Package Insert

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

1. NAME OF MEDICINAL PRODUCT

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

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

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

3. PHARMACEUTICAL FORM

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

4. CLINICAL PARTICULARS

4.1 THERAPEUTIC INDICATIONS

Brexpiprazole is indicated in adult patients for:

- Use as an adjunctive therapy to antidepressants for the treatment of major depressive disorder (MDD). Efficacy was demonstrated in 6-week trials in adults with MDD who had an inadequate response to antidepressant therapy during the current episode (see section 5.1). The long-term efficacy of brexpiprazole as adjunctive treatment in MDD has not been established.
- Treatment of schizophrenia (see section 5.1) in adults and pediatric patients aged 13 years and older.

4.2 POSOLOGY AND METHOD OF ADMINISTRATION

For oral use once daily with or without food

Adjunctive treatment of Major Depressive Disorder (Adults)

The recommended starting dose for brexpiprazole as adjunctive treatment of MDD in adults is

0.5 mg or 1 mg once daily. Dose titration to 1 mg/day and up to the target dose of 2 mg/day should occur at intervals of up to 1 week based on the patient's clinical response and tolerability. Doses up to 3 mg/day have been studied in clinical trials. The benefit of the 3 mg dose has not been clearly established (see section 5.1). Periodically reassess to determine the continued need and appropriate dose for treatment.

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

Schizophrenia (Adults and Pediatric Patients 13 to 17 Years)

Adults

The recommended starting dose for brexpiprazole in the treatment of adult patients with schizophrenia is 1 mg once daily on days 1 to 4. The recommended target dose range is 2 mg to 4 mg once daily. Titrate to 2 mg once daily on Day 5 through Day 7, then to 4 mg on Day 8 based on the patient's clinical response and tolerability. The maximum recommended daily dosage is 4 mg.

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

Pediatric Patients (13 to 17 years of age)

The recommended starting dosage for REXULTI for the treatment of schizophrenia in pediatric patients 13 to 17 years of age is 0.5 mg once daily on Days 1 to 4, taken orally with or without food *[see Special Population (5.2)]*. Titrate to 1 mg once daily on Day 5 through Day 7, then to 2 mg on Day 8 based on the patient's clinical response and tolerability. Weekly dose increases can be made in 1 mg increments. The recommended target REXULTI dosage is 2 mg to 4 mg once daily. The maximum recommended daily dosage is 4 mg.

Dosing Adjustment for Hepatic Impairment

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

Dosing Adjustment for Renal Impairment

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

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

Factors	Adjusted Dosage

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

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

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

4.3 CONTRAINDICATIONS

Hypersensitivity to the active substance or to any of the excipients.

4.4 WARNINGS AND PRECAUTIONS FOR USE

WARNINGS AND PRECAUTIONS

Increased Mortality in Elderly Patients with Dementia-related Psychosis

Elderly patients with dementia-related psychosis treated with antipsychotic drugs are at an increased risk of death compared to placebo. Analyses of 17 placebo-controlled trials (modal duration of 10 weeks), in patients taking atypical antipsychotic drugs (including risperidone, aripiprazole, olanzapine, and quetiapine), revealed a risk of death in drug-treated patients of between 1.6 to 1.7 times the risk of death in placebo-treated patients. Over the course of a typical 10-week controlled trial, the rate of death in drug treated patients was about 4.5%, compared to a rate of about 2.6% in the placebo group. Brexpiprazole is not approved for the treatment of dementia-related psychosis.

Cerebrovascular Adverse Reactions

In placebo-controlled trials with some antipsychotic drugs in elderly patients with dementia,

there was a higher incidence of cerebrovascular adverse reactions (cerebrovascular accidents and transient ischemic attacks), including fatalities, compared to placebo-treated patients.

REXULTI is not approved for the treatment of patients with dementia-related psychosis.

Suicidal Risk

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

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

In pooled analyses of placebo-controlled trials of antidepressant drugs (SSRIs and other antidepressant classes) that included approximately 77,000 adult patients, and over 4,400 paediatric patients, the incidence of suicidal thoughts and behaviours in patients age 24 years and younger was greater in antidepressant-treated patients than in placebo-treated patients. The drug-placebo differences in the number of cases of suicidal thoughts and behaviours per 1000 patients treated are provided in Table 3.

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

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

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

*REXULTI is not approved in pediatric patients with MDD.

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

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

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

Venous thromboembolism

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

Neuroleptic Malignant Syndrome (NMS)

A potentially fatal symptom complex sometimes referred to as Neuroleptic Malignant Syndrome (NMS) has been reported in association with administration of antipsychotic drugs including 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 creatine phosphokinase, myoglobinuria (rhabdomyolysis), and acute renal failure. If a patient develops signs and symptoms indicative of NMS, or presents with unexplained high fever without additional clinical manifestations of NMS, all antipsychotic drugs including brexpiprazole must be discontinued. If a patient requires antipsychotic drug treatment after recovery from NMS, the potential reintroduction of drug therapy should be carefully considered.

Tardive Dyskinesia

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

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

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

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

duration of treatment needed to produce a satisfactory clinical response. Periodically reassess the need for continued treatment.

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

Metabolic Parameters

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

Hyperglycemia and Diabetes Mellitus

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

Major Depressive Disorder

In the 6-week placebo-controlled, fixed-dose clinical trials in adult patients with MDD, the proportions of patients with shifts in fasting glucose from normal (<100 mg/dL) to high (≥126 mg/dL) and borderline (≥100 and <126 mg/dL) to high were similar in patients treated with REXULTI and placebo.

In the long-term, open-label depression studies, 5% of adult patients with normal baseline fasting glucose experienced a shift to high while taking REXULTI plus an antidepressant (ADT); 25% of patients with borderline fasting glucose experienced shifts to high. Combined, 9% of patients with normal or borderline fasting glucose experienced shifts to high fasting glucose during the long-term depression studies.

Schizophrenia

Adults

In the 6-week placebo-controlled, fixed-dose clinical trials in adult patients with schizophrenia, the proportions of patients with shifts in fasting glucose from normal (<100 mg/dL) to high (≥126 mg/dL) or borderline (≥100 and <126 mg/dL) to high were similar in patients treated with REXULTI and placebo.

In the long-term, open-label schizophrenia studies, 8% of adult patients with normal baseline fasting glucose experienced a shift from normal to high while taking REXULTI; 17% of patients with borderline fasting glucose experienced shifts from borderline to high. Combined, 10% of patients with normal or borderline fasting glucose experienced shifts to high fasting glucose during the long-term schizophrenia studies.

Pediatric Patients (13 to 17 years of age)

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

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.

Major Depressive Disorder

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

Table 4 Change in Fasting Triglycerides in the 6-Week Placebo-Controlled, Fixed-Dose MDD Trials

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

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

n=the number of patients with shift

In the long-term, open-label depression studies, shifts in baseline fasting cholesterol from normal to high were reported in 9% (total cholesterol), 3% (LDL cholesterol), and shifts in baseline from

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

Schizophrenia

Adults

In the 6-week placebo-controlled, fixed-dose clinical trials in adult patients with schizophrenia, changes in fasting total cholesterol, LDL cholesterol, and HDL cholesterol were similar in REXULTI- and placebo-treated patients. Table 5 shows the proportions of patients with changes in fasting triglycerides.

Table 5 Change in Fasting Triglycerides in the 6-Week Placebo-Controlled, Fixed-Dose Schizophrenia Trials in Adult Patients

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

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

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

Pediatric Patients (13 to 17 years of age)

In the long-term, open-label study in pediatric patients with schizophrenia, shifts in baseline fasting total cholesterol from normal to high (<170 to ≥200 mg/dL) were reported in 7% of patients taking REXULTI, and shifts in baseline HDL cholesterol from normal to low (≥40 to <40 mg/dL) were reported in 12.9% of patients taking REXULTI. Of patients with normal baseline triglycerides, 8.5% experienced shifts from normal to high (<150 to ≥200 mg/dL).

Weight Gain

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

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 Trials

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

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

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

Schizophrenia

Adults

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

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

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

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

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

Pediatric Patients (13 to 17 years of age)

In the long-term, open label study in pediatric patients with schizophrenia, 0.5% of patients discontinued due to weight increase. The mean increase in weight from the open-label study baseline to last visit was 3.8 kg. To adjust for normal growth, z-scores were derived (measured in standard deviations [SD]), which normalize for natural growth of children and adolescents by comparisons to age- and gender- matched population standards. A z-score change <0.5 SD is considered not clinically significant. In this trial, 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.

Leukopenia, Neutropenia, and Agranulocytosis

Leukopenia and neutropenia have been reported during treatment with antipsychotic agents. Agranulocytosis (including fatal cases) has been reported with other agents in this class. Possible risk factors for leukopenia and neutropenia include pre-existing low white blood cell count (WBC) or absolute neutrophil count (ANC) and history of drug-induced leukopenia or neutropenia. In patients with a pre-existing low WBC or ANC or a history of drug-induced leukopenia or neutropenia, perform a complete blood count (CBC) frequently during the first few months of therapy. In such patients, consider discontinuation of REXULTI at the first sign of a clinically significant decline in WBC in the absence of other causative factors.

Monitor patients with clinically significant neutropenia for fever or other symptoms or signs of infection and treat promptly if such symptoms or signs occur. Discontinue REXULTI in patients with ANC <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. Orthostatic vital signs should be monitored in patients who are vulnerable to hypotension, (e.g., elderly patients, patients with dehydration, hypovolemia, concomitant treatment with antihypertensive medication), patients with known cardiovascular disease (history of myocardial infarction, ischemic heart disease, heart failure, or conduction abnormalities), and patients with cerebrovascular disease. REXULTI has not been evaluated in patients with a recent history of myocardial infarction or unstable cardiovascular disease. Such patients were excluded from pre-marketing clinical trials.

Falls

Antipsychotics, including REXULTI, may cause somnolence, postural hypotension, motor and sensory instability, which may lead to falls and, consequently, fractures or other injuries. For patients with diseases, conditions, or medications that could exacerbate these effects, complete fall risk assessments when initiating antipsychotic treatment and recurrently for patients on long-term antipsychotic therapy.

Seizures

As with other antipsychotic drugs, brexpiprazole should be used cautiously in patients with a history of seizures or with conditions that potentially lower the seizure threshold. Conditions that lower the seizure threshold may be more prevalent in patients 65 years or older.

Body Temperature Regulation

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

Dysphagia

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

Impulse-Control Disorder/Compulsive Behaviour

Post-marketing case reports suggest that patients can experience intense urges, particularly for gambling, and the inability to control these urges while taking REXULTI. Other compulsive urges, reported less frequently, include: sexual urges, shopping, eating or binge eating, and other impulsive or compulsive behaviors. Because patients may not recognize these behaviors as

abnormal, it is important for prescribers to ask patients or their caregivers specifically about the development of new or intense gambling urges, compulsive sexual urges, compulsive shopping, binge or compulsive eating, or other urges while being treated with REXULTI. In some cases, although not all, urges were reported to have stopped when the dose was reduced or the medication was discontinued. Compulsive behaviors may result in harm to the patient and others if not recognized. Consider dose reduction or stopping the medication if a patient develops such urges.

Potential for Cognitive and Motor Impairment

REXULTI, like other antipsychotics, has the potential to impair judgment, thinking, or motor skills (see section 4.7).

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

SPECIAL POPULATION

Hepatic Impairment

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

Renal Impairment

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

Paediatric Use

Schizophrenia

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

Major Depressive Disorder

Safety and effectiveness in pediatric patients with major depressive disorder have not been established. Antidepressants increased the risk of suicidal thoughts and behaviors in pediatric patients *[see* **WARNINGS AND PRECAUTIONS- Suicidal Thoughts and Behaviours in Children, Adolescents, and Young Adults** *(4.4))]*.

Geriatric Use

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

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

Antipsychotic drugs increase the risk of death in elderly patients with dementia-related psychosis. REXULTI is not approved for the treatment of patients with dementia-related psychosis.

Other Special Populations

No dosage adjustment for brexpiprazole is required on the basis of a patient's sex, race, or smoking status ***[see 5.2 Special Populations]***

4.5 INTERACTION WITH OTHER MEDICINAL PRODUCTS AND OTHER FORMS OF INTERACTION

Drugs Having Clinically Important Interactions with REXULTI

Table 8: Clinically Important Drug Interactions with REXULTI

Strong CYP3A4 Inhibitors	
Clinical Impact:	Concomitant use of REXULTI with strong CYP3A4 inhibitors increased the exposure of brexpiprazole compared to the use of REXULTI alone *[see Section 5.2)]*
Intervention:	With concomitant use of REXULTI with a strong CYP3A4 inhibitor, reduce the REXULTI dosage *[see Section 4.2]*
Strong CYP2D6 Inhibitors*	
Clinical Impact:	Concomitant use of REXULTI with strong CYP2D6 inhibitors increased the exposure of brexpiprazole compared to the use of REXULTI alone *[see Section 5.2]*
Intervention:	With concomitant use of REXULTI with a strong CYP2D6 inhibitor, reduce the REXULTI dosage *[see Section 4.2]*
Both CYP3A4 Inhibitors and CYP2D6 Inhibitors	

Clinical Impact:	Concomitant use of REXULTI with 1) a strong CYP3A4 inhibitor and a strong CYP2D6 inhibitor; or 2) a moderate CYP3A4 inhibitor and a strong CYP2D6 inhibitor; or 3) a strong CYP3A4 inhibitor and a moderate CYP2D6 inhibitor; or 4) a moderate CYP3A4 inhibitor and a moderate CYP2D6 inhibitor, increased the exposure of brexpiprazole compared to the use of REXULTI alone *[see Section 5.2]*
Intervention:	With concomitant use of REXULTI with 1) a strong CYP3A4 inhibitor and a strong CYP2D6 inhibitor; or 2) a moderate CYP3A4 inhibitor and a strong CYP2D6 inhibitor; or 3) a strong CYP3A4 inhibitor and a moderate CYP2D6 inhibitor; or 4) a moderate CYP3A4 inhibitor and a moderate CYP2D6 inhibitor, decrease the REXULTI dosage *[see Section 4.2]*
Strong CYP3A4 Inducers	
Clinical Impact:	Concomitant use of REXULTI and a strong CYP3A4 inducer decreased the exposure of brexpiprazole compared to the use of REXULTI alone *[see Section 5.2]*
Intervention:	With concomitant use of REXULTI with a strong CYP3A4 inducer, increase the REXULTI dosage *[see Section 4.2]*

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

Drugs Having No Clinically Important Interactions with REXULTI

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

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

FOOD

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

4.6 PREGNANCY AND LACTATION

Teratogenic effects

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

In animal studies, brexpiprazole was not teratogenic and did not cause adverse developmental effects when administered during pregnancy at doses up to 73-fold in rats and 146-fold in rabbits, of the maximum recommended human dose (MRHD) of 4 mg/day on a mg/m^2 body surface area for a 60 kg patient. In a pregnant and lactating rat study, there was an increase in stillbirths and deaths of offspring at 30 mg/kg/day (73-fold MRHD on a mg/m^2 basis).

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

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

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

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

4.7 EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

As with other antipsychotics that have the potential to impair judgment, thinking or motor skills, patients should be cautioned about operating hazardous machinery including motor vehicles until they are certain that brexpiprazole therapy does not affect them adversely.

In the short-term, placebo controlled clinical trials in patients with schizophrenia, somnolence (including sedation and hypersomnia) was reported in 5% of brexpiprazole-treated patients compared to 4% of placebo-treated patients.

4.8 UNDESIRABLE EFFECTS

4.8.1 Clinical Trial Data

CLINICAL TRIAL DATA FOR MAJOR DEPRESSIVE DISORDER

Table 9 shows the incidence of treatment-emergent adverse events (TEAEs) that occurred in at least 2% of patients treated with brexpiprazole and observed more frequently than with placebo.

Table 9 **Adverse Reactions in Pooled 6-week Placebo-controlled, Fixed-dose MDD Trials in Adults (Studies 1, 2, 3) and 6-week Placebo-controlled, Flexible-dose MDD Trial (Study 4)***

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

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

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

Selected Adverse Reactions

Extrapyramidal Symptoms

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

Weight Gain

In the long-term, placebo controlled MDD study, the mean change in body weight from baseline at week 24 was 2.2 kg (N=349) for brexpiprazole and 0.8 kg (N=380) for placebo. The proportion of patients with a ≥7% increase in body weight was 19% (84/440) in brexpiprazole group and 8.3% (36/436) in placebo group and with a ≥7% decrease in body weight it was 1.4% (6/441) in brexpiprazole group and 4.1% (18/436) in placebo. Weight increased led to discontinuation in 0.7% and 0.2% of patients in brexpiprazole and placebo groups, respectively.

In the long-term, open-label MDD studies, the mean change in body weight from baseline to last visit was 2.6 kg (N=2232). The proportion of patients with a ≥7% increase in body weight at last visit was 22.12% (494/2232) and with a ≥7% decrease in body weight was 3.2% (72/2232). At 52 weeks, the proportion of patients with a ≥7% increase in body weight was 28.2 % (286/1013) and with a ≥7% decrease in body weight was 3.7% (37/1013). Weight gain led to discontinuation of study medication in 3.8% (84/2240) of patients.

Clinical Chemistry Findings

Fasting Glucose

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

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

Fasting Lipids

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

Table 10: Mean Changes from Baseline and Shift in Lipids, Long-term Placebo-controlled Study

Fasting Lipids	Mean change from baseline (mg/dL)		Shift (%) *Normal to high*: total cholesterol, LDL, triglycerides *Normal to low*: HDL	
	Brexpiprazole	Placebo	Brexpiprazole	Placebo
LDL	3.14	0.77	4.8	3.1
HDL	-2.43	-0.74	9	7.3

Total cholesterol	3.84	0.87	13.5	9.6
Triglycerides	13.57	6.59	15.5	12.7

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

CLINICAL TRIAL DATA FOR SCHIZOPHRENIA

Table 11 shows the incidence of treatment-emergent adverse events (TEAEs) that occurred in at least 2% of the patients treated brexpiprazole and observed more frequently than with placebo.

Table 11 Adverse Reactions in Pooled 6-week Placebo-controlled, Fixed-dose Schizophrenia Trials in adult patients (Studies 5, 6, 7) and 6-week Placebo-controlled, Flexible-dose Schizophrenia Trials (Studies 8, 9) in adult patients*

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

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

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

Extrapyramidal Symptoms

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

Weight Gain

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

Clinical Chemistry Findings

Fasting Glucose

In the long-term, open-label schizophrenia studies, 7% of patients with normal baseline fasting glucose experienced a shift from normal to high while taking brexpiprazole, 17% of subjects with borderline fasting glucose experienced shifts from borderline to high. Combined, 9% of patients with normal or borderline fasting glucose experienced shifts to high fasting glucose during the long-term schizophrenia studies. The mean change from baseline for fasting glucose to last visit in the long-term, open label trials was 2.35 [2.00] mg/dL.

Fasting Lipids

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

Additional Findings Observed in Schizophrenia Clinical Trials

The adverse reactions reported in a 52-week maintenance phase of a randomized, placebo-

controlled withdrawal trial in adults with schizophrenia were comparable with those reported in short-term, fixed-dose trials for schizophrenia.

4.8.2 Post-marketing Experience

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

- Nervous System disorders: Neuroleptic malignant syndrome
- Psychiatric disorders : Somnambulism and Sleep-related eating disorders (SRED)

4.9 OVERDOSE

No specific information is available on the treatment of overdose with brexpiprazole. Gastric lavage and treatment with an emetic may be useful immediately after overdose. An electrocardiogram should be obtained in case of overdosage and if QT interval prolongation is present, cardiac monitoring should be instituted. Otherwise, management of overdose should concentrate on supportive therapy, maintaining an adequate airway, oxygenation and ventilation, and management of symptoms. Close medical supervision and monitoring should continue until the patient recovers.

Oral activated charcoal and sorbitol (50 g/240 mL), administered one hour after ingesting oral brexpiprazole, decreased brexpiprazole Cmax and AUC by approximately 5% to 23% and 31% to 39% respectively; however, there is insufficient information available on the therapeutic potential of activated charcoal in treating an overdose with brexpiprazole. Although there is no information on the effect of hemodialysis in treating an overdose with brexpiprazole, hemodialysis is unlikely to be useful in overdose management since brexpiprazole is highly bound to plasma proteins.

5. PHARMACOLOGICAL PROPERTIES

5.1 PHARMACODYNAMIC PROPERTIES

Pharmacotherapeutic group: Psycholeptics, other antipsychotics
ATC code: N05AX16

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

Mechanism of Action

The mechanism of action of brexpiprazole in the treatment of major depressive disorder or schizophrenia is unknown. However, the efficacy of brexpiprazole may be mediated through a

combination of partial agonist activity at serotonin 5-HT_{1A} and dopamine D_2 receptors, and antagonist activity at serotonin 5-HT_{2A} receptors.

CLINICAL STUDIES

ADJUNCTIVE TREATMENT OF MAJOR DEPRESSIVE DISORDER

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

The primary endpoint was change from baseline to Week 6 in the Montgomery-Asberg Depression Rating Scale (MADRS), a 10-item clinician-related scale used to assess the degree of depressive symptomatology (apparent sadness, reported sadness, inner tension, reduced sleep, reduced appetite, concentration difficulties, lassitude, inability to feel, pessimistic thoughts and suicidal thoughts). The key secondary endpoint was the Sheehan Disability Scale (SDS), a 3-item self-rated instrument used to assess the impact of depression on three domains of functioning (work/school, social life, and family life) with each item scored from 0 (not at all) to 10 (extreme).

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

The summary of efficacy results for pivotal studies in adjunctive treatment of MDD are shown below in Table 12.

Table 12: Primary Efficacy Results for Pivotal Studies in Adjunctive Treatment of MDD

		Baseline End of Phase A	Mean Change End of Phase B		Treatment Comparison vs Placebo	
Study Treatment Group	**N**	**Mean (SD)**	**LS Mean (SE)[a]**	**LS Mean Difference[b]**	**95% CI[a]**	**P-value[a]**
Study 1[c]						
2 mg Brex+ADT*	187	26.61 (5.79)	-8.27 (0.61)	-3.12	(-4.70, -1.54)	0.0001
Placebo+ADT	191	27.14 (5.60)	-5.15 (0.63)	-	-	-
Study 2[c]						
1 mg Brex+ADT	225	26.69 (5.61)	-7.65 (0.50)	-1.19	(-2.58, 0.20)	0.0925
3 mg Brex+ADT*	226	26.31 (5.24)	-7.98 (0.51)	-1.52	(-2.92, -0.13)	0.0327
Placebo+ADT	218	26.23 (5.27)	-6.45 (0.51)	-	-	-
Study 3						
2 mg Brex+ADT*	191	27.05 (5.67)	-10.4 (0.63)	-2.30	(-3.97, -0.62)	0.0074
Placebo+ADT	202	26.20 (6.20)	-8.07 (0.61)	-	-	-
Study 4						
2-3 mg Brex+ADT*	191	25.28 (5.02)	-6.04 (0.43)	-1.48	(-2.56, -0.39)	0.0078
Quetiapine	99	25.56 (5.44)	-4.86 (0.57)	-0.30	(-1.63, -1.04)	0.6642
Placebo+ADT	205	25.39 (5.19)	-4.57 (0.41)	-	-	-

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

** Treatment statistically significantly superior to placebo*

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

a MMRM with model terms treatment, site, visit, treatment-by-visit, and baseline-by-visit interaction as covariates, where baseline is MADRS Total Score at end of Phase A (Week 8). An unstructured covariance was used. To control Type 1 error for testing two doses in Study 2, the brexpiprazole vs placebo treatment difference was statistically significant only if the larger of the two p-values was <0.05 or the smaller p-value was <0.025.

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

c Results for the primary analysis populations for Studies 1 and 2 are presented and include approximately 6% of patients who were randomized prior to the revised definition of inadequate response, which required an inadequate response throughout the 8-week duration of prospective antidepressant treatment

The long-term efficacy and safety of REXULTI were evaluated in a phase 3, 24-week placebo-controlled trial. The adult patients in this trial fulfilled the DSM-IV-TR criteria for MDD, and demonstrated an inadequate response to 1-3 prior antidepressant therapy(ies) in the current episode and an inadequate response throughout 8 weeks of prospective antidepressant treatment. Inadequate response during the prospective antidepressant treatment phase was defined as having persistent symptoms without substantial improvement throughout the course of the 8 weeks prospective treatment. The primary efficacy endpoint was full remission (defined as a MADRS total score ≤10 and a ≥50% decrease from randomisation in MADRS total score for at least 8 consecutive weeks during randomised treatment). This trial did not show efficacy of brexpiprazole+antidepressant treatment over placebo+antidepressant treatment.

Schizophrenia

In the 3 fixed-dose, short-term trials (Studies 5, 6, and 7), subjects were randomised to brexpiprazole 2 mg once daily, 4 mg once daily or placebo.

Study 8 assessed the efficacy, safety, and tolerability of brexpiprazole in a flexible dose range of 2 to 4 mg/day and 400 to 800 mg quetiapine XR for assay sensitivity. In the short-term trials, the primary efficacy endpoint was defined as the mean change from baseline to week 6 in Positive and Negative Syndrome Scale (PANSS) total scores, a multi-item inventory composed of five factors to evaluate positive symptoms, negative symptoms, disorganised thoughts, uncontrolled hostility/excitement, and anxiety/depression.

The key secondary endpoint in Studies 5, 6, and 8 was the Clinical Global Impression of Severity (CGI-S) of schizophrenia, a 7-point clinician's assessment of the severity of disease. The CGI-S was also assessed in Study7 as a secondary endpoint.

The effects of brexpiprazole were also evaluated across a number of pre-specified secondary endpoints; the specific aspects of symptoms of schizophrenia (PANSS Positive Subscale score, PANSS Negative Subscale score, PANSS Excited Component [PEC] score, PANSS Marder factors positive, negative, disorganized thoughts, uncontrolled hostility/excitement and anxiety/depression), and analyses of response (defined as 30 % improvement in PANSS total score compared to baseline or a CGI-I score of 1 [very much improved] or 2 [much improved]).

Efficacy was demonstrated in Study 5 for both brexpiprazole 2 mg/day and 4 mg/day and replicated in Study 6 only for brexpiprazole 4 mg/day and in Study 7 only for brexpiprazole 2 mg/day.

In the flexible-dose Study 8, at week 6, subjects in the brexpiprazole treatment group had numerically greater improvements on PANSS total score than the subjects in the placebo group, although, the difference at week 6 did not reach statistical significance for the primary efficacy analysis (p = 0.0560) (see table 13). In the same trial the active reference, quetiapine XR added for assay sensitivity only, separated from placebo.

Table 13: Primary efficacy results for 6-week trial in schizophrenia

Trial	**Treatment group**	**n**	**Primary efficacy measure: PANSS**			
			Mean baseline score (SD)	**LS mean change from baseline (SE)**	**LS mean difference[a, b] (95 % CI)**	p-value
5	Brexpiprazole (2 mg/day)*	180	95.85 (13.75)	−20.73 (1.55)	−8.72 (−13.1, −4.37)	< 0.0001
	Brexpiprazole (4 mg/day)*	178	94.70 (12.06)	−19.65 (1.54)	−7.64 (−12.0, −3.30)	0.0006
	Placebo	178	95.69 (11.46)	−12.01 (1.60)	--	--

6	Brexpiprazole (2 mg/day)	179	96.30 (12.91)	−16.61 (1.49)	−3.08 (−7.23, 1.07)	0.1448
	Brexpiprazole (4 mg/day)*	181	94.99 (12.38)	−20.00 (1.48)	−6.47 (−10.6, −2.35)	0.0022
	Placebo	180	94.63 (12.84)	−13.53 (1.52)	--	--
7	Brexpiprazole (2 mg/day)*	113	96.55 (19.20)	−14.95 (2.00)	−7.32 (−13.04, −1.59)	0.0124
	Brexpiprazole (4 mg/day)	109	96.39 (15.73)	−11.49 (2.10)	−3.86 (−9.71, 2.00)	0.1959
	Placebo	113	97.19 (19.27)	−7.63 (2.11)	--	--
8	Brexpiprazole (2-4 mg/day)	150	97.82 (10.25)	−19.99 (1.51)	−4.1 (−8.2, 0.1)	0.0560
	Placebo	159	98.38 (10.30)	−15.93 (1.49)	--	--

SD Standard deviation
SE Standard error
LS Mean Least-squares mean.
CI Confidence interval
* Treatment statistically significantly superior to placebo
a Difference (brexpiprazole minus placebo) in least-squares mean change from baseline, at week 6
b The LS Mean, 95 % CI, and p-values for individual trials were derived from an MMRM analysis as follows: fixed effects of site, treatment, visit, and treatment-by-visit interaction, with baseline and baseline-by-visit interaction as covariates. Unstructured variance-covariance matrix structure was used

The primary statistical analysis was performed using an MMRM model with MAR imputation. Results of a sensitivity analysis using placebo based multiple imputation (PMI) were consistent with the primary analysis.

Results for the (key) secondary outcome parameter and additional endpoints were supportive of the primary endpoint.

In Study 5, statistically significant greater improvement on the CGI-S, the key secondary efficacy measure, at week 6 was also shown for the 2 and 4 mg/day compared to the placebo dose group. Due to the testing hierarchy the greater improvement shown for both 2 and 4 mg/day on the CGI-S can only be considered supportive for Studies 6, 7 and 8 (see table 14).

Table 14: Key secondary efficacy results for 6-week trial in schizophrenia

Trial	**Treatment group**	**n**	Key secondary efficacy **measure: CGI-S**			
			Mean baseline score (SD)	**LS mean change from baseline (SE)**	**LS mean difference[a] (95 % CI)**	p-value
5	Brexpiprazole (2 mg/day)*	181	4.90 (0.64)	−1.15 (0.08)	−0.33 (−0.56, −0.10)	0.0056
	Brexpiprazole (4 mg/day)*	178	4.81 (0.64)	−1.20 (0.08)	−0.38 (−0.61, −0.15)	0.0012
	Placebo	181	4.84	−0.82	--	--

Trial	Treatment group	n	Key secondary efficacy **measure: CGI-S**			
			Mean baseline score (SD)	**LS mean change from baseline (SE)**	**LS mean difference[a] (95 % CI)**	p-value
			(0.66)	(0.09)		
6	Brexpiprazole (2 mg/day)	180	4.96 (0.65)	−0.99 (0.09)	−0.19 (−0.42, 0.05)	0.1269
	Brexpiprazole (4 mg/day)*	183	4.85 (0.64)	−1.19 (0.08)	−0.38 (−0.62, −0.15)	0.0015
	Placebo	181	4.87 (0.61)	−0.81 (0.09)	--	--
7	Brexpiprazole (2 mg/day)*	113	4.80 (0.78)	−0.84 (0.11)	−0.35 (−0.67, −0.03)	0.0308
	Brexpiprazole (4 mg/day)	109	4.71 (0.75)	−0.64 (0.12)	−0.16 (−0.48, 0.17)	0.3461
	Placebo	113	4.73 (0.71)	−0.48 (0.12)	--	--
8	Brexpiprazole* (2-4 mg/day)[b]	150	4.96 (0.59)	−1.21 (0.08)	−0.27 (−0.49, −0.06)	0.0142
	Placebo	159	4.94 (0.57)	−0.93 (0.08)	--	--

SD Standard deviation
SE Standard error
LS Mean Least-squares mean
CI Confidence interval
* Treatment statistically significantly superior to placebo
a Difference (brexpiprazole minus placebo) in least-squares mean change from baseline, at week 6
b Mean dose 3.5 mg/day

Maintenance of efficacy trial:

In a long-term trial designed to assess the maintenance of effect of brexpiprazole by assessing the delay in time to impending relapse of schizophrenia, patients with schizophrenia, who responded to treatment with brexpiprazole 1-4 mg/day, were stabilised over 12-36 weeks, and then randomised in a double-blind manner to either continue treatment with the stabilisation dose of brexpiprazole (n = 96) or to receive placebo (n = 104) for 52 weeks or until relapse occurred.

In the primary analysis of time to impending relapse, patients on brexpiprazole showed a significantly longer time to relapse compared with patients on placebo ($p < 0.0001$). At week 52 brexpiprazole (13.5 %) reduced the risk of impending relapse by 71 % compared with placebo (38.5 %). During the stabilisation, brexpiprazole improved clinical symptomology (as assessed by PANSS, CGI-S and CGI-I [ANCOVA LOCF]) and functioning (as assessed by Global Assessment of Functioning (GAF) [ANCOVA LOCF]). These improvements were maintained during the 52-week double-blind maintenance phase in patients on brexpiprazole whereas patients randomised to placebo showed deterioration in PANSS, CGI-S and CGI-I, and GAF scores [ANCOVA LOCF]). Brexpiprazole maintained symptom control and functioning compared to placebo..

5.2 PHARMACOKINETIC PROPERTIES

Absorption

After single dose administration of REXULTI tablets, the peak plasma brexpiprazole concentrations occurred within 4 hours after administration; and the absolute oral bioavailability was 95%. Brexpiprazole steady-state concentrations were attained within 10-12 days of dosing.

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

Distribution

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

Elimination

Metabolism

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

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

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

Excretion

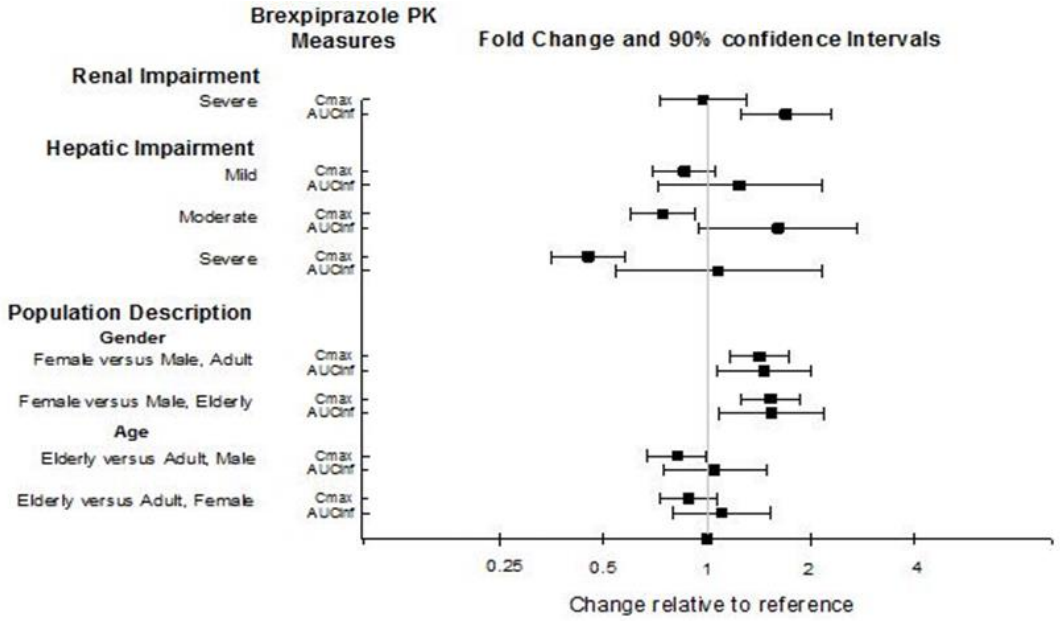
Following a single oral dose of [^{14}C]-labeled brexpiprazole, approximately 25% and 46% of the administered radioactivity was recovered in the urine and feces, respectively. Less than 1% of unchanged brexpiprazole was excreted in the urine and approximately 14% of the oral dose was recovered unchanged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

Studies In Specific Populations

Exposure of brexpiprazole in specific populations are summarized in Figure 1. Population PK

analysis indicated exposure of brexpiprazole in patients with moderate renal impairment was higher compared to patients with normal renal function.

Figure 1 Effect of Intrinsic Factors on Brexpiprazole Pharmacokinetics



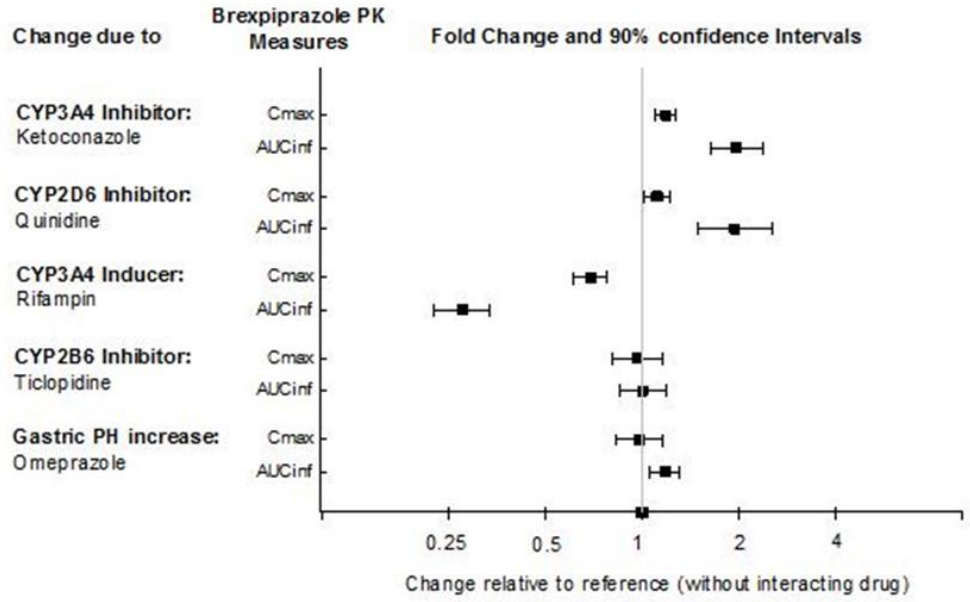
Pediatric Patients

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

Drug Interaction Studies

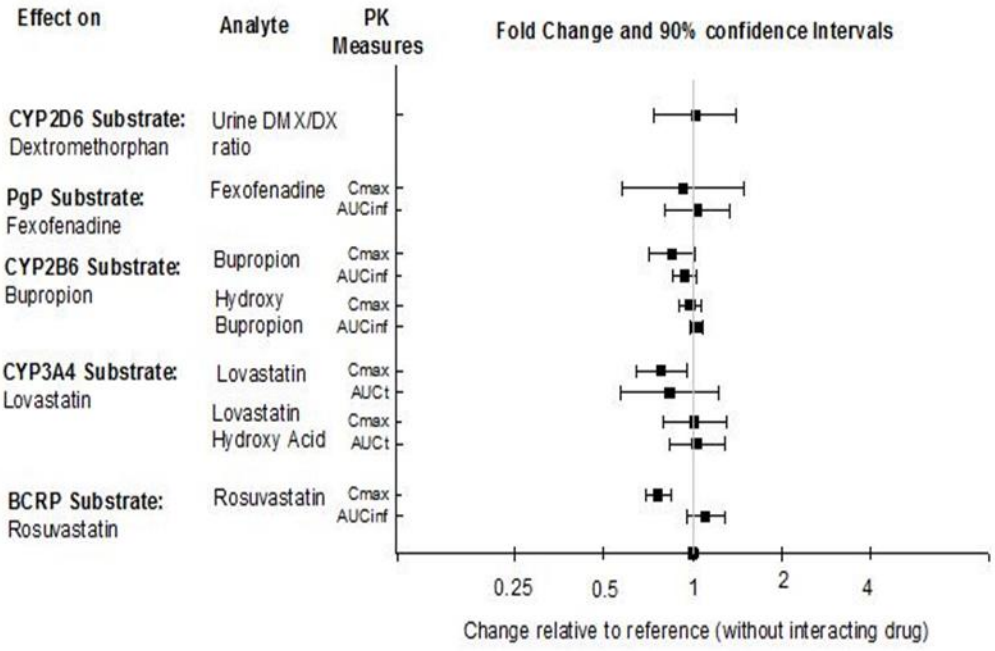
Effect of other drugs on the exposures of brexpiprazole are summarized in Figure 2. Based on simulation, a 5.1-fold increase in AUC values at steady-state is expected when extensive metabolizers of CYP2D6 are administered with both strong CYP2D6 and CYP3A4 inhibitors. A 4.8-fold increase in mean AUC values at steady-state is expected in poor metabolizers of CYP2D6 administered with strong CYP3A4 inhibitors *[see section 4.5]*.

Figure 2 The Effects of Other Drugs on Brexpiprazole Pharmacokinetics



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

Figure 3 Effects of Brexpiprazole on Pharmakokinetics of Other Drugs



SPECIAL POPULATION

Age/Gender

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

Race

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

CYP2D6 Poor Metabolisers:

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

Smoking

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

5.3 PRECLINICAL SAFETY DATA

Abuse/liability

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

Carcinogenicity, mutagenesis, and impairment of fertility

The lifetime carcinogenic potential of brexpiprazole was evaluated in a two year study in ICR mice and Sprague-Dawley rats. Brexpiprazole was administered orally (gavage) for two years to mice at doses of 0.75, 2 and 5 mg/kg/day (0.9 to 6.1-fold the 4 mg oral maximum recommended human dose [MRHD] for a 60 kg patient based on body surface area). There was no increase in the incidence of tumors in males at any dose group. In female mice, there was an increased incidence of mammary gland adenocarcinoma and adenosquamous carcinoma, and pars distalis adenoma of the pituitary gland. Brexpiprazole was administered orally (gavage) for two years to rats at doses of 1, 3 and 10 mg/kg/day in male rats or 3, 10 and 30 mg/kg/day in female rats (for males 2.4 to 24.3-fold and for females 7.3 to 72.9-fold the 4 mg oral MRHD for a 60 kg patient

based on body surface area). Long-term administration of brexpiprazole to rats did not induce neoplastic lesions.

Proliferative and/or neoplastic changes in the mammary and pituitary glands of rodents have been observed following chronic administration of antipsychotic drugs and are considered to be prolactin mediated. The potential for increasing serum prolactin level of brexpiprazole was shown in both mice and rats. The relevance for human risk of the findings of prolactin-mediated endocrine tumors in rodents is unknown.

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

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

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

Teratogenic effects

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

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

Cardiovascular Toxicity

Decreased blood pressure and prolonged QT interval and QTc were noted in the conscious dog in the safety pharmacology study in the 13-week repeat-dose toxicity study with monkeys and in

the juvenile toxicity study with dogs. The effect of brexpiprazole on decreased blood pressure was suggested to be due to a blockade of α_1- adrenoceptors in peripheral blood vessels, which is consistent with the pharmacological profile for this compound.

6. PHARMACEUTICAL PARTICULARS

6.1 LIST OF EXCIPIENTS

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

6.2 INCOMPATIBILITIES

Not applicable.

6.3 SHELF LIFE

36 months.

6.4 SPECIAL PRECAUTIONS FOR STORAGE

Store below 30°C

6.5 NATURE AND CONTENTS OF CONTAINER

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

Not all pack sizes may be marketed.

6.6 SPECIAL PRECAUTIONS FOR DISPOSAL

No special requirements.

7. PRODUCT REGISTRANT

Lundbeck Singapore Pte. Ltd,
101 Thomson Road,
United Square #13-05
Singapore 307591

8. DATE OF REVISION OF THE TEXT

February 2023