maximum recommended dosage is 2 mg once daily for patients with MDD, and 3 mg once daily for patients with schizophrenia . In subjects with severe renal impairment (CLcr <30 mL/min), AUC of oral brexpiprazole (2 mg single dose) compared to matched healthy subjects was increased by 68% while its Cmax was not changed.

5.2.1 Pregnancy and Lactation

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.

Clinical Considerations

Foetal/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.

REXULTI should be used during pregnancy only if the potential benefit justifies the risk to the foetus.

Data

Animal Data

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

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

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

Lactation

Risk Summary

Lactation studies have not been conducted to assess the presence of brexpiprazole in human milk, the effects of REXULTI on the breastfed infant, or the effects of REXULTI 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.

5.2.2 Pediatric Use

Safety and effectiveness in pediatric patients have not been established. Antidepressants increased the risk of suicidal thoughts and behaviours in paediatric patients (See *5 Warnings and Precautions for Use*).

5.2.3 Geriatric Use

Clinical studies of brexpiprazole did not include sufficient numbers of subjects aged 65 and older to determine whether they respond differently from younger subjects. In long-term trials, no new safety concerns were identified in patients 65 years of age or older with MDD (N=132) treated with 1-3 mg of REXULTI as adjunctive treatment to continued antidepressant therapy during 26 weeks In general, dose selection for an elderly patient should be cautious, usually starting at the low end of the dosing range, reflecting the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy.

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

Agitation Associated with Alzheimer's Dementia (AAD)

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

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

Elderly patients with dementia-related psychosis treated with antipsychotic drugs are at an increased risk of death compared to placebo. REXULTI is not approved for the treatment of patients with dementia related psychosis without symptoms of agitation associated with Alzheimer's dementia.

5.2.4 Other Special Populations

No dosage adjustment for brexpiprazole is required on the basis of a patient's sex, race, or smoking status *(see 9.2.4 Special Populations)*.

6 DRUG INTERACTIONS

Drugs Having Clinically Important Interactions with REXULTI

Table 4: 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 Pharmacological properties (9.2)]*
Intervention:	With concomitant use of REXULTI with a strong CYP3A4 inhibitor, reduce the REXULTI dosage [*see Dosing precautions (3.2)*]
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 Pharmacological properties (9.2)]*
Intervention:	With concomitant use of REXULTI with a strong CYP2D6 inhibitor, reduce the REXULTI dosage [*see Dosing precautions (3.2)*]
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 Pharmacological properties (9.2)]*
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 Dosing precautions (3.2)*]
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 Pharmacological properties (9.2)]*
Intervention:	With concomitant use of REXULTI with a strong CYP3A4 inducer, increase the REXULTI dosage [*see Dosing precautions (3.2)]*
Examples:	rifampin, St. John's wort

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

Drugs Having No Clinically Important Interactions with REXULTI

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

As with other antipsychotics, caution should be used if REXULTI is administered concomitantly with medicinal products known to cause QT prolongation or electrolyte imbalance.

6.1 Food

Intake of food has no effect on the pharmacokinetics of REXULTI.

7 UNDESIRABLE EFFECTS

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.

As with other drugs belonging to the therapeutic class of atypical antipsychotics, cases of restless legs syndrome and urinary retention have been reported for REXULTI.

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

7.1 Clinical Trial Data

CLINICAL TRIAL DATA FOR MAJOR DEPRESSIVE DISORDER

Table 5 shows the incidence of treatment-emergent adverse events (TEAEs) that occurred in at least 2% of patients treated with REXULTI and observed more frequently than with placebo.

Table 5 Adverse Reactions in Pooled 6-week Placebo-controlled, Fixed-dose MDD Trials (Studies 1 [Study 228], 2 [Study 227], 3 [Study 214]) and 6-week Placebo-controlled, Flexible-dose MDD Trial (Study 4 [Study 282])*

		REXULTI				
	Placebo (N=819)	**1 mg/day (N=226)**	**2 mg/day (N=380)**	**3 mg/day (N=229)**	**2-3 mg/day (N=197)**	**All REXULTI (N=1032)**
Eye Disorders						
Vision blurred	0%	1%	2%	2%	1%	2%
Gastrointestinal Disorders						
Constipation	1%	3%	3%	1%	1%	2%
Dry mouth	1%	1%	3%	1%	1%	2%
General Disorders and Administrative Site Conditions						
Fatigue	1%	3%	2%	5%	2%	3%
Infections and Infestations						
Nasopharyngitis	3%	7%	3%	3%	5%	4%
Investigations						
Weight increased	2%	7%	7%	6%	4%	6%
Metabolism and Nutrition Disorders						
Increased appetite	2%	3%	4%	2%	3%	3%
Nervous System Disorders						
Akathisia	3%	4%	8%	14%	6%	8%
Somnolence	1%	4%	5%	6%	6%	5%
Tremor	1%	4%	2%	5%	1%	3%
Dizziness	1%	1%	4%	2%	4%	3%
Psychiatric Disorders						
Restlessness	1%	2%	6%	4%	3%	4%
Insomnia	2%	2%	3%	3%	3%	3%
Anxiety	1%	2%	3%	4%	1%	2%

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

Agitation Associated with Alzheimer's Dementia (AAD)

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

Discontinuation of Treatment Due to Adverse Events

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

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

Adverse reactions associated with REXULTI (incidence ≥2% and greater than placebo) during the 12-week fixed-dose clinical studies in geriatric patients for treatment of AAD are shown in Table 10.

Table 10 Adverse Reactions in ≥2% of REXULTI-Treated Patients and Greater than Placebo in Pooled 12-Week Placebo-Controlled, Fixed-Dose AAD Studies (Study 6 and Study 7)

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

Adverse reactions that occurred <2% and the difference between REXULTI and placebo ≥0.5% in the short-term; placebo-controlled MDD adjunctive therapy clinical trials included palpitations, blepharospasm, toothache, salivary hypersecretion, urinary tract infection, blood prolactin increased, blood cortisol decreased, aspartate aminotransferase increased, muscle spasms, tension, night sweats and hypertension.

Selected Adverse Reactions

Extrapyramidal Symptoms

In the three 6-week, placebo-controlled, fixed-dose and one 6-week, placebo-controlled, flexible-dose MDD studies for REXULTI-treated patients, the incidence of reported EPS-related events, excluding akathisia events, was 5% versus 3% for placebo-treated patients. The incidence of akathisia events for REXULTI-treated patients was 8% versus 3% for placebo-treated patients.

Agitation Associated with Alzheimer's Dementia

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

In the 12-week placebo-controlled, fixed-dose studies in AAD, data was objectively collected on the Simpson-Angus Rating Scale (SAS) for EPS, the Barnes Akathisia Rating Scale (BARS) for akathisia and the Abnormal Involuntary Movement Scale (AIMS) for dyskinesia. The mean change from baseline at last visit for REXULTI-treated patients for the SAS, BARS and AIMS was comparable to placebo-treated

patients. The percentage of patients who shifted from normal to abnormal was greater in REXULTI-treated patients versus placebo for the SAS (6% versus 2%).

Dystonia

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

Other Adverse Reactions Observed during Clinical Trial Evaluation of REXULTI

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

Eye Disorders: Vision Blurred

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

Investigations: Blood Prolactin Increased

Musculoskeletal and Connective Tissue Disorders: Myalgia

Psychiatric Disorders: Abnormal Dreams

Skin and Subcutaneous Tissue Disorders: Hyperhidrosis

Clinical Chemistry Findings

Fasting Glucose

In the long-term, placebo-controlled MDD study, 7.1% of patients in the REXULTI group and 3.4% of patients in the placebo group had shifts from normal or impaired to high in fasting glucose. The mean change from baseline for fasting glucose to last visit was 1.74 mg/dL and 0.21 mg/dL for REXULTI and placebo, respectively.

In the long-term, open-label MDD studies, 5.22% of patients with normal baseline fasting glucose experienced a shift from normal to high while taking REXULTI, 24.35% of subjects with borderline fasting glucose experienced shifts from borderline to high. Combined, 9.06% of patients with normal or borderline fasting glucose experienced shifts to high fasting glucose during the long-term MDD studies. The mean change from baseline for fasting glucose to last visit in the long-term, open label trials was 3.53 [2.00] mg/dL.

Fasting Lipids

In the long-term, placebo-controlled study mean changes from baseline and shifts in lipids are presented in the below table.

Table 6: Mean Changes from Baseline and Shift in Lipids, Long-term Placebo-controlled Study

Fasting Lipids	Mean change from baseline (mg/dL)		Shift (%) *Normal to high:* total cholesterol, LDL, triglycerides *Normal to low*: HDL	
	REXULTI	Placebo	REXULTI	Placebo
LDL	3.14	0.77	4.8	3.1
HDL	-2.43	-0.74	9	7.3
Total cholesterol	3.84	0.87	13.5	9.6
Triglycerides	13.57	6.59	15.5	12.7

In the long-term open-label studies, shifts in fasting cholesterol from normal to high were reported in 8.65% (total cholesterol), 3.20% (LDL cholesterol), and shifts from normal to low were reported in 13.30% (HDL cholesterol) of patients taking REXULTI. Of patients with normal baseline triglycerides, 17.26% experienced shifts to high, and 0.22% experienced shifts to very high triglycerides. Combined, 0.61% of patients with normal or borderline fasting triglycerides experienced shifts to very high fasting triglycerides during the long-term MDD studies. The mean changes from baseline for fasting HDL cholesterol, fasting LDL cholesterol, fasting cholesterol and fasting triglycerides to last visit in the long-term, open label trials were -2.13 [-2.00] mg/dL, 1.36 [1.00] mg/dL, 0.05 [0.00] mg/dL and 11.46 [8.00] mg/dL, respectively.

CLINICAL TRIAL DATA FOR SCHIZOPHRENIA

Table 7 shows the incidence of treatment-emergent adverse events (TEAEs) that occurred in at least 2% of patients treated with REXULTI and observed more frequently than placebo.

Table 7 Adverse Reactions in Pooled 6-week Placebo-controlled, Fixed-dose Schizophrenia Trials (Studies 6 [Study 231], 7 [Study 230], 8 [Study 002]) and 6-week Placebo-controlled, Flexible-dose Schizophrenia Trials (Studies 9 [Study 14644A], 10 [Study 203])*

	Placebo (N=740)	REXULTI			
		2 mg/day (N=482)	4 mg/day (N=477)	2-4 mg/day (N=150)	All REXULTI (N=1199)
Gastrointestinal Disorders					
Diarrhoea	2%	3%	4%	3%	3%
Nausea	3%	5%	2%	3%	3%
Investigation					
Weight increased	2%	3%	3%	5%	4%
Blood creatinine phosphokinase increased	1%	2%	2%	1%	2%
Musculoskeletal and Connective Tissue Disorders					
Backpain	2%	2%	3%	1%	2%
Nervous System Disorder					
Akathisia	4%	5%	7%	6%	6%
Tremor	1%	3%	3%	3%	3%
Dizziness	1%	2%	3%	3%	2%

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

Adverse reactions that occurred <2% and the difference between REXULTI and placebo ≥0.5% in the short-term; placebo-controlled schizophrenia clinical trials included abdominal pain upper, dental caries, flatulence, pain, blood pressure increased, blood triglycerides increased, pain in extremity, myalgia, sedation, cough and rash.

Extrapyramidal Symptoms

In the 6-week, placebo-controlled, fixed-dose schizophrenia studies for 2-4 mg REXULTI -treated patients, the incidence of reported EPS-related events, excluding akathisia events, was 12% versus 10% for placebo-treated patients. The incidence of akathisia events for REXULTI -treated patients was 6% versus 5% for placebo treated patients.

Weight Gain

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

Clinical Chemistry Findings

Fasting Glucose

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

studies. The mean change from baseline for fasting glucose to last visit in the long-term, open label trials was 2.35 [2.00] mg/dL.

Fasting Lipids

In the long-term open-label studies, shifts in baseline fasting cholesterol from normal to high were reported in 6% (total cholesterol), 3% (LDL cholesterol), and shifts in baseline from normal to low were reported in 20% (HDL cholesterol) of patients taking brexpiprazole. Of patients with normal baseline triglycerides, 14% experienced shifts to high, and 0.3% experienced shifts to very high triglycerides. Combined, 0.5% of patients with normal or borderline fasting triglycerides experienced shifts to very high fasting triglycerides during the long-term schizophrenia studies. The mean changes from baseline for fasting HDL cholesterol, fasting LDL cholesterol, fasting cholesterol and fasting triglycerides to last visit in the long-term, open label trials were 0.89 [1.00] mg/dL, -0.97 [-1.00] mg/dL, 0.05 [0.00] mg/dL and -0.40 [-2.00] mg/dL, respectively.

Additional Findings Observed in Schizophrenia Clinical Trials

The adverse reactions reported in a 52-week maintenance phase of a randomized, placebo-controlled withdrawal trial in adults with schizophrenia were comparable with those reported in short-term, fixed-dose trials for schizophrenia.

7.2 Post-marketing Experience

The following adverse reaction has been reported during the post-marketing period with brexpiprazole. The frequency of the reported adverse reaction is unknown.

- Nervous System disorders: Neuroleptic malignant syndrome

8 OVERDOSE

No specific information is available on the treatment of overdose with REXULTI. Gastric lavage and treatment with an emetic may be useful immediately after overdose. An electrocardiogram should be obtained in case of overdosage and if QT interval prolongation is present, cardiac monitoring should be instituted. Otherwise, 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.

Consult a certified POISON CONTROL CENTER for up to date guidance and advice.

Oral activated charcoal and sorbitol (50 g/240 mL), administered one hour after ingesting oral brexpiprazole, decreased brexpiprazole Cmax and 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 brexpiprazole. Although there is no information on the effect of hemodialysis in treating an overdose with REXULTI, hemodialysis is unlikely to be useful in overdose management since brexpiprazole is highly bound to plasma proteins.

9 PHARMACOLOGICAL PROPERTIES

9.1 Pharmacodynamic Properties

Pharmacotherapeutic group: Psycholeptics, other antipsychotics
ATC code: N05AX16

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

Cardiac Electrophysiology

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

9.1.1 Mechanism of Action

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

9.2 Pharmacokinetics

9.2.1 Absorption

After single dose administration of REXULTI tablets, the peak plasma brexpiprazole concentrations occurred within 4 hours after administration; and the absolute oral bioavailability was 95%. Brexpiprazole steady-state concentrations were attained within 10-12 days of dosing.
REXULTI can be administered with or without food. Administration of a 4 mg REXULTI tablet with a standard high fat meal did not significantly affect the C_{max} or AUC of brexpiprazole. After single and multiple once daily dose administration, brexpiprazole exposure (C_{max} and AUC) increased in proportion to the dose administered. *In vitro* studies of brexpiprazole did not indicate that brexpiprazole is a substrate of efflux transporters such as MDRI (P-gp) and BCRP.

9.2.2 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.

9.2.3 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.

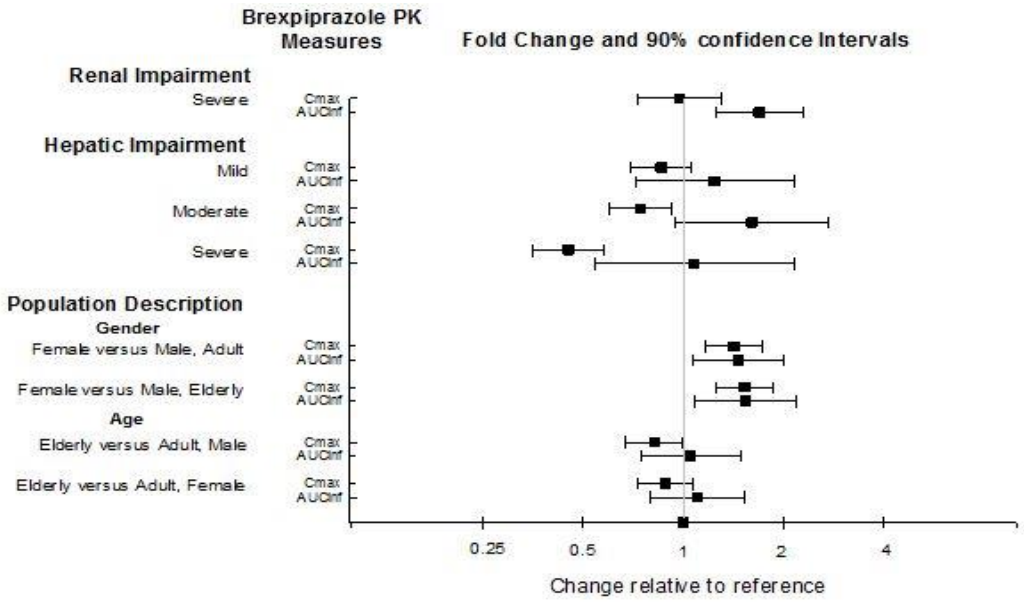
Excretion

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 REXULTI 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.

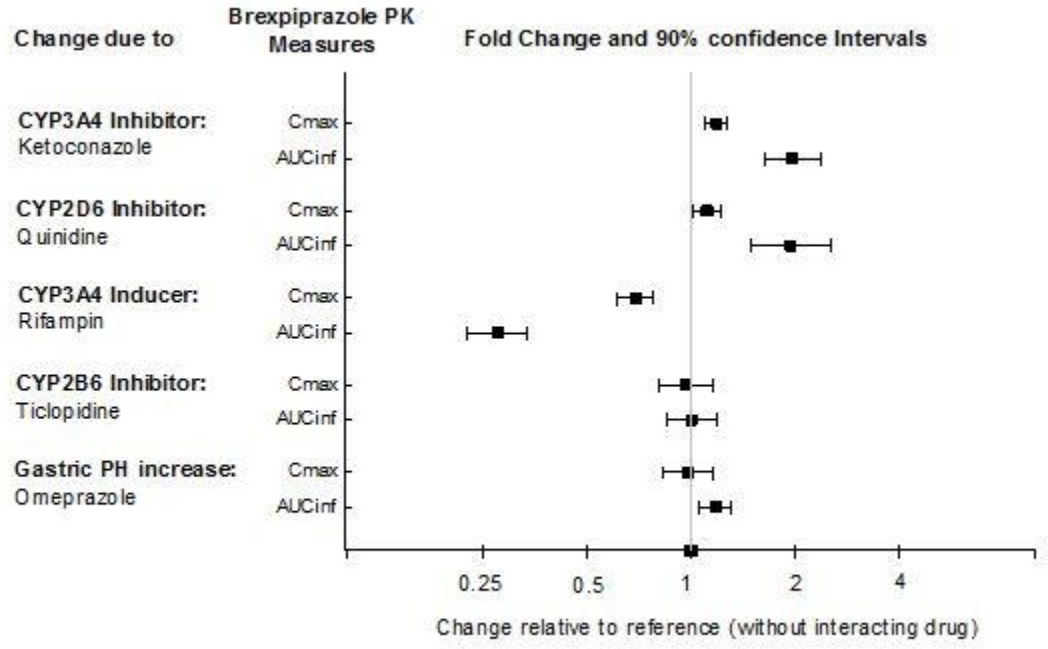
Figure 1: Effects of Intrinsic Factors on Brexpiprazole Pharmacokinetics



Drug Interaction Studies

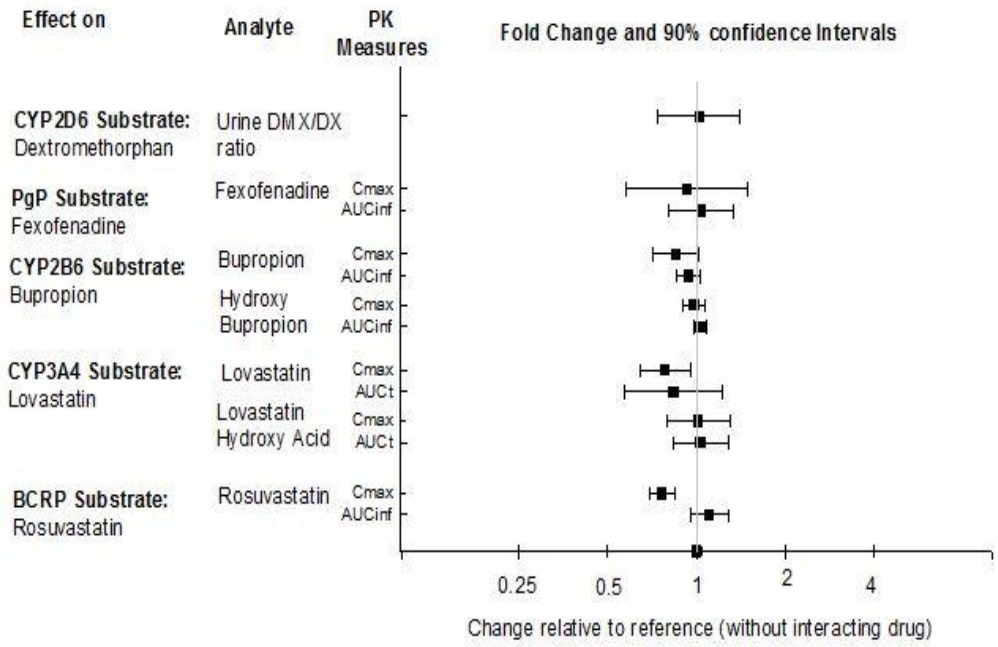
Effects of other drugs on the exposures of brexpiprazole are summarized in Figure 2. Based on simulation, a 5.1-fold increase in AUC values at steady-state is expected when extensive metabolizers of CYP2D6 are administered with both strong CYP2D6 and CYP3A4 inhibitors. A 4.8-fold increase in mean AUC values at steady-state is expected in poor metabolizers of CYP2D6 administered with strong CYP3A4 inhibitors *[see 6 Drug Interactions]*.

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


Effect on
Analyte
PK Measures
Fold Change and 90% confidence Intervals
CYP2D6 Substrate: Dextromethorphan
Urine DMX/DX ratio
PgP Substrate: Fexofenadine
Fexofenadine
Cmax
AUCinf
CYP2B6 Substrate: Bupropion
Bupropion
Cmax
AUCinf
Hydroxy Bupropion
Cmax
AUCinf
CYP3A4 Substrate: Lovastatin
Lovastatin
Cmax
AUCt
Lovastatin Hydroxy Acid
Cmax
AUCt
BCRP Substrate: Rosuvastatin
Rosuvastatin
Cmax
AUCinf
0.25
0.5
1
2
4
Change relative to reference (without interacting drug)

9.2.4 Special Population

Age/Gender

After single dose administration of brexpiprazole (2 mg), elderly subjects (older than 65 years old) exhibited similar brexpiprazole systemic exposure (Cmax and AUC) in comparison with the adult subjects (18-45 years old) and female subjects exhibited approximately 40-50% higher brexpiprazole systemic exposure (Cmax and AUC) in comparison to the male subjects. Population pharmacokinetic evaluation identified age and female sex as statistically significant covariates affecting brexpiprazole PK but the effects on PK were not considered clinically relevant.

Race

Although no specific pharmacokinetic study was conducted to investigate the effects of race on the disposition of brexpiprazole, population pharmacokinetic evaluation revealed no evidence of clinically significant race-related differences in the pharmacokinetics of brexpiprazole.

CYP2D6 Poor Metabolisers:

Approximately 8% of whites and 3–8% of blacks/African Americans lack the capacity to metabolize CYP2D6 substrates and are classified as poor metabolizers (PM), whereas the rest are extensive metabolizers (EM). Population pharmacokinetic evaluation shows that CYP2D6 PMs have 47% higher exposure to brexpiprazole compared to EMs.

Smoking

Based on studies utilizing human liver enzymes in vitro, brexpiprazole is not a substrate for CYP1A2. Smoking should, therefore, not have an effect on the pharmacokinetics of brexpiprazole.

10 CLINICAL STUDIES

Adjunctive Treatment of Major Depressive Disorder

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

The primary endpoint was change from baseline to Week 6 in the Montgomery-Asberg Depression Rating Scale (MADRS), a 10-item clinician-related scale used to assess the degree of depressive symptomatology (apparent sadness, reported sadness, inner tension, reduced sleep, reduced appetite, concentration difficulties, lassitude, inability to feel, pessimistic thoughts and suicidal thoughts). The key secondary endpoint was the Sheehan Disability Scale (SDS), a 3-item self-rated instrument used to assess

the impact of depression on three domains of functioning (work/school, social life, and family life) with each item scored from 0 (not at all) to 10 (extreme).

At randomization, the mean MADRS total score was 27. In the three 6-week, placebo-controlled trials, brexpiprazole +ADT 2 mg/day and 3 mg/day demonstrated efficacy over placebo +ADT in reducing mean MADRS total scores. Brexpiprazole +ADT 2 mg/day and 3 mg/day also demonstrated efficacy over placebo +ADT in improving functioning as measured by the SDS mean score. Brexpiprazole 2 to 3 mg/day +ADT also showed statistically significantly greater improvement on the MADRS total score than placebo+ADT in the flexible-dose trial. Results from the primary and key secondary efficacy parameters for both fixed dose and flexible dose trials are shown below. In the three, fixed-dose clinical trials, pooled analysis of response rate provided support for the efficacy of brexpiprazole+ADT 2 mg/day and 3 mg/day. The response rate was higher in the brexpiprazole+ADT 2 and 3 mg/day group (28.0%) compared to placebo+ADT (21.1%).

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

Table 8 Summary of Efficacy Results for Pivotal Studies in Adjunctive Treatment of MDD

		Baseline End of Phase A	***Mean Change End of Phase B***		***Treatment Comparison vs Placebo***	
Study Treatment Group	***N***	***Mean (SD)***	***LS Mean (SE)[a]***	***LS Mean Difference[b]***	***95% CI[a]***	***P-value[a]***
Study 1 (Study 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)*	*-*	*-*	*-*
Study 2 (Study 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)*	*-*	*-*	*-*
Study 3 (Study 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)*	*-*	*-*	*-*
Study 4 (Study 282)						
*2-3 mg Brex+ADT**	*191*	*25.28 (5.02)*	*-6.04 (0.43)*	*-1.48*	*(-2.56, -0.39)*	*0.0078*
Quetiapine	*99*	*25.56 (5.44)*	*-4.86 (0.57)*	*-0.30*	*(-1.63, -1.04)*	*0.6642*
Placebo+ADT	*205*	*25.39 (5.19)*	*-4.57 (0.41)*	*-*	*-*	*-*

Legend: ADT=antidepressant treatment; SD=standard deviation; SE=standard error; LS Mean=least-squares mean; CI=unadjusted confidence interval.

** Treatment statistically significantly superior to placebo*

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 2 (Study 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 p-value was <0.025.

b LS Mean Difference was the difference between LS mean of brexpiprazole and placebo.

c Results for the primary analysis populations for Studies 1 and 2 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

The long-term efficacy and safety of REXULTI were evaluated in a phase 3, 24 week placebo-controlled trial (Study 5 (Study 14570A)). The adult patients in this trial fulfilled the DSM-IV-TR criteria for MDD, and demonstrated an inadequate response to 1-3 prior antidepressant therapy(ies) in the current episode and an inadequate response throughout 8 weeks of prospective antidepressant treatment.

Inadequate response during the prospective antidepressant treatment phase was defined as having persistent symptoms without substantial improvement throughout the course of the 8 weeks prospective treatment. The primary efficacy endpoint was full remission (defined as a MADRS total score ≤10 and a ≥50% decrease from randomisation in MADRS total score for at least 8 consecutive weeks during randomised treatment). This trial did not show efficacy of REXULTI over placebo.

Schizophrenia

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

The primary efficacy endpoint of all trials was change from baseline to Week 6 in Positive and Negative Syndrome Scale (PANSS) total score using MMRM analysis. The primary instrument for evaluating efficacy was the Positive and Negative Syndrome Scale, a validated multi-item inventory composed of five factors to evaluate positive symptoms, negative symptoms, disorganized thoughts, uncontrolled hostility/excitement, and anxiety/depression. PANSS total score may range from 30 (absent symptoms) to 210 (extreme).

Efficacy was demonstrated in Study 6 (Study 231) for both brexpiprazole 2 mg/day and 4 mg/day and replicated in Study 7 (Study 230) only for brexpiprazole 4 mg/day and in Study 8 (Study 002) only for brexpiprazole 2 mg/day. The key secondary endpoint of both trials was change from baseline to Week 6 in Clinical Global Impression Severity of Illness Scale (CGI-S) total score, a validated clinician-related scale that measures the patient's current illness state and overall clinical state on a 1 (normal, not at all ill) to 7-point (extremely ill) scale.

In two fixed-dose clinical trials, REXULTI 4 mg/day demonstrated efficacy over placebo in the PANSS total score and showed greater improvement in CGI-S score compared to placebo. In two trials, REXULTI 2 mg/day demonstrated efficacy over placebo in the PANSS total score. Results from the primary and key secondary efficacy parameters for the fixed dose trials are shown below. In the three,

fixed-dose clinical trials, pooled analysis of response rate provided support for the efficacy of REXULTI 2 mg/day and 4 mg/day. The response rate was higher in the REXULTI 4 mg/day group (42.5%) and 2 mg/day group (39.0%) compared to placebo (28.5%). In the flexible-dose Study 9 (Study 14644A), at week 6, subjects in the REXULTI group had numerically greater improvements on PANSS total score than the subjects in the placebo group, although, the difference at week 6 did not reach statistical significance for the primary efficacy analysis ($p = 0.0560$) (see table 9). In the same study the active reference, quetiapine XR added for assay sensitivity only, separated from placebo.

The effects of REXULTI were evaluated across a number of pre-specified secondary endpoints; specific aspects of symptoms of schizophrenia (PANSS Positive Subscale score, PANSS Negative Subscale score, PANSS Excited Component (PEC) score, PANSS Marder factors Positive, Negative, Disorganized Thoughts, Uncontrolled Hostility/Excitement and Anxiety/Depression), improvement in Global Clinical Impression (CGI-I) and functioning (Personal and Social Performance scale and the Global Assessment of Functioning (GAF, maintenance Study 11 (Study 232) only)). Analyses of response (defined as 30 % improvement in PANSS total score compared to baseline and a CGI-I score of 1 (very much improved) or 2 (much improved)) and discontinuation for lack of efficacy were also performed. In Study 6 (Study 231), improvement in the change from baseline to week 6 for REXULTI compared to placebo was observed PANSS Positive (2 mg and 4 mg) and PANSS Negative Subscale scores (2 mg and 4 mg), PEC score (2 mg and 4 mg), PANSS Marder factors Positive, Negative, Disorganized Thought, and Uncontrolled Hostility/Excitement (2 mg and 4 mg); CGI-I score (2 mg and 4 mg) and in PSP score (2 mg); response rate for REXULTI at week 6 (2 mg and 4 mg) was larger, and discontinuation for lack of efficacy (4 mg/day) lower than for placebo. In Study 7 (Study 230), improvement in the change from baseline to week 6 for REXULTI compared to placebo in PANSS Positive and PANSS Negative Subscale scores, PEC score, PANSS Marder factors Negative, Disorganized Thought, and Uncontrolled Hostility/Excitement at 4 mg dose and PANSS Marder factor Anxiety/Depression at 2 mg and 4 mg doses; CGI-I (2 mg and 4 mg) and PSP score (4 mg); the response rate at week 6 was larger for REXULTI than for placebo for the 4 mg dose. In trial 3, improvement in the change from baseline at week 6 for REXULTI compared to placebo for the PANSS Negative Subscale score (2 mg and 4 mg), the PEC score (2 mg), the PANSS Marder Factors Negative Symptoms (2 mg and 4 mg), Disorganized Thought, and Anxiety/Depression scores (both 2 mg).

Examination of population subgroups based on age, gender and race did not show any statistical evidence of differential responsiveness.

Table 9 Summary of Efficacy Results for Pivotal Studies in Schizophrenia

Study	Treatment group	n	Primary efficacy measure: PANSS			
			Mean baseline score (SD)	LS mean change from baseline (SE)	LS mean difference[a, b] (95 % CI)	p-value
6 (Study 231)	Brexpiprazole (2 mg/day)*	180	95.85 (13.75)	−20.73 (1.55)	−8.72 (−13.1, −4.37)	< 0.0001
	Brexpiprazole (4 mg/day)*	178	94.70 (12.06)	−19.65 (1.54)	−7.64 (−12.0, −3.30)	0.0006
	Placebo	178	95.69 (11.46)	−12.01 (1.60)	--	--
7 (Study 230)	Brexpiprazole (2 mg/day)	179	96.30 (12.91)	−16.61 (1.49)	−3.08 (−7.23, 1.07)	0.1448
	Brexpiprazole (4 mg/day)*	181	94.99 (12.38)	−20.00 (1.48)	−6.47 (−10.6, −2.35)	0.0022
	Placebo	180	94.63 (12.84)	−13.53 (1.52)	--	--
8 (Study 002)	Brexpiprazole (2 mg/day)*	113	96.55 (19.20)	−14.95 (2.00)	−7.32 (−13.04, −1.59)	0.0124
	Brexpiprazole (4 mg/day)	109	96.39 (15.73)	−11.49 (2.10)	−3.86 (−9.71, 2.00)	0.1959
	Placebo	113	97.19 (19.27)	−7.63 (2.11)	--	--
9 (Study 14644A)	Brexpiprazole (2-4 mg/day)	150	97.82 (10.25)	−19.99 (1.51)	−4.1 (−8.2, 0.1)	0.0560
	Placebo	159	98.38 (10.30)	−15.93 (1.49)	--	--

SD Standard deviation
SE Standard error
LS Mean Least-squares mean.
CI Confidence interval
* Treatment statistically significantly superior to placebo
a Difference (brexpiprazole minus placebo) in least-squares mean change from baseline, at week 6

Maintenance: The safety and efficacy of REXULTI as maintenance treatment in adults with schizophrenia aged 18 to 65 years were demonstrated in a 52-week maintenance phase of a randomized withdrawal trial (Study 232). A pre-specified interim analysis demonstrated a statistically significantly longer time to impending relapse in patients randomized to the REXULTI group (1 mg/day to 4 mg/day) compared to placebo-treated patients and the trial was subsequently terminated early because maintenance of efficacy had been demonstrated. The final analysis demonstrated a longer time to impending relapse in patients randomized to the REXULTI group compared to placebo. The key secondary endpoint, the proportion of patients who met the criteria for impending relapse, was lower in REXULTI -treated patients (13.5%) compared with placebo group (38.5%). REXULTI reduced the risk of impending relapse by 71% compared to placebo. REXULTI improved clinical symptomology (as assessed by PANSS, CGI-S and GGI-I [LOCF]) and functioning (as assessed by GAF [LOCF]) during the stabilization phase. These improvements were maintained during the 52-week double-blind maintenance phase in patients on REXULTI whereas patients randomized to placebo showed deterioration in PANSS, CGI-S and GGI-I, and GAF scores [LOCF]). REXULTI maintained symptom control and functioning compared to placebo.

Agitation Associated with Alzheimer's Dementia

The efficacy of REXULTI in the treatment of agitation associated with Alzheimer's dementia (AAD) was demonstrated in two 12-week, randomized, double-blind, placebo-controlled, fixed dose studies (Study 6, NCT01862640 and Study 7, NCT03548584) who met a diagnosis of probable Alzheimer's Disease according to NINCDS-ADRDA criteria and a Mini-Mental State Examination (MMSE) score of ≥5 and ≤22 and have a total score of ≥4 by the agitation/aggression item of the NPI/NPI-NH. Patients were required to be exhibiting sufficient agitation behaviors at time of entry to warrant use of pharmacotherapy, after excluding other factors.

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

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

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

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

As shown in Table 14 and Figure 7, the mean change from baseline in the CMAI score after 12 weeks in patients treated with 2 mg per day or 3 mg per day of REXULTI was statistically significantly superior to placebo. The once daily 1 mg dose did not demonstrate significantly greater mean changes at baseline from placebo in the CMAI score in this patient population. The 1 mg once day REXULTI dosage is not

approved and is not recommended for the treatment of agitation associated with dementia due to Alzheimer's disease *[see Dosage and Administration (2.4)]*.

Table 16: Change in CMAI Total Score from Baseline at Week 12 in Patients with Agitation Associated with Alzheimer's Dementia in Study 6 and Study 7

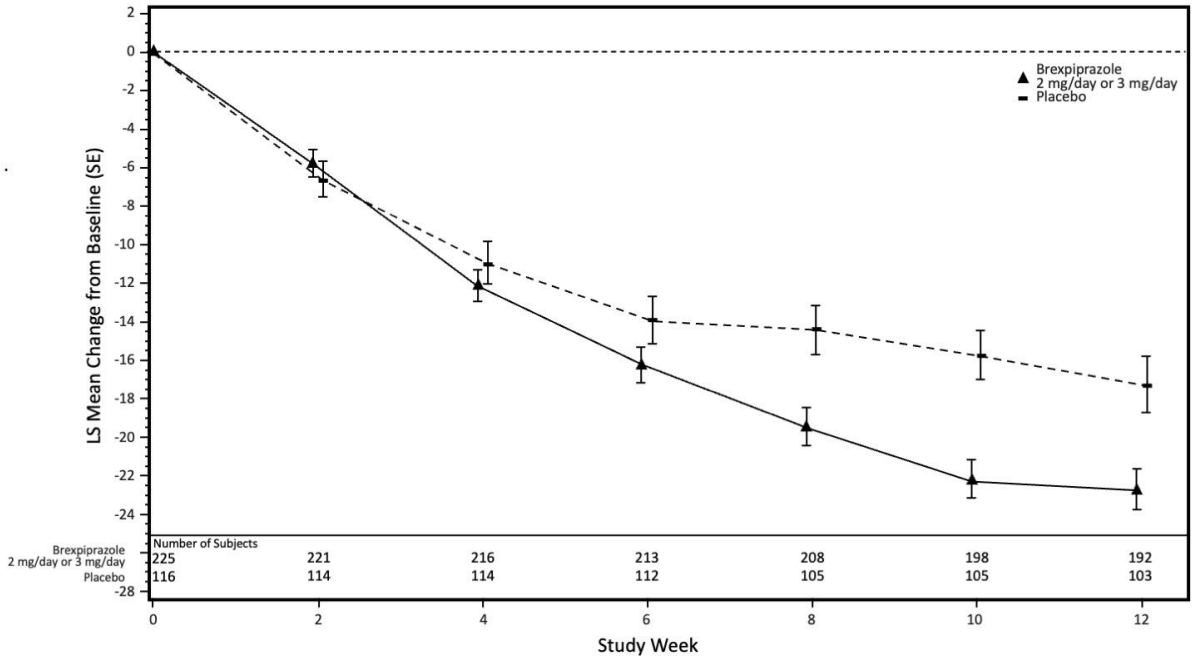
Study	Treatment Group	N	Mean Baseline Score (SD)	LS Mean Change (SE)	Treatment Difference* (95% CI)
6	REXULTI 1 mg/day	134	70.5 (16.0)	-17.6 (1.3)	0.2 (-3.4, 3.9)
	REXULTI 2 mg/day†	138	71.0 (16.6)	-21.6 (1.3)	-3.8 (-7.4, -0.2)
	Placebo	131	72.2 (17.9)	-17.8 (1.3)	—
7	REXULTI 2 mg/day or 3 mg/day†	225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

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

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

†Dosages statistically significantly superior to placebo

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



11 NON-CLINICAL SAFETY

Abuse/liability: Brexpiprazole showed neither a potential to produce physical dependence in rats nor a reinforcing effect in rhesus monkeys. In a drug abuse liability study in rats, no withdrawal signs suggestive of physical dependence were evident. Brexpiprazole is not considered to have potential to produce physical dependence.

11.1 Carcinogenicity, mutagenesis, and impairment of fertility

The lifetime carcinogenic potential of brexpiprazole was evaluated in a two year study in ICR mice and Sprague-Dawley rats. Brexpiprazole was administered orally (gavage) for two years to mice at doses of 0.75, 2 and 5 mg/kg/day (0.9 to 6.1-fold the 4 mg oral maximum recommended human dose [MRHD] for a 60 kg patient based on body surface area). There was no increase in the incidence of tumors in males at any dose group. In female mice, there was an increased incidence of mammary gland adenocarcinoma and adenosquamous carcinoma, and pars distalis adenoma of the pituitary gland. Brexpiprazole was administered orally (gavage) for two years to rats at doses of 1, 3 and 10 mg/kg/day in male rats or 3, 10 and 30 mg/kg/day in female rats (for males 2.4 to 24.3-fold and for females 7.3 to 72.9-fold the 4 mg oral MRHD for a 60 kg patient based on body surface area). Long-term administration of brexpiprazole to rats did not induce neoplastic lesions.

Proliferative and/or neoplastic changes in the mammary and pituitary glands of rodents have been observed following chronic administration of antipsychotic drugs and are considered to be prolactin mediated. The potential for increasing serum prolactin level of brexpiprazole was shown in both mice and

rats. The relevance for human risk of the findings of prolactin-mediated endocrine tumors in rodents is unknown.
The mutagenic potential of brexpiprazole was tested in the *in vitro* bacterial reverse mutation assay, the *in vitro* forward gene mutation assay in mouse lymphoma cells, the *in vitro* chromosomal aberration assay in Chinese hamster ovary (CHO) cells, the *in vivo* micronucleus assay in rats, and the unscheduled DNA synthesis assay in rats. *In vitro* with mammalian cells brexpiprazole was mutagenic and clastogenic but occurred at doses that induced cytotoxicity. No mutagenicity or genotoxicity was observed in other studies. Based on a weight of evidence, brexpiprazole is not considered to present a genotoxic risk to humans at therapeutic doses and exposures.

Brexpiprazole was given once daily by oral gavage to female rats at doses of 0, 0.3, 3 or 30 mg/kg/day prior to mating with untreated males and continuing through conception and implantation. Prolonged diestrus and decreased fertility were observed at 3 and 30 mg/kg/day. At 30 mg/kg/day a slight prolongation of the mating phase was observed and significantly increased preimplantation losses were seen. The no observed adverse effect level in brexpiprazole was 0.3 mg/kg/day (0.7-fold the 4 mg oral MRHD for a 60 kg patient based on body surface area).

Brexpiprazole was given once daily by oral gavage to male rats at 0, 3, 10 or 100 mg/kg/day. Following 63 days of dosing, treated males were cohabited with untreated females for a maximum of 14 days. No noticeable differences were noted in the duration of mating or fertility indices in any brexpiprazole treated group.

11.2 Teratogenic effects

Brexpiprazole was not teratogenic and did not cause adverse developmental effects in developmental toxicity studies in which pregnant rats and rabbits were given brexpiprazole during the period of organogenesis at doses up to 30 mg/kg/day (73-fold and 146-fold for rats and rabbits, respectively of the 4 mg/day oral MRHD for a 60 kg patient based on body surface area, with respective rat and rabbit exposures (plasma AUC) 3.3-fold and 5.9-fold the clinical exposure at the 4mg/day MRHD)

In a rabbit embryo-fetal development study (at 150 mg/kg/day, a dose that induced maternal toxicity), decreased body weight, retarded ossification, and increased incidences of visceral and skeletal variations were observed in fetuses.

11.3 Cardiovascular Toxicity

Decreased blood pressure and prolonged QT interval and QTc were noted in the conscious dog in the safety pharmacology study in the 13-week repeat-dose toxicity study with monkeys and in the juvenile toxicity study with dogs. The effect of brexpiprazole on decreased blood pressure was suggested to be due to a blockade of α_1- adrenoceptors in peripheral blood vessels, which is consistent with the pharmacological profile for this compound.

12 PHARMACEUTICAL PARTICULARS

12.1 List of excipients

Lactose monohydrate, corn starch, microcrystalline cellulose, hydroxypropyl cellulose, low-substituted hydroxypropyl cellulose, magnesium stearate, hypromellose, talc, titanium dioxide, iron oxide red (0.25 mg, 0.5 mg, 3 mg), iron oxide yellow (0.25 mg, 0.5 mg, 1 mg, 2 mg), ferrosoferric oxide (0.25 mg, 2 mg, 3mg)

12.2 Shelf Life

3 years

12.3 Special Precautions for Storage

Store below 30°C.

12.4 Special Instructions for Use, Handling and Disposal

No special requirements.

12.5 Incompatibilities

Not applicable

12.6 Nature and Contents of Container

Blisters: PVC/Aluminum blister packs of 7, 10 or 28 tablets.

Not all pack sizes may be marketed.

13 Name and Address of Manufacturer/Product Registration Holder

Manufacturer

Otsuka Pharmaceutical Co., Ltd.
Second Tokushima Factory,
224-18, Hiraishi Ebisuno,
Kawauchi-cho,Tokushima-shi,
Tokushima 771-0182,Japan

Product Registration Holder:

Lundbeck Malaysia Sdn. Bhd. (1027116-X)
A-05-01, Oasis Square Jalan PJU 1A/7A,
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Selangor Darul Ehsan

Date of Revision

26-May-2025