To be sold by retail on the prescription of neurologist and psychiatrist only

BREXILO™

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

Increased Mortality in Elderly Patients with Dementia-Related Psychosis

Elderly patients with dementia-related psychosis treated with antipsychotic drugs are at an increased risk of death. Brexpiprazole is not approved for the treatment of patients with dementia-related psychosis without agitation associated with dementia due to Alzheimer's disease *[see Special warnings and precautions for use (4.4)]*.

Suicidal Thoughts and Behaviors

Antidepressants increased the risk of suicidal thoughts and behaviors in pediatric patients and young adult patients in short-term studies.

Closely monitor all antidepressant-treated patients for clinical worsening, and for emergence of suicidal thoughts and behaviors *[see Special warnings and precautions for use (4.4)]*. The safety and effectiveness of brexpiprazole have not been established in pediatric patients with MDD *[see Special warnings and precautions for use (4.4), Use in special populations (4.6)]*.

1. **Generic Name**

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

2. **Qualitative and quantitative Composition:**

   Brexpiprazole Tablets 0.25 mg

   Each film coated tablet contains:

   Brexpiprazole .....0.25 mg

   Excipients..... Q.S.

   Colours: Titanium dioxide IP, yellow iron oxide, red iron oxide and black iron oxide

   Brexpiprazole Tablets 0.5 mg

   Each film coated tablet contains:

   Brexpiprazole .....0.5 mg

   Excipients..... Q.S.

   Colours: Titanium dioxide IP, yellow iron oxide and red iron oxide.

   Brexpiprazole Tablets 1 mg

   Each film coated tablet contains:

   Brexpiprazole .....1 mg

   Excipients..... Q.S.

   Colours: Titanium dioxide IP, yellow iron oxide and red iron oxide.

   Brexpiprazole Tablets 2 mg

   Each film coated tablet contains:

Brexpiprazole .....2 mg

Excipients..... Q.S.

Colours: Titanium dioxide IP, yellow iron oxide and black iron oxide.

Brexpiprazole Tablets 3 mg

Each film coated tablet contains:

Brexpiprazole .....3 mg

Excipients..... Q.S.

Colours: Titanium dioxide IP, yellow iron oxide, red iron oxide and black iron oxide.

Brexpiprazole Tablets 4 mg

Each film coated tablet contains:

Brexpiprazole .....4 mg

Excipients.....Q.S.

Colour: Titanium dioxide IP

3. Dosage form and strength

Dosage form: Film coated tablet

Strength: Brexpiprazole 0.25 mg, 0.5 mg, 1 mg, 2 mg, 3 mg and 4 mg

Brexpiprazole Tablets 0.25 mg:

Light brown, round, biconvex, beveled edge, film coated tablets plain on both sides.

Brexpiprazole Tablets 0.5 mg

Light orange, round, biconvex, beveled edge, film coated tablets plain on both sides.

Brexpiprazole Tablets 1 mg

Light yellow, round, biconvex, beveled edge, film coated tablets plain on both sides.

Brexpiprazole Tablets 2 mg

Light green, round, biconvex, beveled edge, film coated tablets plain on both sides.

Brexpiprazole Tablets 3 mg

Light purple, round, biconvex, beveled edge, filmcoated tablets plain on both sides.

Brexpiprazole Tablets 4 mg

White, round, biconvex, beveled edge, film coated tablets plain on both sides.

4. Clinical particulars

4.1 Therapeutic indication

Brexpiprazole is indicated for treatment of schizophrenia.

4.2 Posology and method of administration

Method of administration

Administer brexpiprazole orally, once daily with or without food [see *Pharmacokinetic properties (5.3)*].

Posology

Recommended Dosage for Schizophrenia

Adults

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

Recommended Dosage in Patients with Hepatic Impairment

The maximum recommended dosage in patients with moderate to severe hepatic impairment (Child-Pugh score ≥7) is 3 mg orally once daily in patients with schizophrenia *[see Use in special populations (4.6), Pharmacokinetic properties (5.3)]*.

Recommended Dosage in Patients with Renal Impairment

The maximum recommended dosage in patients with creatinine clearance CrCl <60 mL/minute is 3 mg orally once daily in patients with schizophrenia *[see Use in special populations (4.6), Pharmacokinetic properties (5.3)]*.

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

Dosage modifications are recommended in patients who are known cytochrome P450 (CYP) 2D6 poor metabolizers and in patients taking concomitant CYP3A4 inhibitors, CYP2D6 inhibitors, or strong CYP3A4 inducers (see Table 1). If the concomitant drug is discontinued, adjust the brexpiprazole dosage to its original level. If the concomitant CYP3A4 inducer is discontinued, reduce the brexpiprazole dosage to the original level over 1 to 2 weeks *[see Drugs interactions (4.5), Pharmacokinetic properties (5.3)]*.

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

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

4.3 Contraindications

Brexpiprazole is contraindicated in patients with a known hypersensitivity to brexpiprazole or

any of its components. Reactions have included rash, facial swelling, urticaria, and anaphylaxis.

4.4 Special warnings and precautions for use

Increased Mortality in Elderly Patients with Dementia-Related Psychosis

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

Although the causes of death were varied, most of the deaths appeared to be either cardiovascular (e.g., heart failure, sudden death) or infectious (e.g., pneumonia) in nature. Brexpiprazole is not approved for the treatment of patients with dementia-related psychosis without agitation associated with dementia due to Alzheimer's disease *[see Boxed Warning, Special warnings and precautions for use (4.4)]*.

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

In pooled analyses of placebo-controlled trials of antidepressant drugs (SSRIs and other antidepressant classes) that included approximately 77,000 adult patients and over 4,400 pediatric patients, the incidence of suicidal thoughts and behaviors in patients 24 years of age and younger was greater in antidepressant-treated patients than in placebo-treated patients. The drug-placebo differences in the number of cases of suicidal thoughts and behaviors per 1,000 patients treated are provided in Table 2.

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

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

Age Range (years)	Drug-Placebo Difference in Number of Patients with Suicidal Thoughts or Behaviors per 1,000 Patients Treated
	Increases Compared to Placebo
<18	14 additional patients
18 to 24	5 additional patients
	Decreases Compared to Placebo
25 to 64	1 fewer patient
≥65	6 fewer patients

*Brexpiprazole is not approved in pediatric patients with MDD.

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

Monitor all antidepressant-treated patients for clinical worsening and emergence of suicidal thoughts and behaviors, especially during the initial few months of drug therapy and at times of dosage changes. Counsel family members or caregivers of patients to monitor for changes in

behavior and to alert the healthcare provider. Consider changing the therapeutic regimen, including possibly discontinuing brexpiprazole, in patients whose depression is persistently worse or who are experiencing emergent suicidal thoughts or behaviors.

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

In placebo-controlled trials in elderly patients with dementia, patients randomized to risperidone, aripiprazole, and olanzapine had a higher incidence of stroke and transient ischemic attack, including fatal stroke. Brexpiprazole is not approved for the treatment of patients with dementia-related psychosis without agitation associated with dementia due to Alzheimer's disease *[see Boxed Warning, Special warnings and precautions for use (4.4)]*.

Neuroleptic Malignant Syndrome (NMS)

Neuroleptic Malignant Syndrome (NMS), a potentially fatal symptom complex, has been reported in association with administration of antipsychotic drugs, including brexpiprazole.

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 brexpiprazole and provide intensive symptomatic treatment and monitoring.

Tardive Dyskinesia

Tardive dyskinesia, a syndrome consisting of potentially irreversible, involuntary, dyskinetic movements, may develop in patients treated with antipsychotic drugs. The risk appears to be highest among the elderly, especially elderly women, but it is impossible to predict which patients will develop the syndrome. Whether antipsychotic drugs differ in their potential to cause tardive dyskinesia is unknown.

The risk of tardive dyskinesia and the likelihood that it will become irreversible appear to increase as the duration of treatment and the cumulative dose increases. The syndrome can develop after relatively brief treatment periods, at low doses. It may also occur after discontinuation of treatment.

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

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

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

Metabolic Changes

Atypical antipsychotic drugs, including brexpiprazole, 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/Diabetes Mellitus

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

Adjunctive Treatment of Major Depressive Disorder

In the 6-week placebo-controlled, fixed-dose clinical studies in adult patients with MDD, the proportions of patients with shifts in fasting glucose from normal (<100 mg/dL) to high (≥126 mg/dL) and borderline (≥100 and <126 mg/dL) to high were similar in patients treated with brexpiprazole and placebo. In the long-term, open-label depression studies, 5% of adult patients with normal baseline fasting glucose experienced a shift to high while taking brexpiprazole plus an antidepressant (ADT); 25% of patients with borderline fasting glucose experienced shifts to high. Combined, 9% of patients with normal or borderline fasting glucose experienced shifts to high fasting glucose during the long-term depression studies.

Schizophrenia (Adults)

In the 6-week placebo-controlled, fixed-dose clinical studies in adult patients with schizophrenia, the proportions of patients with shifts in fasting glucose from normal (<100 mg/dL) to high (≥126 mg/dL) or borderline (≥100 and < 126 mg/dL) to high were similar in patients treated with brexpiprazole and placebo. In the long-term, open-label schizophrenia studies, 8% of adult patients with normal baseline fasting glucose experienced a shift from normal to high while taking brexpiprazole; 17% of patients with borderline fasting glucose experienced shifts from borderline to high. Combined, 10% of patients with normal or borderline fasting glucose experienced shifts to high fasting glucose during the long-term schizophrenia studies.

Schizophrenia Pediatric Patients (13 to 17 years of age)

In a 6-week, placebo-controlled study in pediatric patients with schizophrenia, the proportion 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 brexpiprazole and placebo. In this study, 1.1% of pediatric patients with normal baseline fasting glucose experienced a shift from normal (<100 mg/dL) to high (≥126 mg/dL) while taking brexpiprazole.

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

Agitation Associated with Dementia Due to Alzheimer's Disease

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

Of the patients who were previously treated with brexpiprazole 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 brexpiprazole; 30% of patients with impaired fasting glucose experienced shifts from impaired fasting glucose (≥100 and < 126 mg/dL) to high fasting glucose. Combined, 20% of patients with normal or impaired fasting glucose experienced shifts to high fasting glucose.

Dyslipidemia

Atypical antipsychotics cause adverse alterations in lipids. Before or soon after initiation of antipsychotic medication, obtain a fasting lipid profile at baseline and monitor periodically during treatment.

Adjunctive Treatment of Major Depressive Disorder

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

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

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

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

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

Schizophrenia (Adults)

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

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

Proportion of Patients with Shifts Baseline to Post-Baseline				
Triglycerides	**Placebo**	**1 mg/day**	**2 mg/day**	**4 mg/day**

Normal to High (<150 mg/dL to ≥200 and <500 mg/dL	6% (15/253)*	10% (7/72)*	8% (19/232)*	10% (22/226)*
Normal/Borderline to Very High (<200 mg/dL to ≥500 mg/dL)	0% (0/303)*	0% (0/94)*	0% (0/283)*	0.4% (1/283)*

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

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

Schizophrenia [Pediatric Patients (13 to 17 years of age)]

The safety and efficacy of brexpiprazole have not been established in patients under the age of 13 years. In a 6 week, placebo-controlled study in pediatric patients with schizophrenia, no clinically meaningful changes in fasting cholesterol, LDL cholesterol, HDL cholesterol, and triglycerides were observed between the brexpiprazole and placebo groups.

In the long-term, open-label study in pediatric patients with schizophrenia, shifts in baseline fasting total cholesterol from normal to high (<170 to ≥200 mg/dL) were reported in 7% of patients taking brexpiprazole, and shifts in baseline HDL cholesterol from normal to low (>45 to < 40 mg/dL) were reported in 10%% of patients taking brexpiprazole. Of patients with normal baseline triglycerides, 15% experienced shifts from normal to high (<90 to ≥130 mg/dL).

Agitation Associated with Dementia Due to Alzheimer's Disease

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

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

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

Table 5 Change in Fasting Triglycerides in the 12-Week Placebo-Controlled, Fixed-Dose Agitation Associated with Dementia Due to Alzheimer's Disease Studies				
Proportion of Patients with Shifts Baseline to Post-Baseline				
Triglycerides	**Placebo**	**1 mg/day**	**2 mg/day**	**3 mg/day**
to High (<200 mg/dL to 200 and < 500 mg/dL)	(13/183)*	(11/105)*	(24/158)*	(12/117)*d

*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 brexpiprazole for 12 weeks and continued into a 12-week, active treatment extension study, 9% of patients taking brexpiprazole showed shifts in baseline fasting total cholesterol from normal (<200 mg/dL) to high (≥240 mg/dL), and 16% of patients taking brexpiprazole 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 brexpiprazole. Monitor weight at baseline and frequently thereafter.

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

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

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

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

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

Schizophrenia (Adults)

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

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

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

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

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

Schizophrenia [Pediatric Patients (13 to 17 years of age)]

In a 6-week, placebo-controlled study in pediatric patients with schizophrenia, no patients discontinued due to weight increase. The mean increase in weight from baseline to last visit was 0.8 kg in the brexpiprazole group and no changes were seen in the placebo groups. The percentage of pediatric patients demonstrating a ≥7% increase in body weight was 8.2% in the brexpiprazole group and 4.9% in the placebo group.

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

Agitation Associated with Dementia Due to Alzheimer's Disease

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

In patients who were previously treated with brexpiprazole 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 brexpiprazole. 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.

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 brexpiprazole. 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 brexpiprazole. In some cases, although not all, urges were reported to have stopped when the dose was reduced, or the medication was discontinued. Compulsive behaviors may result in harm to the patient and others if not recognized. Consider dose reduction or stopping the medication if a patient develops such urges.

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 brexpiprazole 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 brexpiprazole 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 the short-term, placebo-controlled clinical studies of brexpiprazole plus ADT in adult patients with MDD, the incidence of orthostatic hypotension-related adverse reactions in brexpiprazole plus ADT-treated patients compared to placebo plus ADT-treated patients included: dizziness (2% versus 2%) and orthostatic hypotension (0.1% versus 0%). In the short-term, placebo-controlled clinical studies of brexpiprazole in adult patients with schizophrenia, the incidence of orthostatic hypotension-related adverse reactions in brexpiprazole -treated patients compared to placebo patients included: dizziness (2% versus 2%), orthostatic hypotension (0.4% versus 0.2%), and syncope (0.1% versus 0%). In 12-week, placebo controlled clinical studies of brexpiprazole in patients with agitation associated with dementia due to Alzheimer's disease, the incidence of orthostatic hypotension-related adverse reactions in patients treated with brexpiprazole compared to patients treated with placebo included: dizziness (3% versus 3%), orthostatic hypotension (1% versus 1%), and syncope (0.2% versus 0.8%).

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

Falls

Antipsychotics, including brexpiprazole, 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 treatment.

Seizures

Like other antipsychotic drugs, brexpiprazole 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 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 brexpiprazole with caution in patients who may experience these conditions.

Dysphagia

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

Potential for Cognitive and Motor Impairment

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

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

In the 12-week placebo-controlled, fixed-dose clinical studies in patients (51 to 90 years of age) with agitation associated with dementia due to Alzheimer's disease, somnolence (including sedation) was reported in 3% of patients treated with brexpiprazole 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 brexpiprazole therapy does not affect them adversely.

4.5 Drugs interactions

Drugs Having Clinically Important Interactions with Brexpiprazole

See Table 8 for clinically important drug interactions with Brexpiprazole.

Table 8 Clinically Important Drug Interactions with Brexpiprazole

Strong CYP3A4 Inhibitors	
Clinical Impact:	Concomitant use of brexpiprazole with strong CYP3A4 inhibitors increased the exposure of brexpiprazole compared to the use of brexpiprazole alone *[see Pharmacokinetic properties (5.3)]*.
Intervention:	With concomitant use of brexpiprazole with a strong CYP3A4 inhibitor, reduce the brexpiprazole dosage *[see Posology and method of administration (4.2)]*.

Strong CYP2D6 Inhibitors	
Clinical Impact:	Concomitant use of brexpiprazole with strong CYP2D6 inhibitors increased the exposure of brexpiprazole compared to the use of brexpiprazole alone *[see Pharmacokinetic properties (5.3)]*.
Intervention:	With concomitant use of brexpiprazole with a strong CYP2D6 inhibitor, reduce the brexpiprazole dosage *[see Posology and method of administration (4.2)]*.
Both CYP3A4 Inhibitors and CYP2D6 Inhibitors	
Clinical Impact:	Concomitant use of brexpiprazole 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 brexpiprazole alone *[see Pharmacokinetic properties (5.3)]*.
Intervention:	With concomitant use of brexpiprazole 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 brexpiprazole dosage *[see Posology and method of administration (4.2)]*.
Strong CYP3A4 Inducers	
Clinical Impact:	Concomitant use of brexpiprazole and a strong CYP3A4 inducer decreased the exposure of brexpiprazole compared to the use of brexpiprazole alone *[see Pharmacokinetic properties (5.3)]*.
Intervention:	With concomitant use of brexpiprazole with a strong CYP3A4 inducer, increase the brexpiprazole dosage *[see Posology and method of administration (4.2)]*.

Drugs Having No Clinically Important Interactions with Brexpiprazole

Based on pharmacokinetic studies, no dosage adjustment of brexpiprazole 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 brexpiprazole.

4.6 Use in special populations (such as pregnant women, lactating women, pediatric patients geriatric patients etc.)

Pregnancy

Risk Summary

Adequate and well-controlled studies have not been conducted with brexpiprazole in pregnant women to inform drug-associated risks. However, neonates whose mothers are exposed to antipsychotic drugs, like brexpiprazole, 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/m2 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. The background risk of major birth defects and miscarriage for the indicated population(s) is unknown. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2 to 4% and 15 to 20%, respectively.

Clinical Considerations

Fetal/Neonatal Adverse Reactions

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

Data

Animal Data

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

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

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

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 brexpiprazole and any potential adverse effects on the breastfed infant from brexpiprazole or from the underlying maternal condition.

Pediatric Use

Schizophrenia

The safety and effectiveness of brexpiprazole for treatment of schizophrenia have been established in pediatric patients 13 years of age and older. Use of brexpiprazole in this population is supported by evidence from adequate and well-controlled studies in adults and pediatric patients with schizophrenia, pharmacokinetic data from adults and pediatric patients, and safety data in pediatric patients 13 to 17 years of age *[see Special warnings and precautions for use (4.4), Undesirable effects (4.8), Pharmacokinetic properties (5.3), Pharmacodynamic properties (5.2)]*.

The safety and effectiveness of brexpiprazole for the treatment of schizophrenia have not been established in pediatric patients less than 13 years of age.

Major Depressive Disorder

The safety and effectiveness of brexpiprazole for treatment of major depressive disorder have not been established in pediatric patients. Antidepressants increased the risk of suicidal thoughts and behaviors in pediatric patients *[see Boxed Warning, Special warnings and precautions for use (4.4)]*.

Irritability Associated with Autism Spectrum Disorder

The safety and effectiveness of brexpiprazole for the treatment of irritability associated with autism spectrum disorder have not been established in pediatric patients. Effectiveness was not demonstrated, in an 8-week, double-blind, placebo-controlled, flexible-dose clinical study conducted in 119 brexpiprazole -treated pediatric patients 5 to 17 years of age with irritability associated with autism spectrum disorder diagnosed by the Diagnostic and Statistical Manual of Mental Disorders, 5th Edition [DSM-5] criteria. In this study, somnolence (including sedation) occurred at a higher rate than reported in other brexpiprazole studies evaluating adults and elderly patients (16% in brexpiprazole -treated pediatric patients versus 5% for placebo). The mean increase in age-and-gender adjusted body weight z-score from baseline to last visit was 0.3 for brexpiprazole -treated patients versus 0.1 for placebo-treated patients. Increases in age-and-gender adjusted body weight z-score of at least 0.5 SD from baseline was higher in brexpiprazole -treated patients versus placebo (19% versus 5%).

Of the 119 patients from this study, 95 patients entered the open-label treatment study and received up to 26 weeks of daily treatment with brexpiprazole. During the open-label treatment period, 2% of patients discontinued due to weight increase. In patients previously treated with brexpiprazole for 8 weeks, the mean increase in weight from the open-label study baseline to last visit was 4.5 kg. and 26% of patients had an increase in age-and-gender-adjusted body weight z-score of at least 0.5 SD from baseline.

Juvenile Animal Studies

Juvenile rats were administered oral doses of brexpiprazole of 3, 10, and 20 mg/kg/day once daily beginning from weaning (postnatal day 21) through adulthood (postnatal day 90), followed by a 4-week recovery (non dosing) period. Results were similar to those observed in previous repeat-dose toxicity studies in adolescent (8-week-old) rats. Mortality occurred at the high-dose of 20 mg/kg/day, as well as delayed sexual maturation in males and decreased rearing and motor activity. There was no evidence of neurotoxicity or effects on fertility and reproductive function. Histopathologic changes in reproductive organs and mammary glands occurred at all doses, were related to the pharmacology of brexpiprazole and were comparable to those in adult rats. All findings were at least partially reversible. Juvenile dogs were administered oral doses of brexpiprazole of 1, 3, and 30 mg/kg/day once daily starting at 8 or 9 weeks of age for 26 weeks,

followed by an 8-week recovery (non-dosing) period. Decreases in body weight, lethargy, changes in heart rate, and immature male sex organs were observed at 30 mg/kg/day. These findings were at least partially reversible.

Geriatric Use

Antipsychotic drugs increase the risk of death in elderly patients with dementia-related psychosis. Brexpiprazole is not approved for the treatment of patients with dementia-related psychosis *[see Boxed Warning, Special warnings and precautions for use (4.4)]*.

Adjunctive Treatment of Major Depressive Disorder (MDD) and Schizophrenia

Of the total number of brexpiprazole -treated patients in the clinical studies for the adjunctive therapy to antidepressants for MDD and for schizophrenia, 248 (3%) were 65 years of age and older (which included 45 (18%) patients who were 75 years of age and older). Clinical studies of brexpiprazole in these patients did not include sufficient numbers of patients 65 years of age and older to determine whether they respond differently from younger adult patients. In general, dosage selection for the treatment of MDD or schizophrenia in a geriatric patient should be cautious, usually starting at the low end of the dosing range, reflecting the greater frequency of decreased hepatic, renal, and cardiac function, concomitant diseases, and other drug therapy.

Agitation Associated with Dementia Due to Alzheimer's Disease

The total number of brexpiprazole -treated patients 65 years of age and older in the clinical studies for agitation associated with dementia due to Alzheimer's disease (Studies 6 and 7) was 448 (86%) including 170 (33%) patients 65 to 74 years of age, 228 (44%) patients 75 to 84 years of age, and 50 (10%) patients 85 years of age and older *[see Pharmacodynamic properties (5.2)]*.

In clinical studies of brexpiprazole 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.

CYP2D6 Poor Metabolizers

Dosage adjustment is recommended in known CYP2D6 poor metabolizers because these patients have higher brexpiprazole concentrations than normal metabolizers of CYP2D6. Approximately 8% of Caucasians and 3 to 8% of Black/African Americans cannot metabolize CYP2D6 substrates and are classified as poor metabolizers.*[see Posology and method of administration (4.2), Pharmacodynamic properties (5.2)]*

Hepatic Impairment

The maximum recommended dosage in patients with moderate to severe hepatic impairment (Child-Pugh score ≥7) is lower than those with mild hepatic impairment and those with normal hepatic function *[see Posology and method of administration (4.2)]*. Patients with moderate to severe hepatic impairment generally had higher exposure to brexpiprazole than patients with normal hepatic function *[see Pharmacodynamic properties (5.2)]*. Greater exposure may increase the risk of brexpiprazole-associated adverse reactions.

Renal Impairment

The maximum recommended dosage in patients with CrCl <60 mL/minute is lower than those with mild renal impairment and those with normal renal function *[see Posology and method of administration (4.2)]*. Patients with renal impairment had higher exposure to brexpiprazole than patients with normal renal function *[see Pharmacodynamic properties (5.2)]*. Greater exposure may increase the risk of brexpiprazole-associated adverse reactions.

Other Specific Populations

The recommended dosage for brexpiprazole is the same in males and females, in different racial groups, and in smokers and nonsmokers *[see Pharmacodynamic properties (5.2)]*.

4.7 Effects on ability to drive and use machines

Brexpiprazole has minor to moderate influence on the ability to drive and use machines due to potential nervous system effects, such as sedation and dizziness that are common adverse drug reactions.

4.8 Undesirable effects

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, Special warnings and precautions for use (4.4)]*
- Suicidal Thoughts and Behaviors in Adolescents and Young Adults *[see Boxed Warning, Special warnings and precautions for use (4.4)]*
- Cerebrovascular Adverse Reactions Including Stroke in Elderly Patients with Dementia-Related Psychosis *[see Special warnings and precautions for use (4.4)]*
- Neuroleptic Malignant Syndrome (NMS) *[see Special warnings and precautions for use (4.4)]*
- Tardive Dyskinesia *[see Special warnings and precautions for use (4.4)]*
- Metabolic Changes *[see Special warnings and precautions for use (4.4)]*
- Pathological Gambling and Other Compulsive Behaviors *[see Special warnings and precautions for use (4.4)]*
- Leukopenia, Neutropenia, and Agranulocytosis *[see Special warnings and precautions for use (4.4)]*
- Orthostatic Hypotension and Syncope *[see Special warnings and precautions for use (4.4)]*
- Falls *[see Special warnings and precautions for use (4.4)]*
- Seizures *[see Special warnings and precautions for use (4.4)]*
- Body Temperature Dysregulation *[see Special warnings and precautions for use (4.4)]*
- Dysphagia *[see Special warnings and precautions for use (4.4)]*
- Potential for Cognitive and Motor Impairment *[see Special warnings and precautions for use (4.4)]*

Summary Of Adverse Events Reported In Phase-III Clinical Trial In Indian Patients With Acute Schizophrenia:

Torrent Pharmaceuticals Ltd. has conducted phase-III clinical trial to evaluate the efficacy and safety of brexpiprazole in comparison to aripiprazole tablet in 304 Indian patients with acute schizophrenia. In this study no SAE (Serious Adverse Event) was reported. Total of 131 AEs (adverse events) were reported in 104 subjects (34.32%) during the study. Among the 131 AEs, 53 AEs were reported in 44 subjects (28.95%) receiving brexpiprazole treatment, and 78 AEs were reported in 60 subjects (39.74%) receiving the aripiprazole treatment.

Incidence (>2%) of AEs:

Somnolence and headache were most common AEs. Among all the reported AEs, headache was most common in the aripiprazole group (7.95%), while somnolence was most common AE in

brexpiprazole group (5.26%).

Incidence of Extrapyramidal Symptoms (EPS)-related AEs:

Overall incidence of EPS-related AEs was comparable between aripiprazole group (4.63%) and brexpiprazole group (2.63%).

Discontinuation due to AEs:

Overall, study discontinuation rate was comparable between the brexpiprazole group (3.9%) & aripiprazole group (3.3%).

Three subjects were discontinued from the brexpiprazole treatment group due to AE which were EPS & are moderate in severity and considered as possibly related to study drug treatment. No subject was discontinued due to AE in the aripiprazole treatment group.

AEs with Severity:

No severe AE was reported in this study. Among the 131 AEs, 112 AEs with mild severity (29.70%), while 19 AEs (10 in brexpiprazole arm and 9 in aripiprazole arm) with moderate severity reported (5.61%).

Vital Signs, Physical Findings and Other Observation Related to Safety:

Mean values of each vital signs (blood pressure, pulse rate, respiratory rate and body temperature) were comparable between the two treatment groups. Vital signs were within clinically acceptable limits for all the subjects.

Mean weight gain from baseline was comparable between both treatment groups (0.47kg in brexpiprazole group & 0.45kg in aripiprazole group).

The mean of each hematology and biochemistry parameter value was comparable and no notable difference was observed between the two treatment groups.

No clinically significant findings were observed during the physical examination and 12- Lead ECG.

Table 9 Most Common Adverse Events (≥2%) by Preferred Term - Safety Population:

Preferred Term	Brexpiprazole (N=152) n (%) [E]	Aripiprazole (N=151) n (%) [E]
Somnolence	8(5.26%)[8]	8(5.30%)[8]
Headache	6(3.95%)[6]	12(7.95%)[12]
Any EPS (Extrapyramidal Symptom) Event[#]	4(2.63%)[4]	7*(4.63%)[8]
Vomiting	4(2.63%)[4]	5(3.31%)[6]
Anemia	4(2.63%)[4]	1(0.66%)[1]
Constipation	1(0.66%)[1]	5(3.31%)[5]
Pyrexia	1(0.66%)[1]	6(3.97%)[6]
Nasopharyngitis	1(0.66%)[1]	4(2.65%)[4]

Abbreviation(s): SOC =System organ class; PT =Preferred term; AE = Adverse Event.
[#]EPS: Mild rigidity, bradykinesia, stiffness in body parts, tremors, dystonia, akathisia
*One subject has experienced both tremors and bradykinesia in aripiprazole group.
Note:
[1] Percentages were calculated using respective Safety count as denominator.
[2] Percentages were calculated using respective column header count as denominator.
General Note:
•Zero frequencies were presented by "0" and percentage as "0(0.0%)" and Event as "[0]"
•Adverse events were represented as: Subject count (Percentage of subjects) [Event Count].
•Adverse Events were coded using MedDRA version 27.1 or later. Subjects might have reported more than one event per system organ class or preferred term. Subjects were only counted once for each system organ class or preferred term.

Global Clinical Trials Experience

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

The most common adverse reactions in adult patients in clinical trials (≥5%) were weight increased, akathisia, headache, somnolence, and insomnia.

The most common adverse reactions in pediatric patients in clinical trials (≥5%) were weight increased, somnolence, headache, akathisia, and nasopharyngitis.

Brexpiprazole has been evaluated for safety in 12,550 adult patients who participated in multiple-dose clinical trials for major depressive disorder, schizophrenia, agitation associated with dementia due to Alzheimer's disease, attention deficit hyperactivity disorder (ADHD), post-traumatic stress disorder (PTSD), bipolar mania, and borderline personality disorder (BPD). Among them, 3,870 patients were treated with brexpiprazole for at least 180 days, and 1,910 patients were treated for at least one year of exposure.

Additionally, brexpiprazole has been evaluated for safety in 119 pediatric patients who participated in short term trials, and 314 patients in long-term multiple-dose clinical trials for pediatric schizophrenia and autism spectrum disorders (ASD).

Adjunctive Treatment in Major Depressive Disorder (MDD)

The safety of brexpiprazole was evaluated in 1054 adult patients (18 to 65 years of age) diagnosed with MDD who participated in two 6-week placebo-controlled, fixed-dose clinical studies in patients with major depressive disorder in which brexpiprazole was administered at doses of 1 mg to 3 mg daily as adjunctive treatment to continued antidepressant therapy; patients in the placebo group continued to receive antidepressant therapy *[see Pharmacodynamic properties (5.2)]*.

Adverse Reactions Reported as Reasons for Discontinuation of Treatment

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

Adverse Reactions in brexpiprazole Studies for Adjunctive MDD in Adults

Adverse reactions associated with the adjunctive use of brexpiprazole (incidence of 2% or greater and adjunctive brexpiprazole incidence greater than adjunctive placebo) that occurred during acute therapy (up to 6-weeks in patients with MDD) are shown in Table 10.

Table 10 Adverse Reactions in ≥2% of brexpiprazole -Treated Patients and Greater than Placebo in Pooled 6-Week Placebo-Controlled, Fixed-Dose Adjunctive MDD Studies in Adults (Study 1 and Study 2)

		Brexpiprazole			
	Placebo (N=411) %	**1 mg/day (N=226) %**	**2 mg/day (N=188) %**	**3 mg/day (N=229) %**	**All brexpiprazole (N=643) %**
Gastrointestinal Disorders					
Constipation	1	3	2	1	2
General Disorders and Administration Site Conditions					

	Placebo (N=411) %	Brexpiprazole			
		1 mg/day (N=226) %	2 mg/day (N=188) %	3 mg/day (N=229) %	All brexpiprazole (N=643) %
Fatigue	2	3	2	5	3
Infections and Infestations					
Weight Increased	2	7	8	6	7
Blood Cortisol Decreased	1	4	0	3	2
Metabolism and Nutrition					
Increased Appetite	2	3	3	2	3
Nervous System Disorders					
Akathisia	2	4	7	14	9
Headache	6	9	4	6	7
Somnolence	0.5	4	4	6	5
Tremor	2	4	2	5	4
Dizziness	1	1	5	2	3
Psychiatric Disorders					
Anxiety	1	2	4	4	3
Restlessness	0	2	3	4	3

Dose-Related Adverse Reactions in the Adjunctive MDD Studies

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

Schizophrenia

Adults

The safety of brexpiprazole was evaluated in 852 adult patients (18 to 65 years of age) diagnosed with schizophrenia who participated in two 6-week placebo-controlled, fixed-dose clinical studies in which brexpiprazole was administered at daily doses of 1 mg, 2 mg, and 4 mg *[see Pharmacodynamic properties (5.2)]*.

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

Adverse reactions associated with brexpiprazole (incidence of 2% or greater and brexpiprazole incidence greater than placebo) during short-term (up to 6 weeks) studies in adult patients with schizophrenia are shown in Table 11.

Table 11 Adverse Reactions in ≥2% of Brexpiprazole-Treated Patients and Greater than Placebo in Pooled 6-Week Placebo-Controlled, Fixed-Dose Schizophrenia Studies in Adult Patients (Study 3 and Study 4)

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

Pediatric Patients (13 to 17 years of age)]

The safety of brexpiprazole was evaluated in 110 pediatric patients (13 to 17 years of age) diagnosed with schizophrenia who participated in a 6-week, placebo-controlled, clinical study in which brexpiprazole was administered at daily doses of 2 mg to 4 mg *[see Pharmacodynamic properties (5.2)]*.

Adverse Reactions Occurring at an Incidence of 2% or More in Pediatric Patients (13 to 17 years of age) Treated with brexpiprazole for Schizophrenia

Adverse reactions associated with brexpiprazole (incidence of 2% or greater and brexpiprazole incidence greater than placebo) during short-term (up to 6 weeks) study in pediatric patients with schizophrenia are shown in Table 12.

Table 12 Adverse Reactions in ≥2% of brexpiprazole -Treated Patients and Greater than Placebo in 6 Week Placebo- and Active Controlled, Schizophrenia Study in Pediatric Patients 13 to 17 years of age (Study 5)

	Placebo (N=104) %	**Brexpiprazole (N=110) %**
Gastrointestinal Disorders		
Nausea	4	6
Nervous System Disorders		
Akathisia	3	4
Extrapyramidal Symptoms*	3	6
Headache	5	6

*Extrapyramidal Symptoms includes: blepharospasm, dystonia, extrapyramidal disorder, eye movement disorder, hypokinesia, muscle rigidity, musculoskeletal stiffness, psychomotor hyperactivity, tremor

Agitation Associated with Dementia Due to Alzheimer's Disease

The safety of brexpiprazole was evaluated in 503 patients (51 to 90 years of age), with a probable diagnosis of agitation associated with dementia due to Alzheimer's disease, who participated in two 12-week placebo controlled, fixed-dose clinical studies in which Brexpiprazole was administered at daily doses of 2 mg to 3 mg *[see Pharmacodynamic properties (5.2)]*.

Discontinuation of Treatment Due to Adverse Reactions

In two 12-week placebo-controlled, fixed-dose, clinical studies, a total of 5.6% (28/503) of patients treated with brexpiprazole 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 brexpiprazole for Agitation Associated with Dementia Due to Alzheimer's Disease

Adverse reactions associated with brexpiprazole (incidence ≥2% and greater than placebo) during the 12-week fixed-dose clinical studies in geriatric patients for treatment of agitation associated with dementia due to Alzheimer's disease are shown in Table 13.

Table 13 Adverse Reactions in ≥2% of brexpiprazole-Treated Patients and Greater than Placebo in Pooled 12-Week Placebo-Controlled, Fixed-Dose Agitation Associated with Dementia due to Alzheimer's Disease Studies (Study 6 and Study 7)

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

*1 mg once day Brexpiprazole dosage is not a recommended dosage for the treatment of agitation associated with dementia due to Alzheimer's disease
†Dizziness and Vertigo are grouped to Dizziness
‡Sedation and somnolence are grouped to somnolence.
§ Initial insomnia and insomnia are grouped to insomnia

Extrapyramidal Symptoms

Adjunctive Treatment of Major Depressive Disorder

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

In the 6-week placebo-controlled MDD studies, data was objectively collected on the Simpson-

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

Schizophrenia(Adults)

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

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

Schizophrenia [Pediatric Patients (13 to 17 years of age)]

The incidence of reported EPS-related adverse reactions, excluding akathisia, was 6.4% for brexpiprazole-treated pediatric patients versus 2.9% for placebo-treated patients. The incidence of akathisia events for brexpiprazole treated pediatric patients was 3.6% versus 2.9% for placebo-treated patients.

In the 6-week placebo-and active controlled, schizophrenia study in pediatric patients, 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 brexpiprazole-treated pediatric 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 brexpiprazole-treated patients versus placebo for the BARS (0.9% versus 0%) and the SAS (5.5% versus 2.9%).

Agitation Associated with Dementia Due to Alzheimer's Disease

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

In the 12-week placebo-controlled, fixed-dose studies in agitation associated with dementia due to Alzheimer's disease, data was objectively collected on the Simpson-Angus Rating Scale (SAS) for EPS, the Barnes Akathisia Rating Scale (BARS) for akathisia and the Abnormal Involuntary Movement Scale (AIMS) for dyskinesia. The mean change from baseline at last visit for brexpiprazole -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 brexpiprazole -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 brexpiprazole

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

Eye Disorders: Vision Blurred

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

Investigations: Blood Prolactin Increased

Musculoskeletal and Connective Tissue Disorders: Myalgia

Psychiatric Disorders: Abnormal Dreams

Skin and Subcutaneous Tissue Disorders: Hyperhidrosis

Pediatric Patients (13 to 17 years of age)

In a short-term, randomized, double-blind, placebo- controlled study in pediatric patients 13 to 17 years of age with schizophrenia, safety was assessed in 110 patients in which 100 received brexpiprazole for at least 6 weeks. In an on-going, 2 year, open-label study in pediatric patients 13 to 17 years of age with schizophrenia, in which safety was assessed in 194 patients of which 140 received brexpiprazole for at least 6 months. Adverse reactions reported in clinical studies for this age group were generally similar to those observed in adult patients.

Hyperprolactinemia

In a 6-week, placebo-controlled study in pediatric patients with schizophrenia, a 3.3 ng/mL mean increase (from baseline to last visit) was observed in the brexpiprazole group (versus a 2.8 ng/mL mean decrease in the placebo group) in females. Additionally, more female subjects in the brexpiprazole group (28.9%, n=13) compared to the placebo group (4.7%, n=2) had shifts from normal (≤30 ng/mL) prolactin levels at baseline to abnormal (>30 ng/mL) during the course of treatment. In males, overall mean shifts in the brexpiprazole group were not consistent with an increase in prolactin however, more male subjects in the brexpiprazole group (21.4%, n=9) compared to the placebo group (7.0%, n=3) had shifts from normal (≤20 ng/mL) prolactin levels at baseline to abnormal (>20 ng/mL) during the course of treatment. One subject in the study experienced TEAE of galactorrhea without elevated prolactin.

Postmarketing Experience

The following adverse reaction has been identified during post-approval use of brexpiprazole. 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

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important.

It allows continued monitoring of the benefit/risk balance of the medicinal product. Report suspected adverse reactions via any point of contact available at www.torrentpharma.com or at email: pv@torrentpharma.com or call on 1800-120-3001.

4.9 Overdose

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

Management of a brexpiprazole 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.

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

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

5. Pharmacological properties

5.1 Mechanism of Action

The mechanism of action of brexpiprazole in the adjunctive treatment of major depressive disorder, treatment of agitation associated with dementia due to Alzheimer's disease, or treatment of schizophrenia is unknown. However, the efficacy of brexpiprazole may be mediated through a combination of partial agonist activity at serotonin 5-HT1A and dopamine D2 receptors, and antagonist activity at serotonin 5-HT2A receptors.

5.2 Pharmacodynamic properties

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

Cardiac Electrophysiology

At a dose 3 times the MRHD for the treatment of schizophrenia and 4 times the MRHD for adjunctive therapy to antidepressants for the treatment of MDD or agitation associated with dementia due to Alzheimer's disease, brexpiprazole does not prolong the QTc interval to any clinically relevant extent.

Phase-III Clinical Trial In Indian Patients with Acute Schizophrenia:

Torrent Pharmaceuticals Ltd. has conducted phase-III clinical trial to evaluate the efficacy and safety of brexpiprazole in comparison to aripiprazole tablet in patients with acute schizophrenia. This was a phase III, randomized, multi-centric, double-blind, double-dummy, active controlled, parallel-group, non-inferiority clinical study in 304 patients suffering from acute schizophrenia. This study involved screening period of 14 days, treatment period of 6 weeks and safety follow-up 1 week (± 2 days) of the end of treatment.

The primary end point was mean change from baseline in PANSS (Positive and Negative Syndrome Scale) total score at the end of the treatment (week 6). The mean change from baseline in PANSS total score to week 6 was -34.62 with the brexpiprazole treatment and -34.81 with the

aripiprazole treatment (refer below table). Overall, Brexpiprazole tablets were comparable to aripiprazole tablets & non-inferiority was proved.

Table 14 Non-inferiority analysis of mean change from baseline in PANSS total score at week-6 using ANCOVA - mITT Population.

Primary Endpoint	Statistics	Change from baseline	
		Brexpiprazole (N=147)	Aripiprazole (N=149)
Mean Change form baseline in PANSS total score at week 6	LS Means (SE) [1]	-34.62 (1.10)	-34.81(1.09)
	Difference (95% CI of difference*) [1]	0.19 (-2.86:3.24)	
	p-value [2] for Testing of Inferiority as Null Hypothesis	<0.0001	

Abbreviation(s): N = Number of subjects in specified treatment; PANSS = Positive and Negative syndrome scale; SE: Standard Error

Note:

[1] LS Means, Differences, 95% CI of difference between treatment for non-inferiority test was obtained by using ANCOVA considering change in total PANSS score as dependent variable, treatment as independent variable and baseline PANSS as covariate.

[2] Significant p-value <0.0001 towards testing of inferiority using ANCOVA concludes non-inferiority at 0.025 as level of significance.

* Test product was considered non-inferior to comparator product, as the upper limit of the two-sided 95% confidence interval (CI) for the mean difference PANSS Total score was not beyond the worsening side of non-inferiority limit of 10.40

** Non-inferiority limit was considered 30% of comparator's real time response of 34.68.

Table 15 Summary of Secondary Efficacy Endpoints results at week 6- Brexpiprazole VS Aripiprazole in mITT population:

Secondary Efficacy Endpoints	Brexpiprazole (N=147)	Aripiprazole (N=149)
Mean change from baseline in PANSS total score	-34.75	-34.68
Proportion of responders	67.35 %	69.13%
Mean change from baseline on the CGI-S scale score	-1.84	-1.91
CGI-I scale: Percentage of patients achieving CGI-I scale score-1 (very much improved)	9.52%	12.75%
CGI-I scale: Percentage of patients achieving CGI-I scale score-2 (much improved)	43.54%	46.31%
Mean change from baseline on the PANSS positive subscale	-11.00	-10.97
Mean change from baseline on the PANSS negative subscale	-8.36	-8.03
Mean change from baseline on the PANSS psychopathology subscale	-15.39	-15.68

Note:

Proportion of responders: Proportion of participants with ≥ 30% reduction in PANSS total score from baseline

For all secondary efficacy endpoints mentioned in the above table, progressively both treatments showed similar improvement on all the scales & both the treatments remain comparable at each of the visit i.e. no statistically significant difference was observed between the two treatment groups (p>0.05).

Clinical Studies

Adjunctive Treatment of Major Depressive Disorder

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

Patients in Study 1 (NCT01360645) were randomized to brexpiprazole 2 mg once a day or placebo. Patients in Study 2 (NCT01360632) were randomized to brexpiprazole 1 or 3 mg once a day or placebo. For patients randomized to brexpiprazole, all patients initiated treatment at 0.5 mg once daily during Week 1. At Week 2, the brexpiprazole dosage was increased to 1 mg in all treatment groups, and either maintained at 1 mg or increased to 2 mg or 3 mg once daily, based on treatment assignment, from Week 3 onwards. The dosages were then maintained for the 4 remaining weeks.

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

At randomization, the mean MADRS total score was 27. In Studies 1 and 2, brexpiprazole (plus ADT) 2 mg once daily and 3 mg once daily were superior to placebo plus ADT in reducing mean MADRS total scores. Results from the primary efficacy parameters for both fixed dose studies are shown below in Table 16. Figure 1 below shows the time course of response based on the primary efficacy measure (MADRS) in Study 1.

Table 16 Change in MADRS from Baseline at Week 6 in Adult Patients for Adjunctive Treatment of MDD (Study 1 and Study 2)

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

Study	Treatment Group	N	Mean Baseline Score (SD)	LS Mean Change from Baseline (SE)	Placebo-subtracted Difference* (95% CI)
	ADT				

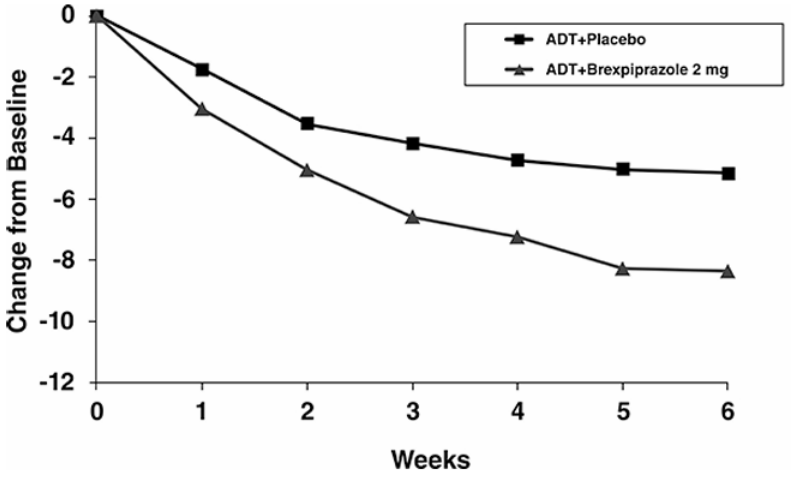
SD: standard deviation; SE: standard error; LS Mean: least-squares mean; CI: unadjusted confidence interval

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

†Dosages statistically significantly superior to placebo

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

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



Schizophrenia

Adult Patients

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

In both studies, Study 3 (NCT01396421) and Study 4 (NCT01393613), patients were randomized to brexpiprazole 2 or 4 mg once per day or placebo. Patients in the brexpiprazole groups initiated treatment at 1 mg once daily on Days 1 to 4. The brexpiprazole dosage was increased to 2 mg on Days 5 to 7. The dosage was then either maintained at 2 mg once daily or increased to 4 mg once daily, depending on treatment assignment, for the 5 remaining weeks.

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

In Study 3, brexpiprazole at both 2 mg once daily and 4 mg once daily was superior to placebo on the PANSS total score. In Study 4, brexpiprazole 4 mg once daily was superior to placebo on the PANSS total score (Table 17). Figure 2 shows the time course of response based on the

primary efficacy measure (change from baseline in PANSS total score) in Study 3.

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

Table 17 Change in PANSS Total Score from Baseline at Week 6 in Adult Patients in Studies of Schizophrenia (Study 3 and Study 4)

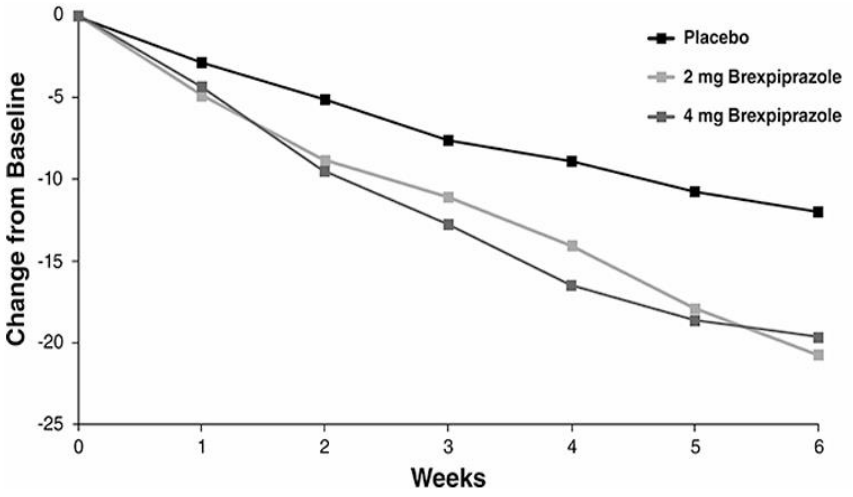
Study	Treatment Group	N	Mean Baseline Score (SD)	LS Mean Change from Baseline (SE)	Placebo-subtracted Difference* (95% CI)
3	Brexpiprazole (2 mg/day)†	180	95.9 (13.8)	-20.7 (1.5)	-8.7 (-13.1, -4.4)
	Brexpiprazole (4 mg/day) †	178	94.7 (12.1)	-19.7 (1.5)	-7.6 (-12.0, -3.1)
	Placebo	178	95.7 (11.5)	-12.0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

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

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

†Dosages statistically significantly superior to placebo

Figure 2 Change from Baseline in PANSS Total Score by Study Visit (Week) in Adult Patients with Schizophrenia (Study 3)



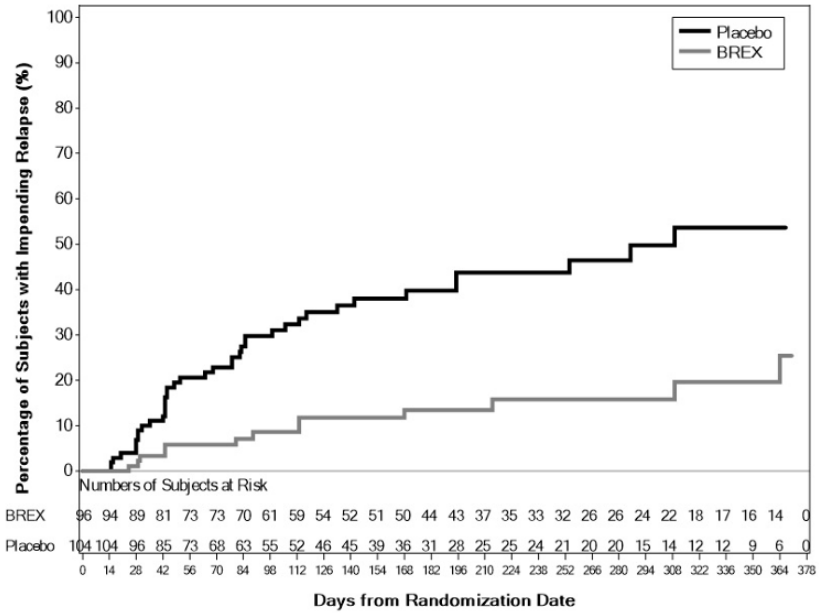
The safety and efficacy of brexpiprazole as maintenance treatment in adults with schizophrenia aged 18 to 65 years were demonstrated in the maintenance phase of a randomized withdrawal study (Study 5, NCT01668797). Patients were stabilized for at least 12 weeks on 1 to 4 mg/day

of brexpiprazole (N=202). They were then randomized in the double-blind treatment phase to either continue brexpiprazole at their achieved stable dose (N=97), or to switch to placebo (N=105).

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

A pre-specified interim analysis demonstrated a statistically significantly longer time to relapse in patients randomized to the brexpiprazole group compared to placebo-treated patients. The study was subsequently terminated early because maintenance of efficacy had been demonstrated. The Kaplan-Meier curves of the cumulative proportion of patients with relapse during the double-blind treatment phase for brexpiprazole and placebo groups are shown in Figure 3. The key secondary endpoint, the proportion of patients who met the criteria for impending relapse, was statistically significantly lower in brexpiprazole-treated patients compared with placebo group.

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



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

Pediatric Patients Ages 13 to 17 years

The efficacy of brexpiprazole in the treatment of schizophrenia in pediatric patients 13 to 17 years of age was demonstrated in a 6-week, randomized and placebo-controlled, clinical study.

In Study 6 (NCT03198078), patients were randomized to brexpiprazole 2 mg to 4 mg once per day, active comparator, or placebo. Patients in the brexpiprazole group initiated treatment at 0.5 mg once daily on Days 1 to 4. The brexpiprazole dosage was increased to 1 mg daily on Days 5 to 7, and then increased to 2 mg on Days 8 to 14. The dosage was then either maintained at 2 mg

or increased to 3 mg once daily from Days 15 to 21 based on patient's tolerability or clinical response. After the titration period, patients were either kept at a maintenance dose, or increased or decreased by 1 mg, for a maximum of brexpiprazole 4 mg daily.

The primary efficacy endpoint was the change from baseline to Week 6 in the PANSS total score.

In Study 6, brexpiprazole group showed a statistically significant improvement compared to placebo on the mean change from baseline in the PANSS total score (Table 18).

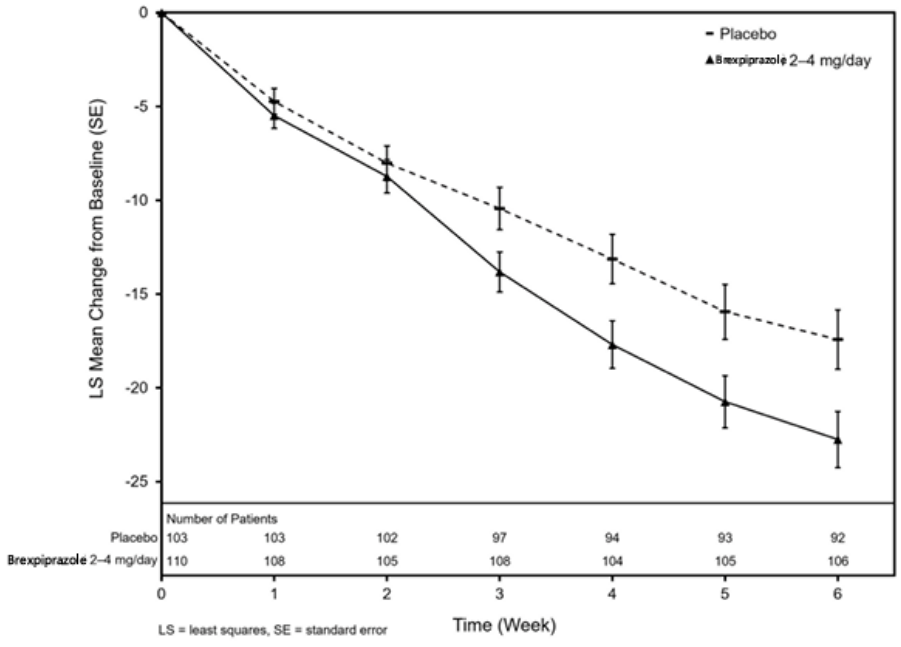
Figure 4 shows the time course of response based on the primary efficacy measure (change from baseline in PANSS total score) in Study 6.

Table 18 Change in PANSS Total Score from Baseline at Week 6 in Pediatric Patients 13 to 17 years of age in Study of Schizophrenia (Study 6)

Study	Treatment Group	N*	Mean Baseline Score (SD)	LS Mean Change from Baseline (SE)	Placebo subtracted Difference† (95% CI)
6	Brexpiprazole (2 - 4 mg/day)‡	110	101.1 (14.9)	-22.8 (1.5)	-5.3 (-9.6, 1.1)
	Placebo	103	102.2 (16.3)	-17.4 (1.6)	--

SD: standard deviation; SE: standard error; LS Mean: least-squares mean; CI: confidence interval
* Efficacy sample includes treated subjects who have baseline and at least 1 post-baseline efficacy evaluation for the PANSS Total Score
†Difference (drug minus placebo) in least-squares mean change from baseline
‡Dosages statistically significantly superior to placebo

Figure 4 Change from Baseline in PANSS Total Score by Study Visit (Week) in Pediatric Patients 13 to 17 years of age with Schizophrenia (Study 6)



Agitation Associated with Dementia Due to Alzheimer's Disease

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

• Have a diagnosis of probable Alzheimer's disease according to NINCDS-ADRDA criteria,

• Have a Mini-Mental State Examination (MMSE) score of ≥5 and ≤22 and have a total score of ≥4 by the agitation/aggression item of the NPI/NPI-NH, and

• Exhibit sufficient agitation behaviors at time of entry to warrant use of pharmacotherapy, after excluding other factors.

Patients in:

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

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

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

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

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

As shown in Table 19 and Figure 5, the mean change from baseline in the total CMAI score after 12 weeks in the 2 mg/or 3 mg brexpiprazole group was statistically significantly superior to the

placebo group. The 1 mg brexpiprazole group did not demonstrate significantly greater mean changes at baseline from the placebo group in the total CMAI score in this patient population. The 1 mg once day brexpiprazole dosage is not approved and is not recommended for the treatment of agitation associated with dementia due to Alzheimer's disease.

Table 19: Change in CMAI Total Score* from Baseline at Week 12 in Patients with Agitation Associated with Dementia Due to Alzheimer's Disease (Study 6 and Study 7)

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

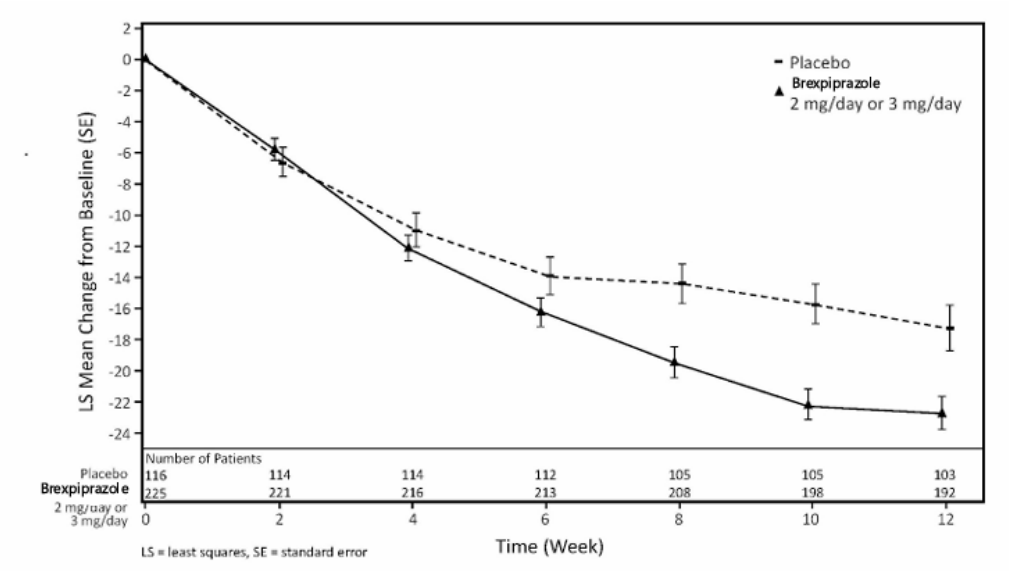
SD: standard deviation; SE: standard error; LS Mean: least-squares mean; CI: unadjusted confidence interval

*In a supplementary analysis to examine the magnitude and direction of CMAI subscale response, Factor 1 (aggressive behavior), Factor 2 (physically non-aggressive behavior), and Factor 3 (verbal agitation) scores trended in the same direction with no single factor overly influencing the CMAI total score.

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

‡Dosages statistically significantly superior to placebo.

Figure 5: Change from Baseline in Total CMAI Score by Study Week in Patients with Agitation Associated with Dementia Due to Alzheimer's Disease (Study 7)



5.3 Pharmacokinetic properties

Absorption

After single-dose administration of brexpiprazole 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.

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

Distribution

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

Elimination

Metabolism

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

In vivo brexpiprazole is metabolized primarily by CYP3A4 and CYP2D6 enzymes. After single- and multiple dose administrations, brexpiprazole and its major metabolite, DM-3411, were the predominant drug moieties in the systemic circulation. At steady-state, DM-3411 represented 23% to 48% of brexpiprazole exposure (AUC) in plasma. DM-3411 is considered not to contribute to the therapeutic effects of brexpiprazole.

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

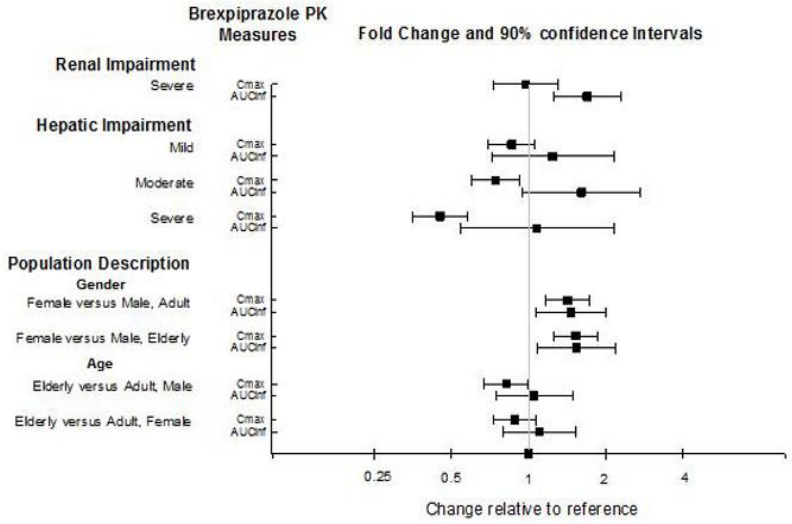
Excretion

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

Studies in Specific Populations

Exposure of brexpiprazole in specific populations are summarized in Figure 6. Population pharmacokinetic (PK) analysis indicated exposure of brexpiprazole in patients with moderate renal impairment was higher compared to patients with normal renal function.

Figure 6 The Effect of Intrinsic Factors on Brexpiprazole Pharmacokinetics



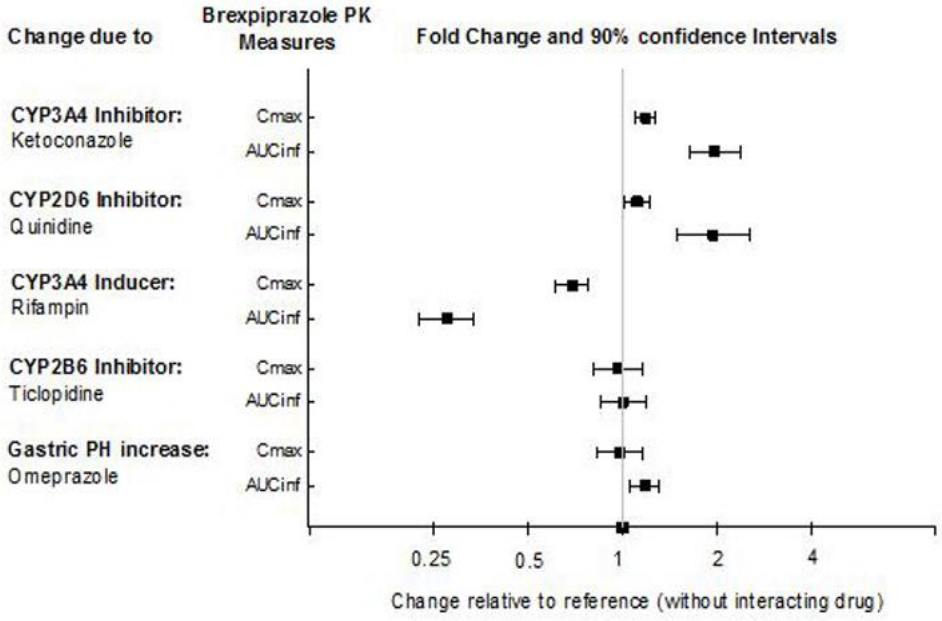
Pediatric Patients

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

Drug Interaction Studies

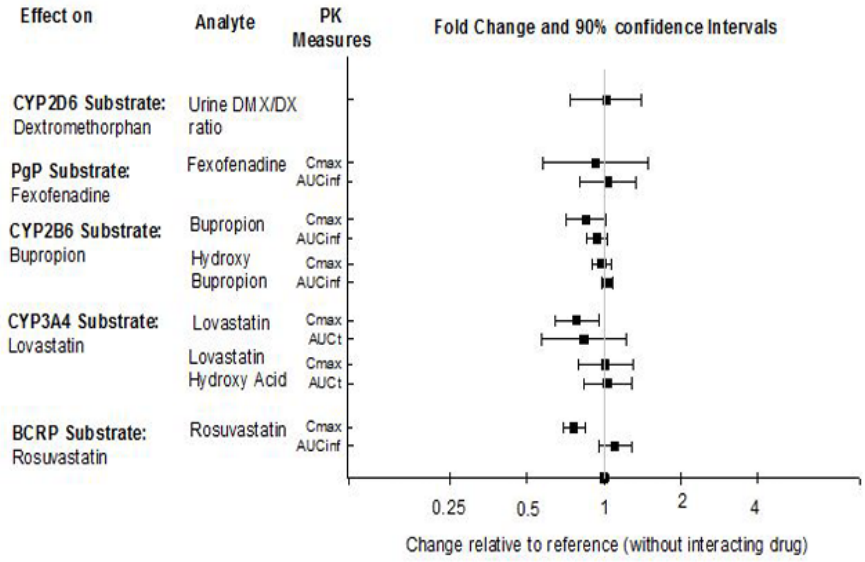
Effect of other drugs on the exposures of brexpiprazole are summarized in Figure 7. Based on simulation, a 5.1-fold increase in AUC values at steady-state is expected when extensive metabolizers of CYP2D6 are administered with both strong CYP2D6 and CYP3A4 inhibitors. A 4.8-fold increase in mean AUC values at steady-state is expected in poor metabolizers of CYP2D6 administered with strong CYP3A4 inhibitors *[see Drugs interactions (4.5)]*.

Figure 7 The Effect of Other Drugs on Brexpiprazole Pharmacokinetics



The effect of brexpiprazole on the exposures of other drugs are summarized in Figure 8.

Figure 8 The Effect of brexpiprazole on Pharmacokinetics of Other Drugs



6. Nonclinical properties

6.1 Animal Toxicology or Pharmacology

Carcinogenesis

Lifetime carcinogenicity studies were conducted in ICR mice and Sprague Dawley rats. Brexpiprazole was administered orally for two years to male and female mice at doses of 0.75, 2, and 5 mg/kg/day (0.9 to 6.1 times the oral MRHD of 4 mg/day based on mg/m2 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

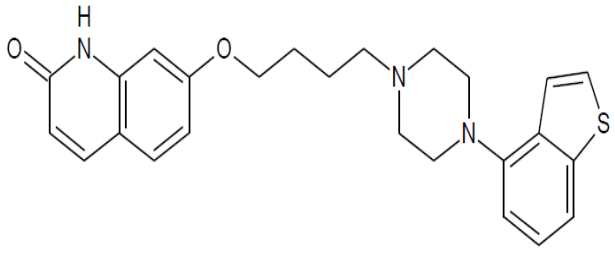
Female rats were treated with oral doses of 0.3, 3, or 30 mg/kg/day (0.7, 7.3, and 73 times the oral MRHD on a mg/m^2 basis) prior to mating with untreated males and continuing through conception and implantation. Estrus cycle irregularities and decreased fertility were observed at 3 and 30 mg/kg/day.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

7. Description

Brexpiprazole:

Brexpiprazole, an atypical antipsychotic, is 7-{4-[4-(1-benzothiophen-4-yl) piperazin-1-yl]butoxy}quinolin-2(1H)-one. It has empirical formula of $C_{25}H_{27}N_3O_2S$ and molecular weight of 433.57 g/mol. The chemical structure is as below:



Brexpiprazole Tablets 0.25 mg

Light brown, round, biconvex, beveled edge, film coated tablets plain on both sides.

The excipients used are Lactose Monohydrate, Corn Starch, Microcrystalline Cellulose, Sodium Starch Glycolate, Povidone, Edetate Disodium, Purified water, Magnesium Stearate, Titanium dioxide IP, yellow iron oxide, red iron oxide and black iron oxide.

Brexpiprazole Tablets 0.5 mg

Light orange, round, biconvex, beveled edge, film coated tablets plain on both sides.

The excipients used are Lactose Monohydrate, Corn Starch, Microcrystalline Cellulose, Sodium Starch Glycolate, Povidone, Edetate Disodium, Purified water, Magnesium Stearate, Titanium dioxide IP, yellow iron oxide and red iron oxide.

Brexpiprazole Tablets 1 mg

Light yellow, round, biconvex, beveled edge, film coated tablets plain on both sides.

The excipients used are Lactose Monohydrate, Corn Starch, Microcrystalline Cellulose, Sodium Starch Glycolate, Povidone, Edetate Disodium, Purified water, Magnesium Stearate, Titanium dioxide IP, yellow iron oxide and red iron oxide.

Brexpiprazole Tablets 2 mg

Light green, round, biconvex, beveled edge, film coated tablets plain on both sides.

The excipients used are Lactose Monohydrate, Corn Starch, Microcrystalline Cellulose, Sodium Starch Glycolate, Povidone, Edetate Disodium, Purified water, Magnesium Stearate, Titanium dioxide IP, yellow iron oxide and black iron oxide.

Brexpiprazole Tablets 3 mg

Light purple, round, biconvex, beveled edge, filmcoated tablets plain on both sides.

The excipients used are Lactose Monohydrate, Corn Starch, Microcrystalline Cellulose, Sodium Starch Glycolate, Povidone, Edetate Disodium, Purified water, Magnesium Stearate, Titanium dioxide IP, yellow iron oxide, red iron oxide and black iron oxide.

Brexpiprazole Tablets 4 mg

White, round, biconvex, beveled edge, film coated tablets plain on both sides.

The excipients used are Lactose Monohydrate, Corn Starch, Microcrystalline Cellulose, Sodium Starch Glycolate, Povidone, Edetate Disodium, Purified water, Magnesium Stearate and Titanium dioxide IP.

8. Pharmaceutical particulars

8.1 Incompatibilities

Not applicable

8.2 Shelf-life

Do not use later than date of expiry.

8.3 Packaging information

Brexpiprazole Tablets is available in Blister strip of 10 Tablets.

8.4 Storage and handing instructions

Store at a temperature not exceeding 30°C, protected from light and moisture.

9. Patient Counselling 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, Special warnings and precautions for use (4.4)]*.

Dosage and Administration

Advise patients that brexpiprazole can be taken with or without food. Advise patients regarding importance of following dosage escalation instructions *[see Posology and method of administration (4.2)]*.

Neuroleptic Malignant Syndrome (NMS)

Counsel patients about a potentially fatal adverse reaction, Neuroleptic Malignant Syndrome (NMS), that has been reported in association with administration of antipsychotic drugs. Advise patients to contact a healthcare provider or report to the emergency room if they experience signs or symptoms of NMS *[see Special warnings and precautions for use (4.4)]*

Tardive Dyskinesia

Counsel patients on the signs and symptoms of tardive dyskinesia and to contact their healthcare provider if these abnormal movements occur *[see Special warnings and precautions for use (4.4)]*.

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 Special warnings and precautions for use (4.4)]*.

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 brexpiprazole. In some cases, but not all, the urges were reported to have stopped when the dose was reduced or stopped *[see Special warnings and precautions for use (4.4)]*.

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 brexpiprazole *[see Special warnings and precautions for use (4.4)]*.

Orthostatic Hypotension and Syncope

Educate patients about the risk of orthostatic hypotension and syncope, especially early in treatment, and also at times of reinitiating treatment or increases in dosage *[see Special warnings and precautions for use (4.4)]*.

Heat Exposure and Dehydration

Counsel patients regarding appropriate care in avoiding overheating and dehydration *[see Special warnings and precautions for use (4.4)]*.

Potential for Cognitive and Motor Impairment

Caution patients about performing activities requiring mental alertness, such as operating hazardous machinery or operating a motor vehicle, until they are reasonably certain that brexpiprazole therapy does not adversely affect their ability to engage in such activities *[see Special warnings and precautions for use (4.4)]*.

Concomitant Medications

Advise patients to inform their healthcare providers of any changes to their current prescription or over-the-counter medications because there is a potential for clinically significant interactions *[see Drugs interactions (4.5)]*.

Pregnancy

Advise patients that third trimester use of brexpiprazole 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 brexpiprazole during pregnancy *[see Use in special; populations (4.6)]*.

10. Details of manufacturer

Torrent Pharmaceuticals Ltd.

Vill. Bhud & Makhnu Majra,

Teh. Baddi - 173 205,

Dist. Solan (H.P.), INDIA

11. Details of permission or licence number with date

Mfg. Licence No: MNB/05/183. Issued On: 17.02.2026.

12. Date of revision

NA

MARKETED BY:

TORRENT PHARMACEUTICALS LTD.

IN/Brexilo™ Tablets (0.25 mg, 0.5 mg, 1 mg, 2 mg, 3 mg and 4 mg)/Feb-26/01/PI