PRODUCT MONOGRAPH

INCLUDING PATIENT MEDICATION INFORMATION

PrREXULTI™

Brexpiprazole Tablets

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

Antipsychotic agent

Otsuka Pharmaceutical Co., Ltd.
Tokyo, 101-8535 Japan

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PrREXULTI™

Brexpiprazole

PART I: HEALTH PROFESSIONAL INFORMATION

SUMMARY REXULTI INFORMATION

Route of Administration	Dosage Form / Strength	Nonmedicinal Ingredients
Oral	Tablet, 0.25 mg, 0.5 mg, 1 mg, 2 mg, 3 mg and 4 mg	lactose monohydrate, corn starch, microcrystalline cellulose, hydroxypropyl cellulose, low-substituted hydroxypropyl cellulose, magnesium stearate, hypromellose, talc, titanium dioxide, ferric oxide yellow (0.25 mg, 0.5 mg, 1 mg, 2 mg), ferric oxide red (0.25 mg, 0.5 mg, 3 mg) and ferrosoferric oxide (0.25 mg, 2 mg, 3 mg)

INDICATIONS AND CLINICAL USE

Adults
REXULTI (brexpiprazole) is indicated for treatment of schizophrenia in adults.

In clinical trials, REXULTI was found to significantly improve both positive and negative symptoms.

Geriatrics (> 65 years of age):
REXULTI is not indicated in elderly patients with dementia (see WARNINGS AND PRECAUTIONS, Serious Warnings and Precaution Box and Special Populations). The safety and efficacy of REXULTI in patients 65 years of age or older have not been established. Caution should be used when treating geriatric patients (see WARNINGS AND PRECAUTIONS, Special Populations and ACTION AND CLINICAL PHARMACOLOGY).

Pediatrics (< 18 years of age):
The safety and efficacy of REXULTI have not been established in patients less than 18 years of age. REXULTI is not indicated in pediatric patients and its use is not recommended in this population (see WARNINGS AND PRECAUTIONS, Special Populations, Pediatrics).

CONTRAINDICATIONS

REXULTI is contraindicated in patients who are hypersensitive to this drug or to any ingredient in the formulation or component of the container. For a complete listing, see the Dosage Forms, Composition and Packaging section of the REXULTI monograph.

WARNINGS AND PRECAUTIONS

Serious Warnings and Precautions
WARNING: INCREASED MORTALITY IN ELDERLY PATIENTS WITH DEMENTIA

Increased Mortality in Elderly Patients with Dementia
Elderly patients with dementia treated with atypical antipsychotic drugs are at an increased risk of death compared to placebo. Analyses of thirteen placebo-controlled trials with various atypical antipsychotics (modal duration of 10 weeks) in these patients showed a mean 1.6-fold increase in the death rate in the drug-treated patients. 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 (see WARNINGS AND PRECAUTIONS, Special Populations, Geriatrics (> 65 years of age)). REXULTI is not approved for the treatment of patients with dementia.

General

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 REXULTI for patients who will be experiencing conditions which 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).

Carcinogenesis and Mutagenesis

For animal data, see Part II: TOXICOLOGY section.

Cardiovascular

Orthostatic Hypotension
In the short-term, placebo-controlled clinical studies of REXULTI in subjects with schizophrenia, the incidence of orthostatic hypotension-related adverse reactions in REXULTI-treated patients compared to placebo subjects included: dizziness (2.3% versus 1.4%), orthostatic hypotension (0.4% versus 0.2%), and syncope (0.1% versus 0%).

Adverse reactions associated with orthostatic hypotension can include dizziness, lightheadedness and tachycardia. Generally, these risks are greatest at the beginning of treatment and during dose

escalation. Patients at increased risk of these adverse reactions or at increased risk of developing complications from hypotension include those with dehydration, hypovolemia, treatment with antihypertensive medication, history of cardiovascular disease (e.g., heart failure, myocardial infarction, ischemia, or conduction abnormalities), history of cerebrovascular disease, as well as patients who are antipsychotic-naïve. In such patients, consider using a lower starting dosage and slower titration, and monitor orthostatic vital signs.

Patients with a recent history of myocardial infarction or unstable cardiovascular disease were excluded from clinical trials.

QT Interval
The effects of REXULTI on the QT/QTc interval were evaluated in a dedicated ECG study (see ACTION AND CLINICAL PHARMACOLOGY, Cardiac Electrophysiology). The trial involved administration of REXULTI at a therapeutic dose of 4 mg/day or a supratherapeutic dose of 12 mg/day for 11 days in 147 clinically stable patients with schizophrenia. On day 11, the maximum placebo-adjusted mean change from baseline in the QTcI interval was 8.3 ms (90% CI 3.7, 12.9) at 6 h post-dosing in the brexpiprazole 4 mg/day group (N=62) and 3.1 ms (90% CI -1.7, 8.0) at 4 h post-dosing in the brexpiprazole 12 mg/day group (N=53).

QTc prolongation may lead to an increased risk of ventricular arrhythmias including torsade de pointes. Torsade de pointes is a polymorphic ventricular tachyarrhythmia. Generally, the risk of torsade de pointes increases with the magnitude of QTc prolongation produced by the drug. Torsade de pointes may be asymptomatic or experienced by the patient as dizziness, palpitations, syncope, or seizures. If sustained, torsade de pointes can progress to ventricular fibrillation and sudden cardiac death.

Particular care should be exercised when administering REXULTI to patients who are suspected to be at an increased risk of experiencing torsade de pointes during treatment with a QTc-prolonging drug (see DRUG INTERACTIONS).

Risk factors for torsade de pointes in the general population include, but are not limited to, the following: female gender; age ≥65 years; baseline prolongation of the QT/QTc interval; presence of genetic variants affecting cardiac ion channels or regulatory proteins, especially congenital long QT syndromes; family history of sudden cardiac death at <50 years of age; cardiac disease (e.g., myocardial ischemia or infarction, congestive heart failure, cardiomyopathy, conduction system disease); history of arrhythmias; electrolyte disturbances (e.g., hypokalemia, hypomagnesemia, hypocalcemia) or conditions leading to electrolyte disturbances (e.g., persistent vomiting, eating disorders); bradycardia; acute neurological events (e.g., intracranial or subarachnoid haemorrhage, stroke, intracranial trauma); diabetes mellitus; and autonomic neuropathy.

When drugs that prolong the QTc interval are prescribed, healthcare professionals should counsel their patients concerning the nature and implications of the ECG changes, underlying diseases and disorders that are considered to represent risk factors, demonstrated and predicted drug-drug interactions, symptoms suggestive of arrhythmia, risk management strategies, and other information relevant to the use of the drug. Patients should be advised to contact their

healthcare provider immediately to report any new chest pain or discomfort, changes in heartbeat, palpitations, dizziness, lightheadedness, fainting, or changes in or new use of other medications.

Dependence/Tolerance

Brexpiprazole has not been systematically studied in humans for its potential for abuse, tolerance, or physical dependence. In drug dependence studies in animals, no withdrawal symptoms were observed upon abrupt cessation of dosing in rats and monkeys, and no frequent self-administration of brexpiprazole was observed in monkeys. While the clinical trials did not reveal any tendency for any drug-seeking behavior, these observations were not systematic and it is not possible to predict on the basis of this limited experience the extent to which a CNS-active drug will be misused, diverted, or abused once marketed. Consequently, patients should be evaluated carefully for a history of drug abuse, and such patients should be observed closely for signs of REXULTI misuse or abuse (e.g., development of tolerance, increases in dose, drug-seeking behavior).

Endocrine and Metabolism

Hyperglycemia and Diabetes Mellitus

In both short-term placebo-controlled trials and long term open label trials with REXULTI, there have been reports of hyperglycemia in subjects treated with REXULTI. Diabetic ketoacidosis has occurred in patients with no reported history of hyperglycemia. Therefore, patients should have baseline and periodic monitoring of blood glucose and body weight.

Assessment of the relationship between atypical antipsychotic use and glucose abnormalities is complicated by the possibility of an increased background risk of diabetes mellitus in patients with schizophrenia and the increasing incidence of diabetes mellitus in the general population. Given these confounders, the relationship between atypical antipsychotic use and hyperglycemia-related adverse events is not completely understood. However, epidemiological studies which did not include REXULTI, suggest an increased risk of treatment-emergent hyperglycemia-related adverse events in patients treated with atypical antipsychotics. Because REXULTI was not marketed at the time these studies were performed, it is not known if brexpiprazole is associated with this increased risk. Precise risk estimates for hyperglycemia-related adverse events in patients treated with atypical antipsychotics are not available.

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

control.

Weight Gain
Antipsychotic drugs have been associated with metabolic changes, including weight gain. Clinical monitoring of weight is recommended (see ADVERSE REACTIONS, Weight Gain).

Dyslipidemia
Undesirable alterations in lipids have been observed in subjects treated with atypical antipsychotics. Therefore, patients should have baseline and periodic monitoring of fasting lipid profile (see ADVERSE REACTIONS, Fasting Lipids).

Hyperprolactinemia
Like other antipsychotics, REXULTI can elevate prolactin levels. Elevations associated with REXULTI treatment are generally mild and may decline during administration, however, in some infrequent cases the effect may persist during chronic administration (see ADVERSE REACTIONS, Prolactin).

Hyperprolactinemia may suppress hypothalamic GnRH, resulting in reduced pituitary gonadotrophin secretion. This, in turn, may inhibit reproductive function by impairing gonadal steroidogenesis in both female and male patients. Galactorrhea, amenorrhea, gynecomastia, and impotence have been reported with prolactin-elevating compounds. Long-standing hyperprolactinemia when associated with hypogonadism may lead to decreased bone mineral density in both female and male patients.

Tissue culture experiments indicate that approximately one-third of human breast cancers are prolactin dependent *in vitro*, a factor of potential importance if the prescription of these drugs is considered in a patient with previously detected breast cancer. As is common with compounds which increase prolactin release, an increase in mammary gland neoplasia was observed in a REXULTI carcinogenicity study conducted in mice (see TOXICOLOGY). The physiological differences between rats and humans with regard to prolactin make the clinical significance of these findings unclear. To date, neither clinical nor epidemiological studies have shown an association between chronic administration of these drugs and mammary tumorigenesis.

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

Hematologic

In clinical trial and/or post-marketing experience, events of leukopenia/neutropenia have been reported temporally related to antipsychotic agents. Agranulocytosis has also been reported. Therefore, it is recommended that patients have their complete blood count (CBC) tested prior to starting REXULTI and then periodically throughout treatment.

Possible risk factors for leukopenia/neutropenia include pre-existing low white blood cell count

(WBC) and history of drug-induced leukopenia/neutropenia. Patients with a history of a clinically significant low WBC or drug-induced leukopenia/neutropenia should have their complete blood count (CBC) monitored frequently during the first few months of therapy and discontinuation of REXULTI should be considered at the first sign of a clinically significant decline in WBC in the absence of other causative factors.

Patients with clinically significant neutropenia should be carefully monitored for fever or other symptoms or signs of infection and treated promptly if such symptoms or signs occur. Discontinue REXULTI in patients with severe neutropenia (absolute neutrophil count $<1x10^9$/L) and follow their WBC counts until recovery.

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

Neurologic

Neuroleptic Malignant Syndrome (NMS)
Neuroleptic malignant syndrome is a potentially fatal symptom complex that has been reported in association with antipsychotic drugs.

Clinical manifestations of NMS are hyperpyrexia, muscle rigidity, altered mental status, and evidence of autonomic instability (irregular pulse or blood pressure, tachycardia, diaphoresis, and cardiac dysrhythmia). Additional signs may include elevated creatine phosphokinase (CPK), myoglobinuria (rhabdomyolysis), and acute renal failure.

In arriving at a diagnosis, it is important to identify cases where the clinical presentation includes both serious medical illness (e.g., pneumonia, systemic infection, etc.), and untreated or inadequately treated extrapyramidal signs and symptoms (EPS). Other important considerations in the differential diagnosis include central anticholinergic toxicity, heat stroke, drug fever, and primary central nervous system pathology.

The management of NMS should include 1) immediate discontinuation of all antipsychotic drugs including REXULTI and other drugs not essential to therapy; 2) intensive symptomatic treatment and medical monitoring; and 3) treatment of any concomitant serious medical problems for which specific treatments are available. There is no general agreement about specific pharmacological treatment for uncomplicated NMS.

If a patient requires antipsychotic drug treatment after recovery from NMS, the potential reintroduction of therapy should be very carefully considered. The patient should be carefully monitored, since recurrence of NMS has been reported.

Tardive Dyskinesia
A syndrome of potentially irreversible, involuntary, dyskinetic movements may develop in

patients treated with antipsychotic drugs. Although the prevalence of the syndrome is highest among the elderly, especially elderly women, it is impossible to rely upon prevalence estimates to predict, at the inception of antipsychotic treatment, which patients are likely to develop the syndrome. Whether antipsychotic drugs differ in their potential to cause tardive dyskinesia is unknown.

The risk of developing tardive dyskinesia and the likelihood that it will become irreversible increase as the duration of treatment and the total cumulative dose of antipsychotic drugs administered to the patient increases. However, the syndrome can develop, although much less commonly, after relatively brief treatment periods at low doses.

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

Given these considerations, REXULTI should be prescribed in a manner that is most likely to minimize the occurrence of tardive dyskinesia. Chronic antipsychotic treatment should generally be reserved for patients who 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 such patients who do require chronic treatment, the smallest dose and the shortest duration of treatment producing a satisfactory clinical response should be sought. The need for continued treatment should be reassessed periodically.

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

Seizure/Convulsion
As with other antipsychotic drugs, REXULTI should be used cautiously 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 a population of 65 years or older.

Potential for Cognitive and Motor Impairment
Like other antipsychotics drugs, REXULTI has the potential to impair judgment, thinking, or motor skills. Because REXULTI may cause somnolence and impair motor skills, patients should be cautioned about performing activities requiring mental alertness, such as operating hazardous machinery, including motor vehicles, until they are reasonably certain that REXULTI therapy does not affect them adversely.

Psychiatric

Suicide
The possibility of a suicide attempt is inherent in psychotic illnesses, therefore close supervision and appropriate clinical management of high-risk patients should accompany drug therapy.

Impulsive behaviours

Post-marketing reports of impulse-control disorders including pathological gambling and hypersexuality have been reported in patients treated with another antipsychotic with partial agonist activity at dopamine receptors. Patients with a prior history of impulse-control disorder may be at increased risk and should be monitored carefully.

Special Populations

Pregnant Women:
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 24-fold in rats and 49-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 (see TOXICOLOGY, Reproductive Toxicity). In a pregnant and lactating rat study, there was an increase in stillbirths and deaths of offspring at doses ≥ 10 mg/kg/day (24-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.

Labor and Delivery: The effect of REXULTI on labor 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.

Pediatrics: (<18 years of age): The safety and effectiveness of REXULTI in patients under the age of 18 years have not been established and its use is not recommended.

Weight gain has been observed with atypical antipsychotic use in pediatric and adolescent patient populations. Independent of any drug-specific effects, weight gain can be associated with

adverse changes in other metabolic parameters (e.g., glucose and lipid metabolism). Abnormal childhood weight and metabolic status can have adverse effects on cardiovascular outcomes in adulthood. Weight gain and adverse effects on other metabolic parameters associated with atypical antipsychotics can be more frequent or severe in pediatric and adolescent patients than in the adult patients.

The long term safety, including cardiometabolic effects and effects on growth, maturation and behavioural development in patients under 18 years of age has not been systematically evaluated.

Geriatrics (> 65 years of age): Clinical studies of REXULTI did not include sufficient numbers of patients aged 65 and older to determine whether they respond differently from younger subjects. In general, dose selection for an elderly patient should be cautious, usually starting at the low end of the dosing range, reflecting the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy (see Serious Warnings and Precautions box, and ACTION AND CLINICAL PHARMACOLOGY).

Use in Elderly Patients with Dementia

Overall Mortality
Elderly patients with dementia treated with atypical antipsychotic drugs showed increased mortality compared to placebo in a meta-analysis of 13 placebo-controlled trials of various atypical antipsychotic drugs. REXULTI is not indicated for the treatment of patients with dementia (e.g. dementia-related psychosis) (see Serious Warnings and Precautions box).

Cerebrovascular Adverse Events, Including Stroke in Elderly Patients with Dementia
In placebo-controlled trials with some atypical antipsychotics, there was a higher incidence of cerebrovascular adverse events (cerebrovascular accidents and transient ischemic attacks) including fatalities compared to placebo-treated subjects. There are insufficient data with brexpiprazole to know if there is an increased risk of cerebrovascular events associated with brexpiprazole. REXULTI is not indicated for the treatment of patients with dementia (e.g. dementia-related psychosis) (see also Serious Warnings and Precautions box).

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

Use in Patients with Hepatic Impairment
For patients with moderate to severe hepatic impairment (Child-Pugh score ≥7), the maximum recommended dosage is 3 mg once daily for patients with schizophrenia (see DOSAGE AND ADMINISTRATION, Dosing Considerations; ACTION AND CLINICAL PHARMACOLOGY, Pharmacokinetics, Special Populations and Conditions).

Use in Patients with Renal Impairment
For patients with moderate, severe or end-stage renal impairment (creatinine clearance CL_{cr}<60 mL/minute), the maximum recommended dosage is 3 mg once daily for patients with schizophrenia (see DOSAGE AND ADMINISTRATION, Dosing Considerations; ACTION AND CLINICAL PHARMACOLOGY, Pharmacokinetics, Special Populations and Conditions).

CYP2D6 Poor Metabolizers
Dosage adjustments are recommended in patients who are known cytochrome P450 (CYP) 2D6 poor metabolizers (see DOSAGE AND ADMINISTRATION, Dosing Considerations; ACTION AND CLINICAL PHARMACOLOGY, Pharmacokinetics, Special Populations and Conditions).

Lactose
REXULTI tablets contain lactose. This should be considered when prescribing to patients with rare hereditary problems of galactose intolerance, lactase deficiency or glucose-galactose malabsorption.

ADVERSE REACTIONS

Adverse Drug Reaction Overview

Clinical Trial Adverse Drug Reactions

Because clinical trials are conducted under very specific conditions the adverse reaction rates observed in the clinical trials may not reflect the rates observed in practice and should not be compared to the rates in the clinical trials of another drug. Adverse drug reaction information from clinical trials is useful for identifying drug-related adverse events and for approximating rates.

The following findings are based on two 6-week, placebo-controlled, fixed-dose clinical trials, and one long term 52-week double blind placebo controlled randomized-withdrawal trial for schizophrenia in which REXULTI was administered at daily doses between 1 mg and 4 mg. These are referred to as Trials 1, 2 and 3 respectively. In Trials 1 and 2, 852 patients received REXULTI at fixed daily doses of 1, 2 or 4 mg and 368 received placebo. In Trial 3, following an open-label stabilization period of up to 36 weeks, 97 patients received REXULTI at flexible daily doses between 1 and 4 mg and 104 patients received placebo in the double-blind randomized withdrawal period; the mean daily REXULTI dose was 3.6 mg at the last visit in the study. This trial was terminated after efficacy was demonstrated in an interim analysis, and only 23 patients (11%), 14 in the brexpiprazole group and 9 in the placebo group, completed the 52-weeks of the double-blind, controlled period.

Safety data is also available for 1265 patients who participated in uncontrolled, open-label studies and received REXULTI daily doses from 1 mg to 4 mg; 604 patients completed at least 26 weeks and 372 completed at least 52 weeks in the open-label studies.

Most Common Adverse Reactions: There are no common adverse reactions that meet the criteria incidence of ≥5% and at least twice the rate of placebo in the Trials 1 and 2, the 6-week, placebo-controlled, fixed-dose trials, or Trial 3, during the double-blind randomized-withdrawal period.

Adverse Reactions Reported as Reasons for Discontinuation of Treatment: A total of 7.8% (67/852) REXULTI-treated subjects and 14.7% (54/368) of placebo-treated subjects discontinued due to adverse reactions. There were no adverse reactions associated with discontinuation in subjects treated with REXULTI that were at least 2% and at least twice the placebo rate.

Adverse reactions associated with REXULTI (incidence of 2% or greater and REXULTI incidence greater than placebo) that occurred during acute therapy (up to 6-weeks in subjects with schizophrenia) are shown in Table 1.

Table 1: TEAEs with Incidence of 2% or More in Any Brex Group and Greater Than Placebo Group in Trials 1 and 2 (6-Week, Placebo-Controlled, Fixed-Dose Trials in Schizophrenia)

	Brexpiprazole (mg/day)				
System Organ Class MedDRA Preferred Term	**1 mg (N=120) %**	**2 mg (N=368) %**	**4 mg (N=364) %**	**ALL (N=852) %**	**Placebo (N=368) %**
Gastrointestinal disorders					
Diarrhoea	1%	3%	3%	3%	2%
Dyspepsia	6%	2%	3%	3%	2%
Dry mouth	1%	2%	2%	2%	1%
Abdominal pain upper	0%	1%	2%	1%	1%
Investigations					
Weight increased	3%	4%	4%	4%	2%
Blood creatine phosphokinase increased	4%	2%	2%	2%	1%
Musculoskeletal and connective tissue disorders					
Back pain	1%	2%	3%	2%	2%
Pain in extremity	3%	2%	2%	2%	1%
Myalgia	2%	1%	1%	1%	1%
Nervous system disorders					
Akathisia	4%	5%	7%	6%	5%
Tremor	2%	2%	3%	3%	1%
Sedation	2%	2%	3%	2%	1%
Dizziness	2%	1%	3%	2%	1%
Psychiatric disorders					
Restlessness	0%	1%	2%	1%	1%
Skin and Subcutaneous tissue disorders					
Rash	3%	2%	1%	2%	<1%

In the longer-term randomized-withdrawal Trial 3, the general treatment-emergent adverse event profile for the initial 12 to 36-week single-blind REXULTI treatment phase of this study was comparable to the one characterised in the 6-week, placebo-controlled, fixed-dose studies 1 and 2 described above. In the double-blind, randomized withdrawal phase of the study, there was only one potentially drug related adverse event that occurred at a rate greater than 2% and double that of placebo (tremor 3%). No additional safety concerns were noted, however, the exposure in the double-blind phase was limited (97 in REXULTI and 104 in placebo, about 40% overall completed at least 6 months, and 11% overall completed the 52 weeks).

Selected Adverse Events

Extrapyramidal Symptoms

In Trials 1 and 2, the incidence of reported EPS-related events, excluding akathisia events, was 5.1% versus 3.5% for placebo-treated subjects. The incidence of akathisia events for REXULTI-treated subjects was 5.4% versus 4.9% for placebo-treated subjects. Akathisia was reported more often during Weeks 1 through 3 and was mild to moderate in severity. The incidence of EPS-related TEAEs is presented in Table 2.

Table 2: Incidence of EPS-related TEAEs for Short-term Controlled Schizophrenia Trials 1 and 2

EPS Class Adverse Event MedDRA Preferred Term	Brexpiprazole (mg/day)				
	1 mg N = 120 %	2 mg N = 368 %	4 mg N = 364 %	ALL N = 852 %	Placebo N = 368 %
Subjects with any adverse event	7%	10%	14%	11%	8%
Total Akathisia Events[a]	5%	5%	7%	6%	5%
Total Dyskinetic Events[b]	0%	<1%	<1%	<1%	<1%
Total Dystonic Events[c]	2%	1%	2%	2%	2%
Total Parkinsonian Events[d]	2%	4%	6%	4%	2%
Total Residual Events[e]	0%	0%	<1%	<1%	0%

[a] Total Akathisia events includes adverse event terms: akathisia, psychomotor hyperactivity
[b] Total Dyskinetic events includes adverse events: dyskinesia, tardive dyskinesia
[c] Total Dystonic events includes adverse event terms: dystonia, muscle rigidity, muscle spasms
[d] Total Parkinsonian events includes adverse event terms: bradykinesia, extrapyramidal disorder, parkinsonism, tremor
[e] Total Residual events includes adverse event terms: muscle twitching

In Trials 1 and 2, data was objectively collected on the Simpson Angus Rating Score (SAS) for extrapyramidal symptoms (EPS), the Barnes Akathisia Global Score (BARS) for akathisia and the Abnormal Involuntary Movement Score (AIMS) for dyskinesia. The incidence of EPS change is presented in Table 3.

Table 3: Change in EPS Compared to Placebo in Schizophrenia Trials 1 and 2

	Proportion of Subjects with Shifts from Baseline			
	Brexpiprazole (mg/day)			
	Placebo	**1 mg**	**2 mg**	**4 mg**
AIMS[a] Total Score	4% (13/361)*	1% (1/120)*	3% (12/361)*	4% (13/362)*
BARS[b] Global Score	1% (5/362)*	1% (1/119)*	1% (2/361)*	2% (9/362)*
SAS[c] Total Score	5% (19/356)*	6% (7/119)*	6% (21/356)*	8% (28/357)*

* denotes n/N where N=the total number of subjects who had a measurement at baseline and at least one post-baseline result.
n=the number of subjects with shift.
[a] Abnormal Involuntary Movement Scale - %shifts from ≤1 at baseline to any post-baseline value ≥2
[b] Barnes Akathisia Rating Scale- %shifts from ≤2 at baseline to any post-baseline value >2
[c] Simpson Angus Scale- %shifts from ≤3 at baseline to any post-baseline value >3

Table 4 presents the reported incidence of concomitant medications used to treat EPS-related TEAEs, including akathisia.

Table 4: Incidence of Reported Concomitant Use to Treat EPS-related TEAEs for Short-term Controlled Schizophrenia Trials 1 and 2

Drug Class Medication Preferred Name	**Brexpiprazole (mg/day)**			
	1 mg N = 120 n (%)	**2 mg N = 368 n (%)**	**4 mg N = 364 n (%)**	**Placebo N = 368 n (%)**
Total using 1 or more medications	5 (4.2)	23 (6.3)	34 (9.3)	19 (5.2)
Anti-Parkinson Drugs	4 (3.3)	18 (4.9)	26 (7.1)	15 (4.1)
Beta Blocking Agents	1 (0.8)	8 (2.2)	11 (3.0)	6 (1.6)

Weight Gain

Table 5 shows weight gain data at last visit and percentage of adult subjects with ≥7% increase in body weight at endpoint from Trials 1 and 2.

Table 5: Changes in Weight (kg) - Trials 1 and 2 (up to 6 weeks)

	Placebo N=362	1 mg/day N=120	2 mg/day N=362	4 mg/day N=362
	Mean Change from Baseline (kg) at Last Visit			
All Subjects	+0. 2	+1.0	+1.2	+1.2
	Proportion of Subjects with a ≥7% Increase in Body Weight (kg) at Any Visit			
	N=368	**N=120**	**N=368**	**N=364**
≥7% Increase	4.1% (15/362)	10.0% (12/120)	10.5% (38/362)	10.2% (37/362)

The percentage of subjects in the 6-week Trials 1 and 2 with an increase of ≥7% in body weight was 10.5% and 10.2% in the REXULTI 2 and 4 mg/day group respectively, compared with 4.1% in the placebo group.

During the longer-term randomized-withdrawal Trial 3 the proportion of subjects with a ≥7% *increase* in body weight at any visit was 5.2% (5/96) in the REXULTI-treated group compared to 1.0% (1/104) in the placebo group. The proportion of subjects with a ≥7% *decrease* in body weight at any visit was 9.3% (9/96) in the REXULTI-treated group compared to 15.3% (16/104) in the placebo group. In the stabilization phase of this trial, the proportion of subjects with a ≥7% *increase* in body weight at any visit was 11.3% (52/462) and with a ≥7% *decrease* in body weight at any visit was 3.9% (18/462).

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 subjects 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 subjects.

Constipation
Patients should be advised of the risk of severe constipation during REXULTI treatment, and they should tell their doctor if constipation occurs or worsens, since they may need medical intervention.

Less Common Clinical Trial Adverse Drug Reactions (<2%)

Other adverse reactions (<2% frequency and greater than placebo) within the short-term, placebo-controlled trials (N=1406 brexpiprazole-treated patients) and the long term maintenance trial (N=97 brexpiprazole-treated patients) in subjects with 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.

Blood and Lymphatic System Disorders:
Infrequent: Anemia
Cardiovascular Disorders:
Infrequent: Sinus Bradycardia, Atrioventricular Block First Degree, Palpitations
Endocrine Disorders:
Infrequent: Hyperprolactinemia
Eye Disorders:
Infrequent: Vision Blurred, Lacrimation increased, Blepharospasm
Gastrointestinal Disorders:
Infrequent: Flatulence, Salivary Hypersecretion, Dental Caries, Abdominal Distension, Gastroesophageal Reflux Disease
General Disorders & Administration Site Conditions:
Frequent: Fatigue
Infrequent: Asthenia, Pyrexia, Chest Pain
Infections and Infestations:
Frequent: Upper Respiratory Tract Infection
Infrequent: Bronchitis, Conjunctivitis
Investigations:
Infrequent: Hepatic Enzyme Increased, Blood Triglycerides Increased, Blood Prolactin Increased
Musculoskeletal and Connective Tissue Disorders:
Infrequent: Musculoskeletal Pain, Musculoskeletal Stiffness, Rhabdomyolysis
Nervous System Disorders:
Infrequent: Psychomotor Activity
Psychiatric Disorders:
Infrequent: Abnormal Dreams, Bruxism
Respiratory, Thoracic and Mediastinal Disorders:
Infrequent: Cough, Dyspnea
Vascular Disorders:
Infrequent: Hypertension, Orthostatic Hypotension, Hypotension, Flushing

Abnormal Hematologic and Clinical Chemistry Findings

Fasting Glucose

In the 6-week Trials 1 and 2, the proportion of patients with changes in fasting glucose to post-baseline high (≥126 mg/dL) results were comparable between REXULTI and placebo treated subjects.

In the longer-term randomized-withdrawal Trial 3, 7% of patients with normal baseline fasting glucose (N=388) had changes to high fasting glucose during the single-blind REXULTI treatment in the Stabilization phase. During the double-blind phase, from the patients with normal baseline fasting glucose, 4.5% in the REXULTI group (3/66) and 0% in the placebo group (0/62) had changes to high 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 REXULTI, 17% of subjects with borderline fasting glucose experienced shifts from borderline to high. Combined, 9% of subjects with normal or borderline fasting glucose experienced shifts to high fasting glucose during the long-term schizophrenia studies.

Fasting Lipids

In Trials 1 and 2, the proportion of patients with clinically significant changes from baseline in fasting total cholesterol, LDL cholesterol, and HDL cholesterol were similar in REXULTI- and placebo-treated subjects. Table 6 shows the proportions of subjects with changes in fasting triglycerides.

Table 6: Change in Fasting Triglycerides in Trials 1 and 2 (up to 6 weeks)

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

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

In the longer-term randomized-withdrawal Trial 3, 22% of patients with normal baseline fasting triglycerides (N=394) had changes to high or very high fasting triglycerides during single-blind REXULTI treatment in the Stabilization phase. During the double-blind phase, from the patients with normal baseline fasting triglycerides, 7% in the REXULTI group (4/57) and 0% in the placebo group (0/60) had changes to high fasting triglycerides.

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 REXULTI. Of patients with normal baseline triglycerides, 14% experienced shifts to high, and 0.3% experienced shifts to very high triglycerides. Combined, 0.5% of subjects with normal or borderline fasting triglycerides experienced shifts to very high fasting triglycerides during the long-term schizophrenia studies.

Prolactin

Table 7 shows the mean change from baseline in prolactin and the proportion of subjects with prolactin elevations.

Table 7: Changes in Prolactin (ng/mL)- Trials 1 and 2 (up to 6 weeks)

		Placebo	1 mg/day	2 mg/day	4 mg/day
Mean Change from Baseline (ng/mL) at Last Visit					
All Male		N=206	N=73	N=220	N=208
		-1.08	-2.16	-1.36	-0.47
All Female		N=127	N=41	N=129	N=132
		-5.57	-1.08	-1.31	-0.81
Male with normal baseline		N=142	N=40	N=139	N=145
		+1.36	+2.61	+2.52	+3.12
Female with normal baseline		N=92	N=29	N=102	N=102
		+2.55	+5.95	+7.00	+6.46
Proportion of Subjects with new onset abnormal results at any time post-baseline					
All Male		N=207	N=73	N=221	N=208
	>1x ULN	12%	10%	12%	17%
	>2x ULN	5%	3%	3%	0.5%
	>3x ULN	2%	0%	0%	2%
All Female		N=127	N=41	N=129	N=132
	>1x ULN	7%	7%	12%	17%
	>2x ULN	5%	7%	6%	3%
	>3x ULN	2%	2%	1%	1%

In the longer-term randomized withdrawal Trial 3, the mean change from baseline at last visit in prolactin in females was -2.17 ng/mL in REXULTI-treated group compared with -4.25 ng/mL in the placebo group. In males, mean change from baseline at last visit in prolactin was -1.73 ng/mL in REXULTI-treated group compared with 1.38 ng/mL in the placebo group. For females with normal prolactin results at baseline, the mean changes to last visit were 4.04 ng/mL in the REXULTI-treated group and -5.95 ng/mL in the placebo group; for males with normal baseline, the mean changes to last visit were 0.05 ng/mL in the REXULTI-treated group and 2.61 ng/mL in the placebo group. The proportion of subjects with prolactin elevations >1X ULN in females was 5.2% in the REXULTI-treated group compared with 2.6% in the placebo group. In males, the proportion of subjects with prolactin elevations > 1X ULN was 3.6% in the REXULTI-

treated group compared with 4.9% in the placebo group. Similarly, prolactin elevations >3X ULN in females was 0.0% in the REXULTI-treated group compared with 5.2% in the placebo group. In males, prolactin elevations >3X ULN was 0.0% in the REXULTI-treated group compared with 3.2% the in placebo group.

In the long-term open-label schizophrenia trials, the mean change from baseline at last visit in prolactin in females was 2.78 ng/mL in REXULTI-treated group and 0.60 ng/mL in males. The proportion of subjects with prolactin elevations >1X ULN was 17.5% in females and 14.0% in males in the REXULTI-treated group, and prolactin elevations >3X ULN was 4.1% in females and 1.7% in males.

Post-Market Adverse Drug Reactions

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

DRUG INTERACTIONS

Overview

REXULTI is predominantly metabolized by cytochrome P450 (CYP)3A4 and CYP2D6.

REXULTI should be used with caution in combination with drugs known to prolong QTc interval or cause electrolyte disturbances (see WARNINGS AND PRECAUTIONS, Cardiovascular, QT Interval).

Drug-Drug Interactions

Potential for other drugs to affect REXULTI

Dosage adjustments are recommended in patients who are known CYP2D6 poor metabolizers and in patients taking concomitant CYP3A4 inhibitors or CYP2D6 inhibitors or strong CYP3A4 inducers (Table 8). If the co-administered drug is discontinued, adjust the REXULTI dosage to its original level. If the co-administered CYP3A4 inducer is discontinued, reduce the REXULTI dosage to the original level over 1 to 2 weeks (see DOSAGE AND ADMINISTRATION, Dosing Considerations).

Table 8: Summary of Effect of Co-administered Drugs on Exposure to REXULTI (brexpiprazole) in Healthy Subjects

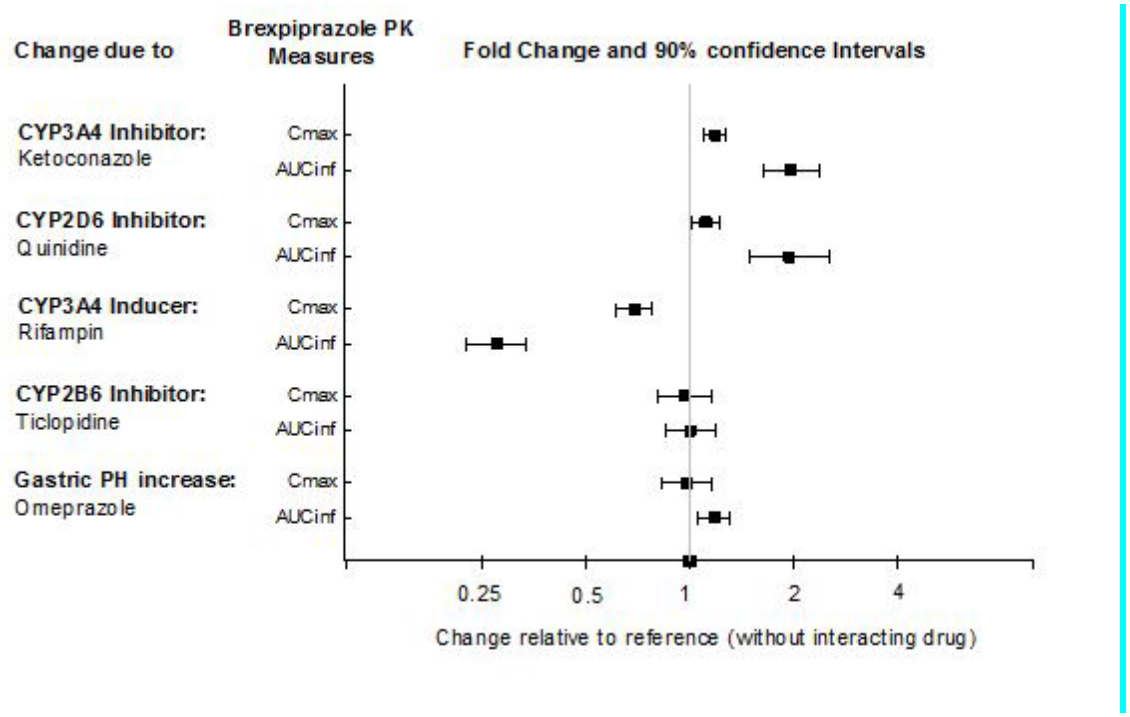
Co-administered Drug	Ref	Dose Schedule Clinical comment		Effect on REXULTI Pharmacokinetics		Recommendation
		Co-administered Drug	REXULTI	C_{max}	AUC	
Ketoconazole (strong CYP34A inhibitor*)	CT	200 mg BID for 7 days	single 2 mg dose	No change	Increased by 97%	Administer half of usual REXULTI dose
Quinidine (strong CYP2D6 inhibitor)	CT	324 mg OD for 7 days	single 2 mg dose	No change	Increased by 94%	Administer half of usual REXULTI dose
Ticlopidine (strong CYP2B6 inhibitor)	CT	250 mg BID for 7 days	single 2 mg dose	No change	No change	No REXULTI dose adjustment required
Rifampin (strong CYP34A inducer)	CT	600 mg BID for 12 days	single 4 mg dose	Decreased by 31%	Decreased by 73%	Double usual REXULTI dose over 1 to 2 weeks, adjust as required based on clinical response
Omeprazole (Gastric Acid pH Modifiers)	CT	40 mg OD for 5 days	single 4 mg dose	No change	No change	No REXULTI dose adjustment required

Legend: CT = Clinical Trial

*Mild and moderate CYP3A4 inhibitors (e.g. erythromycin, grapefruit juice) have not been studied

The effects of other drugs on the exposure of brexpiprazole are summarized in Figure 1.

Figure 1: The Effects of Other Drugs on Brexpiprazole Pharmacokinetics*



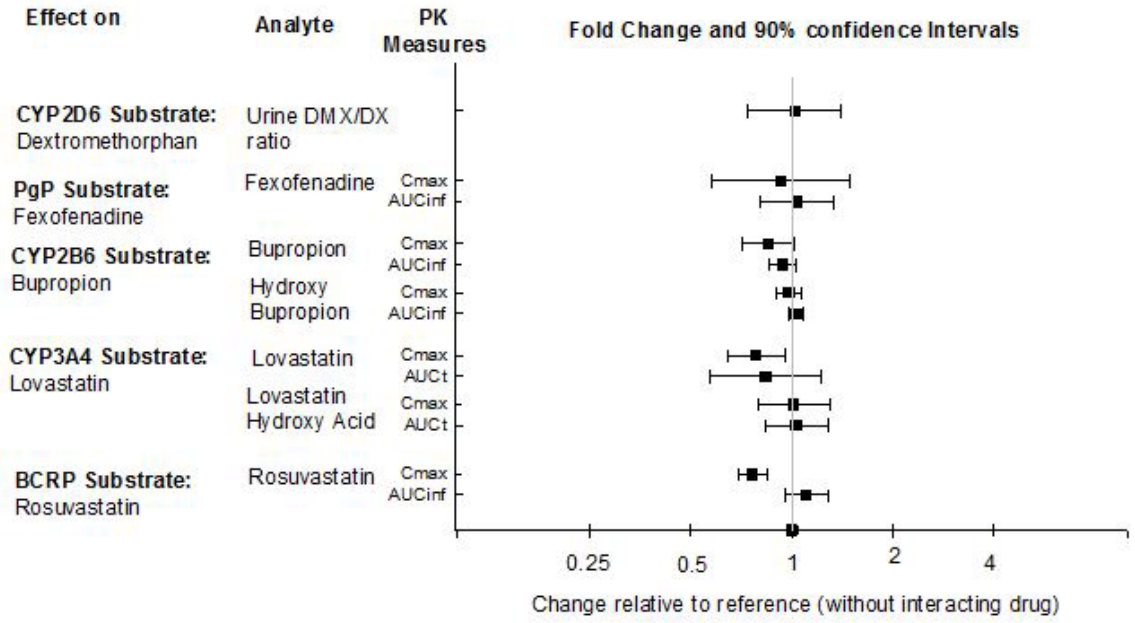
*see also impact for dosage recommendations in Table 8 above.

Potential for REXULTI to affect other drugs

Results of *in vitro* studies suggest that REXULTI is unlikely to cause clinically important pharmacokinetic interactions with drugs metabolized by cytochrome P450 enzymes. Clinical studies showed that oral brexpiprazole (2 mg/day, 5 days) had no effect on the metabolism of single doses of dextromethorphan (a CYP2D6 substrate), lovastatin (a CYP3A4 substrate) or bupropion (a CYP2B6 substrate). REXULTI did not affect absorption of single doses of drugs that are substrates of BCRP transporter (rosuvastatin) and PgP transporter (fexofenadine). No dosage adjustment of CYP2D6, CYP3A4, CYP2B6, BCRP and PgP substrates is required during concomitant administration with REXULTI.

The effects of brexpiprazole on the exposure of other drugs are summarized in Figure 2.

Figure 2: The Effects of Brexpiprazole on Pharmacokinetics of Other Drugs



Drug-Food Interactions

REXULTI may be administered with or without food.

Drug-Herb Interactions

Interactions with herbal products have not been established.

Drug-Laboratory Interactions

Interactions with laboratory tests have not been established

Drug-Lifestyle Interactions

Alcohol/CNS Drugs
Given the primary CNS effects of brexpiprazole, as with most psychoactive medications, combination use of REXULTI with alcohol or other CNS drugs with overlapping undesirable effects such as sedation, should be avoided.

Smoking
Based on studies utilizing human liver enzymes *in vitro*, brexpiprazole is not a substrate for CYP1A2.

DOSAGE AND ADMINISTRATION

Recommended dose and dose adjustment

Table 9: Dose and dose adjustment

Starting Dose	Recommended Dose	Maximum Dose
1 mg/day	2-4 mg/day	4 mg/day

The recommended starting dosage for REXULTI is 1 mg once daily on Days 1 to 4, taken orally with or without food.

The recommended target REXULTI dosage is 2 mg to 4 mg once daily. In clinical trials, the dose was titrated 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. Periodically reassess to determine the continued need and appropriate dosage for treatment.

Patients should be treated with the lowest effective dose that provides optimal clinical response and tolerability.

Dosing Considerations

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

Renal Impairment: For patients with moderate, severe or end-stage renal impairment (creatinine clearance CL_{cr}<60 mL/minute), the maximum recommended dosage is 3 mg once daily for patients with schizophrenia.

CYP isozymes: Dosage adjustments are recommended in patients who are known cytochrome P450 (CYP) 2D6 poor metabolizers and in patients taking concomitant CYP3A4 inhibitors or CYP2D6 inhibitors or strong CYP3A4 inducers (see Table 10). If the co-administered drug is discontinued, adjust the REXULTI dosage to its original level. If the co-administered CYP3A4 inducer is discontinued, reduce the REXULTI dosage to the original level over 1 to 2 weeks.

Table 10: Dosage Adjustments of REXULTI for CYP2D6 Poor Metabolizers and for Concomitant Use with CYP3A4 and CYP2D6 Inhibitors and/or CYP3A4 Inducers

Factors	Adjusted REXULTI Dosage
CYP2D6 Poor Metabolizers	
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	Administer half of the usual dose
Strong/moderate CYP2D6 inhibitors with strong/moderate CYP3A4 inhibitors	Administer a quarter of the usual dose
Patients Taking CYP3A4 Inducers	
Strong CYP3A4 inducers	Double usual dose over 1 to 2 weeks

Geriatrics: The safety and efficacy of REXULTI in patients 65 years of age or older have not been established. Caution should be used when treating geriatric patients (see WARNINGS AND PRECAUTIONS, Special Population, Geriatrics). REXULTI is not indicated in elderly patients with dementia (see WARNINGS AND PRECAUTIONS, Serious Warnings and Precaution Box and Special Populations).

Missed Dose
If a dose is missed then it should be taken as soon as possible unless it is close to the next dose. Two doses should not be taken.

Administration
REXULTI may be given once daily, with or without food.

Switching from Other Antipsychotics
There are no systematically collected data to specifically address switching patients with schizophrenia from other antipsychotics to REXULTI or concerning concomitant administration with other antipsychotics. While immediate discontinuation of the previous antipsychotic treatment may be acceptable for some patients with schizophrenia, more gradual discontinuation may be most appropriate for others. In all cases, the period of overlapping antipsychotic administration should be minimized.

OVERDOSAGE
There is limited clinical trial experience regarding human overdosage with REXULTI. ECG monitoring is recommended in the event of overdose.

For management of a suspected drug overdose, contact your regional Poison Control Centre.

ACTION AND CLINICAL PHARMACOLOGY

Mechanism of Action

The mechanism of action of brexpiprazole in treating schizophrenia is unknown. The efficacy of brexpiprazole may be mediated through a combination of partial agonist activity at serotonergic 5-HT_{1A} and at dopaminergic D_2 receptors with antagonist activity at serotonergic 5-HT_{2A} receptors. The clinical relevance of these receptor interactions with brexpiprazole is unknown.

Pharmacodynamics

Brexpiprazole has high affinity (expressed as Ki values) for serotonin $5HT_{1A}$ (0.12 nM), $5HT_{2A}$ (0.47 nM), $5HT_{2B}$ (1.88 nM), dopamine D_2 (0.3 nM), D_3 (1.14 nM), and noradrenergic α_{1A} (3.78 nM), α_{1B} (0.17 nM), α_{1D} (2.60 nM), and α_{2C} (0.59 nM) receptors.

Brexpiprazole exhibits a moderate affinity for dopamine D_4 (6.3 nM), serotonin 5-HT_{7A} (9.48 nM), noradrenergic α_{2A} (15 nM), α_{2B} (17 nM) and histamine H_1 (19 nM) receptors; and weak affinity for the serotonin 5-HT_{1B} (32 nM) and 5-HT_{2C} (33 nM) receptors (see DETAILED PHARMACOLOGY).

Brexpiprazole acts as a partial agonist at the 5-HT_{1A}, D_2, and D_3 receptors and as an antagonist at $5HT_{2A}$, $5HT_{2B}$, $5HT_7$, α_{1A}, α_{1B}, α_{1D}, and α_{2C} receptors.

Cardiac Electrophysiology: In a multicenter, randomized, double-blind, placebo- and positive-controlled, parallel group, multiple dose ECG assessment study, subjects with schizophrenia or schizoaffective disorder received treatment with brexpiprazole at a therapeutic dose of 4 mg/day or a supratherapeutic dose of 12 mg/day for 11 days. On day 11, the maximum placebo-adjusted mean change from baseline in the QTcI interval was 8.3 ms (90% CI 3.7, 12.9) at 6 h post-dosing in the brexpiprazole 4 mg/day group (N=62) and 3.1 ms (90% CI -1.7, 8.0) at 4 h post-dosing in the brexpiprazole 12 mg/day group (N=53). No exposure-response relationship was apparent.

Sub-group analyses suggested that the QTc prolongation was larger in female subjects than in males. In the brexpiprazole 4 mg/day group, the maximum placebo-adjusted mean change from baseline in the QTcI interval was 5.2 ms (90% CI 1.5, 8.9) in males (N=48) and 15.0 ms (90% CI 7.7, 22.3) in females (N=14) at 6 h post-dosing. In the brexpiprazole 12 mg/day group, the maximum placebo-adjusted mean change from baseline in the QTcI interval was 2.9 ms (90% CI -1.2, 6.9) in males (N=40) at 12 h post-dosing and 10.4 ms (90% CI 2.7, 18.2) in females (N=13) at 24 h post-dosing. Limitations of the gender sub-group analyses included diminished statistical power.

The brexpiprazole 4 mg/day treatment had no effect on heart rate; however, the brexpiprazole 12 mg/day treatment was associated with an increase in heart rate, with a maximum mean difference from placebo of 4.8 bpm (90% CI 1.9, 7.7) at 2 h.

Pharmacokinetics

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

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

In vivo brexpirazole 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.

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 brexpiprazole oral tablet after once daily administration is 19.8 (±11.4) mL/h/kg. After multiple once daily administration of brexpiprazole, the terminal elimination half-life of brexpiprazole and its major metabolite, DM-3411, is 91.4 hours and 85.7 hours, respectively.

Special Populations and Conditions

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

Antipsychotic drugs increase the risk of death in elderly patients with dementia-related psychosis. REXULTI is not approved for the treatment of patients with dementia-related psychosis (see Serious Warning and Precautions box).

CYP2D6 poor metabolism status: Based on the results of the population PK analysis CYP2D6 poor metabolizer subjects exhibited 47% higher exposure (AUC_τ) to brexpiprazole compared with CYP2D6 extensive metabolizer subjects. Dose reduction to ½ of the maintenance dose is recommended in subjects with known poor CYP2D6 metabolism status.

Age/Gender: After single dose administration of brexpiprazole (2 mg), elderly subjects (older than 65 years old) exhibited similar brexpiprazole systemic exposure (C_{max} and AUC) in comparison to the adult subjects (18-45 years old) and female subjects exhibited approximately 40-50% higher brexpiprazole systemic exposure (C_{max} and AUC) in comparison to the male subjects. Population pharmacokinetic evaluation identified age and female sex as statistically significant covariates affecting brexpiprazole PK while the effects were not considered clinically relevant. No dosage adjustment is required in subjects based on age or gender (see WARNINGS AND PRECAUTIONS, Special Populations, Geriatrics).

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. No dosage adjustment is required in patients based on race.

Hepatic Insufficiency: In subjects with varying degrees of hepatic impairment (Child-Pugh Classes A, B, and C; N=22), 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 8% in severe hepatic impairment. Specific dosing considerations are recommended for patients with moderate to severe hepatic impairment (see DOSAGE AND ADMINISTRATION, Dosing Considerations, Hepatic Impairment).

Renal Insufficiency: In subjects with severe renal impairment (CL_{cr} <30 mL/min; N=10), AUC of oral brexpiprazole (2 mg single dose) compared to matched healthy subjects was increased by 68% while its C_{max} was not changed. For patients with moderate, severe or end-stage renal impairment, a maximum dose of 3 mg is recommended for the treatment of schizophrenia (see DOSAGE AND ADMINISTRATION, Dosing Considerations, Renal Impairment).

STORAGE AND STABILITY
Store REXULTI tablets between 15°- 30°C (59°-86°F).

SPECIAL HANDLING INSTRUCTIONS
Keep out of reach of children.

DOSAGE FORMS, COMPOSITION AND PACKAGING
REXULTI is available in bottles of 30 tablets and blister packs of 30 tablets.
REXULTI is available in the following tablet strengths:

Table 11: REXULTI Tablet Presentations

Tablet Strength	Tablet Color/Shape	Tablet Markings
0.25 mg	Light brown, film-coated Round; shallow convex; bevel-edged	"BRX" and "0.25"
0.5 mg	Light orange, film-coated Round; shallow convex; bevel-edged	"BRX" and "0.5"
1 mg	Light yellow, film-coated Round; shallow convex; bevel-edged	"BRX" and "1"
2 mg	Light green, film-coated Round; shallow convex; bevel-edged	"BRX" and "2"
3 mg	Light purple, film-coated Round; shallow convex; bevel-edged	"BRX" and "3"
4 mg	White, film-coated Round; shallow convex; bevel-edged	"BRX" and "4"

REXULTI contains the following inactive ingredients; lactose monohydrate, corn starch, microcrystalline cellulose, hydroxypropyl cellulose, low-substituted hydroxypropyl cellulose, magnesium stearate, hypromellose, and talc.
Colourants: titanium dioxide, ferric oxide yellow (0.25 mg, 0.5 mg, 1 mg, 2 mg), ferric oxide red (0.25 mg, 0.5 mg, 3 mg), and ferrosoferric oxide (0.25 mg, 2 mg, 3 mg).

PART II: SCIENTIFIC INFORMATION

PHARMACEUTICAL INFORMATION

Drug Substance

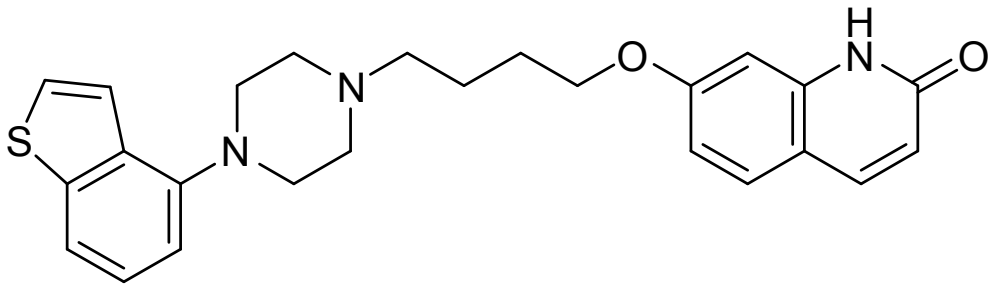
Proper name: brexpiprazole

Chemical name: 7-{4-[4-(1-Benzothiophen-4-yl)piperazin-1-yl]butoxy}quinolin-2(1*H*)-one

Molecular formula: $C_{25}H_{27}N_3O_2S$

Molecular mass: 433.57g/mol.

Structural formula:



Physicochemical properties: Brexpiprazole is nonhygroscopic, with white to off white crystals or crystalline powders, and a melting point of 183°C (decomposition). Brexpiprazole is a weakly basic compound with a pKa of 7.8. It is practically insoluble in water, and the solubility of the drug substance at pH 2 is 0.56 mg/mL, at pH 4 is 0.13 mg/mL, and at pH 6 is 0.0020 mg/mL.

CLINICAL TRIALS

The efficacy of REXULTI in the treatment of adults with schizophrenia was demonstrated in two 6-week, randomized, double blind, placebo controlled fixed dose clinical trials and one longer-term randomized withdrawal trial in subjects who met DSM-IV-TR criteria for schizophrenia and were experiencing an acute exacerbation of psychotic symptoms. The efficacy was also evaluated in a 6-week, randomized, double-blind, placebo-controlled and active-reference flexible dose clinical trial.

In two fixed dose trials, Trial 231 (hereafter "Trial 1") and Trial 230 (hereafter "Trial 2"), subjects were randomized to REXULTI 2 or 4 mg once per day or placebo. Subjects in the REXULTI groups initiated treatment at 1 mg once daily on Days 1 to 4. The REXULTI dosage was increased to 2 mg on Days 5 to 7. The dosage was then either maintained at 2 mg once daily or increased to 4 mg once daily, depending on treatment assignment, for the 5 remaining weeks. The primary efficacy endpoint of both trials was the change from baseline to Week 6 in the Positive and Negative Syndrome Scale (PANSS) total score. The PANSS is a 30-item scale that measures positive symptoms of schizophrenia (7 items), negative symptoms of schizophrenia (7 items), and general psychopathology (16 items), each rated on a scale of 1 (absent) to 7 (extreme); the total PANSS scores range from 30 (best) to 210 (worst). The key secondary endpoint of both trials was the change from baseline to Week 6 in Clinical Global Impression Severity of Illness Scale (CGI-S) total score, a validated clinician-related scale that measures the subject's current illness state and overall clinical state on a 1 (normal, not at all ill) to 7-point (extremely ill) scale.

In Trial 1, REXULTI was superior to placebo (N=178) at both 2 mg/day (n=180) and 4 mg/day (N=178) doses for the primary endpoint (PANSS total score) and key secondary endpoint (CGI-S total score).

In Trial 2, REXULTI at 4 mg/day group (N=181) was superior to placebo (N=180) for the primary endpoint (PANSS total score), but not at the 2 mg/day dose (N=179).

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

In the 6-week flexible-dose study (Study 14644A), REXULTI at doses between 2 and 4 mg/day (N=150) was not superior to placebo (N=159) for the primary endpoint, the mean changes in PANSS total score at Week 6; however, the active reference (N=150) confirmed the assay sensitivity of the study.

The longer term Trial 3 was a randomized-withdrawal, double-blind, placebo-controlled trial to assess the efficacy of REXULTI (1 - 4 mg/day) in adults with schizophrenia experiencing an exacerbation of psychotic symptoms at study entry, who met criteria for stability for at least 12 weeks during single-blind treatment with REXULTI (flexible doses 1- 4 mg/day), and were then randomised to continue on their brexpiprazole dose or to switch to placebo, for up to 52 weeks. The primary endpoint was the time to exacerbation of psychotic symptoms/impending relapse;

the key secondary endpoint was the percentage of subjects with exacerbation of psychotic symptoms/impending relapse.

A pre-specified interim analysis, conducted after 50% of the events planned in the calculation of power, demonstrated a statistically significantly longer time to relapse in subjects randomized to the REXULTI group compared to placebo-treated subjects and the trial was subsequently terminated early because of demonstrated efficacy. The final analysis demonstrated a statistically significantly longer time to relapse in subjects randomized to the REXULTI group (N=96) compared to placebo-treated subjects (N=104). Time to impending relapse was statistically significantly delayed with brexpiprazole compared with placebo in both the interim and final analyses ($p = 0.0008$ and $p < 0.0001$, respectively; log-rank test). For the final analysis, the hazard ratio from the Cox proportional hazard model for the placebo to brexpiprazole comparison was 3.420 (95% CI: 1.825, 6.411); thus, subjects in the placebo group had a 3.4-fold greater risk of experiencing impending relapse than the subjects in the brexpiprazole group.

The key secondary endpoint, the proportion of subjects who met the criteria for impending relapse, was statistically significantly lower in REXULTI-treated subjects compared with placebo group (13.5% vs. 38.5%, $p<0.0001$).

DETAILED PHARMACOLOGY

Brexpiprazole has a broad receptor binding profile with high affinity ($K_i < 5$ nM) for multiple monoaminergic receptors including serotonin 5-HT_{1A}, 5-HT_{2A}, 5-HT_{2B}, dopamine D_2, D_3, and noradrenergic α_{1A}, α_{1B}, α_{1D}, and α_{2C} receptors. Brexpiprazole exhibits a moderate affinity for dopamine D_4, serotonin 5-HT_{7A}, noradrenergic α_{2A}, α_{2B} and histamine H_1 receptors; and weak affinity for the serotonin 5-HT_{1B} and 5-HT_{2C} receptors. Although affinity constants have not been determined, brexpiprazole (at 10 μM) showed occupancy at the muscarinic M1 receptor (64%), dopamine transporter (90%) and serotonin transporter (65%).

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. Dose response occupancy and brain/ plasma exposure relationship were determined *in vivo* or *ex vivo* for D_2/D_3, 5-HT_{2A}, 5-HT_{1A}, and 5-HT_7 receptors as well as the serotonin transporter in preclinical studies. These results are consistent with the relative binding affinities and indicate that brexpiprazole has activity at several targets in the central nervous system at therapeutic plasma exposures.

Brexpiprazole was shown *in vitro* to inhibit both norepinephrine and serotonin uptake into synaptosome preparations from rat brain tissue. Brexpiprazole also inhibited monoamine oxidase B (MAO-B) enzyme activity in rat liver extracts.

Central Nervous System Safety Pharmacology: In safety pharmacology studies, brexpiprazole had a depression effect on the CNS that was related to the exaggerated pharmacological effect of the compound. Brexpiprazole caused a decreased body temperature in repeat-dose toxicity studies at doses ≥30 mg/kg in rats, monkeys and dogs (See TOXICOLOGY).

Cardiovascular Safety Pharmacology: Significant decrease in blood pressure and prolongation of QT interval and QTc were noted in the conscious telemetry dog trial, and on Day 1 of administration at doses ≥3 mg/kg in the repeat-dose toxicity studies with monkeys and in the juvenile toxicity study with dogs (15- and 24-fold the MRHD on a mg/m^2 basis, respectively). In conscious telemetry dogs (N=4), brexpiprazole was administered at sequential oral doses of 0 (vehicle), 1, 3, 10, and 30 mg/kg at intervals of 7-8 days. Brexpiprazole at 10 mg/kg and 30 mg/kg caused statistically significant increases in the QTc interval and the QRS duration compared to the vehicle control group.

In anesthetised dogs (N=4) under phenylephrine-induced hypertensive state, intravenous infusions of brexpiprazole were associated with statistically significant decreases in systolic and diastolic blood pressure at 0.3 mg/kg and 3 mg/kg and decrease in heart rate at 3 mg/kg. The effect of brexpiprazole on blood pressure may be due to a blockade of α_1- adrenoceptors in peripheral blood vessels, which is consistent with the pharmacological profile for this compound.

In Chinese hamster ovary cells CHO-K1 expressing the alpha subunit of the human IKr potassium channel, brexpiprazole caused a statistically significant and concentration-dependent suppression of hERG currents over a 0.01 to 1 μM concentration range, with a IC_{50} of 0.117 μM (51 ng/mL).

TOXICOLOGY

Acute Toxicity

In single-dose oral (gavage) toxicity studies, the minimum oral lethal dose was >1000 and 300 mg/kg, respectively for male and female Sprague Dawley (SD) rats, and > 100 mg/kg for both male and female cynomolgus monkeys. At doses of 1000 and 300 mg/kg, clinical signs observed in male and female rats included hypoactivity, closed eyes or incomplete eyelid closure, fixed stare, lacrimation, abnormal posture, and hypothermia. In monkey, clinical signs included drowsiness, partially closed eyes, crouching or prone positions, tremors of the limbs, decrease in movement, and decrease in body temperature.

Repeat Dose Toxicity

In a repeat-dose toxicity study conducted in rats at oral doses of 0, 3, 10, 30 and 100 mg/kg/day for 26 weeks duration, the no observed adverse effect level (NOAEL) was 3 mg/kg (7-fold MRHD on a mg/m^2 basis). Clinical signs observed at 30 and 100 mg/kg included CNS depression, hypoactivity, hypothermia, gynecomastia, galactorrhea, and increases in blood levels of aspartate aminotransferase and gamma globulin, as well as decrease in body weight and food consumption. Female rats increased in body weight at 3 mg/kg compared to the control group. Major histopathology finding corresponded to atrophy of the uterus, thymus and pituitary glands, and enlargement of adrenal glands at doses ≥10 mg/kg.

In repeat-dose toxicity studies conducted in Cynomolgus monkeys at oral doses of 0, 1, 3 and 30 mg/kg/day for 13 and 39 weeks duration, the NOAEL was 1 mg/kg (5-fold MRHD) for both sexes. At doses ≥3 mg/kg, animals exhibited CNS depression, decrease in blood pressure, decreases in leukocytes and reticulocytes, as well as increases in blood cholesterol and

phospholipids. Major histopathology finding corresponded to death-related gastrointestinal bleeding and ulcers at 30 mg/kg.

Juvenile Repeat Dose Toxicity
In repeat-dose toxicity study conducted in juvenile rats at oral doses of 0, 3, 10 and 20 mg/kg/day for 8 weeks duration, the NOAEL was <3 mg/kg (7-fold MRHD on a mg/m^2 basis) in both sexes. At doses ≥10mg/kg, animals exhibited CNS depression, hypoactivity, as well as increases in blood globulins and phospholipids. Decrease in body weight, pubertal delays and gynecomastia were also noted at the end of the administration period compared with the control group. Female rats increased in body weight at 3 mg/kg. Major histopathology finding corresponded to atrophy of the pituitary glands, liver and kidney at doses ≥10 mg/kg. Following 2 weeks untreated recovery period, differences in fertility and reproductive performance between treatment groups were unremarkable.

In repeat-dose toxicity study conducted in juvenile Beagle dogs at oral doses of 0, 1, 3 and 30 mg/kg/day for 26 weeks duration, the NOAEL was <3 mg/kg (24-fold MRHD) in both sexes. At 30 mg/kg, animals exhibited CNS depression, hypoactivity, decreased respiration rates, lower blood pressure and decrease in reticulocytes, as well as, increases in blood cholesterol and phospholipids. Major histopathology finding corresponded to enlargement of adrenal glands and liver at 30 mg/kg. Toxicology findings were unremarkable after 8 weeks untreated recovery period, except for male pubertal delays noted in the 30 mg/kg group.

Carcinogenesis
The lifetime carcinogenic potential of brexpiprazole was evaluated in two year studies in mice and rats. In mice, brexpiprazole was administered orally (gavage) at doses of 0.75, 2 and 5 mg/kg/day (1 to 6-fold MRHD on a mg/m^2 basis. 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 at all doses. In rats, brexpiprazole was administered orally (gavage) at doses of 1, 3 and 10 mg/kg/day in males or 3, 10 and 30 mg/kg/day in females (for males 2 to 24-fold and for females 7 to 73-fold the MRHD). 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 sexes in 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), *in vivo* in the micronucleus assay in rats, and the unscheduled DNA synthesis assay in rats. Brexpiprazole was mutagenic and clastogenic but occurred only at doses that induced cytotoxicity (20-30 µg/mL) in the *in vitro* forward gene mutation assay in mouse lymphoma cells and in the *in vitro* chromosomal aberration assay in Chinese hamster ovary cells. Based on a

weight of evidence, brexpiprazole is not considered to present a genotoxic risk to humans at therapeutic doses and exposures.

Impairment of Fertility
In female rats treated with brexpiprazole at oral doses of 0, 0.3, 3 or 30 mg/kg/day prior to mating with untreated males and continuing through conception and implantation, the NOAEL in terms of reproductive performance and fertility was 0.3 mg/kg/day (0.7-fold MRHD). Prolonged diestrus and decreased fertility were observed at 3 mg/kg/day. At 30 mg/kg/day a prolongation of the mating phase was observed and significantly increased preimplantation losses were seen.

In male rats treated with brexpiprazole at oral doses of 0, 3, 10 or 100 mg/kg/day for 63 days prior to mating and during copulation (with untreated females), the NOAEL in terms of male fertility and toxicological effects was 10 mg/kg/day (24-fold MRHD).

Reproductive Toxicity
In a prenatal and postnatal developmental study in rats, pregnant dams receiving brexpiprazole at oral doses of 0, 3, 10 and 30 mg/kg/day from implantation until weaning of offspring, the NOAEL for maternal toxicity and newborn viability was 3 mg/kg/day (7-fold MRHD). Increase in the number of stillbirth and death in pups during lactation were observed at 10 and 30 mg/kg. Changes observed at 30 mg/kg/day included impaired nursing in dams, and low birth weight, impaired viability, suppressed body weight gain, delayed pinna unfolding and decreased number of corpora lutea in the offspring.

In a rabbit embryo-fetal development study, pregnant dams receiving brexpiprazole at oral doses of 0, 10, 30 and 150 mg/kg/day during gestation, the NOAEL for reproductive toxicity was 10 mg/kg/day (49-fold MRHD). At doses ≥30 mg/kg, an increase incidence in renal pelvic dilation and caudal vena cava abnormality was observed in fetuses. At 150 mg/kg/day, decreased body weight, retarded ossification, and increased incidences of visceral and skeletal malformations were observed.

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READ THIS FOR SAFE AND EFFECTIVE USE OF YOUR MEDICINE
PATIENT MEDICATION INFORMATION

REXULTI™
brexpiprazole tablets

Read this carefully before you start taking **REXULTI** and each time you get a refill. This leaflet is a summary and will not tell you everything about this drug. Talk to your healthcare professional about your medical condition and treatment and ask if there is any new information about **REXULTI.**

Serious Warnings and Precautions

Increased Risk of Death in Elderly People with Dementia. Medicines like REXULTI can raise the risk of death in elderly people who have dementia. REXULTI is not approved for use in patients with dementia.

What is REXULTI used for?
REXULTI is used for the treatment of schizophrenia in adults.

Schizophrenia is characterized by symptoms such as:
- hallucinations; hearing, seeing or sensing things that are not there,
- suspiciousness, mistaken beliefs,
- incoherent speech and behavior and emotional flatness.

People with schizophrenia may also feel depressed, guilty, anxious or tense.

REXULTI is not a cure, but it can help manage symptoms in adult patients.

How does REXULTI work?
REXULTI belongs to a group of medicines called atypical antipsychotic drugs**.**
Antipsychotic drugs affect the chemicals (neurotransmitters) in the brain that allow nerve cells to talk to each other. Illnesses that affect the brain, like schizophrenia, may be due to certain neurotransmitters in the brain being out of balance. These imbalances may cause some of the symptoms you may be experiencing. Exactly how REXULTI works is unknown.

What are the ingredients in REXULTI?
Medicinal ingredient: brexpiprazole
Non-medicinal ingredients: corn starch, ferric oxide yellow (0.25 mg, 0.5 mg, 1 mg, 2 mg), ferric oxide red (0.25 mg, 0.5 mg, 3 mg), ferrosoferric oxide (0.25 mg, 2 mg, 3 mg), hydroxypropyl cellulose, low-substituted hydroxypropyl cellulose, hypromellose, lactose monohydrate, magnesium stearate, microcrystalline cellulose, titanium dioxide.

REXULTI comes in the following dosage forms:
Tablets: 0.25 mg, 0.5 mg, 1 mg, 2 mg, 3 mg and 4 mg.

Do not use REXULTI if:
- you are allergic (hypersensitive) to brexpiprazole or to any ingredient in the tablets or component of the container.

To help avoid side effects and ensure proper use, talk to your healthcare professional before you take REXULTI. Talk about any health conditions or problems you may have, including if you:
- have or have a family history of diabetes or high blood sugar
- have high levels of cholesterol, or fats (triglycerides) in your blood.
- have or have had seizures (convulsions).
- have or have had high blood pressure.
- have low blood pressure or get dizzy, especially upon standing, or have a history of fainting.
- have sleep apnea.
- have had a stroke.
- have heart problems including “long QT syndrome”.
- have a family history of “long QT syndrome” or sudden cardiac death at less than 50 years of age.
- have had problems with the way your heart beats or if you are taking medication that affects how your heart beats.
- have or have had liver or kidney problems.
- have or have had a low levels of white blood cells.
- are at risk for developing blood clots such as: a family history of blood clots, age over 65, smoking, obesity, recent major surgery (such as hip or knee replacement), being immobile due to air travel or other reason, take oral birth control ("The Pill").
- are dehydrated or suffer from excessive vomiting, diarrhea, or sweating.
- do strenuous exercise or work in a hot, sunny place.
- have a history of drug abuse or addiction.
- drink alcohol or use recreational drugs.
- have problems with impulse control (i.e. gambling or sex addition).
- have had problems tolerating the recommended doses of some drugs.
- have been told you are a “CYP2D6 poor metabolizer”.
- have increased levels of the hormone prolactin, or have a tumour in your pituitary gland.
- have or have had involuntary, irregular muscle movements, especially in the face (tardive dyskinesia).
- have a problem with the movement of your gut (paralytic ileus), a narrowing or blockage of your gut or other serious gut problem.
- are elderly and have dementia (loss of memory and other abilities).
- have one of the following rare hereditary diseases because lactose is a non-medicinal ingredient in REXULTI:
    - Galactose intolerance
    - Lapp lactase deficiency

    - Glucose-galactose malabsorption
- are pregnant or plan to become pregnant. It is not known if REXULTI may harm your unborn baby. Using REXULTI in the last trimester of pregnancy may cause muscle movement problems, medicine withdrawal symptoms, or both of these in your newborn. If you become pregnant while taking REXULTI, contact your healthcare professional immediately.
- are breastfeeding or plan to breastfeed. It is not known if REXULTI passes into your breast milk. You and your healthcare professional should decide if you will take REXULTI or breastfeed.

Other warnings you should know about:
Your healthcare professional should take blood tests before starting REXULTI. Blood tests will include checking the number of infection fighting white blood cells, cholesterol levels, blood fat levels and levels of the hormone prolactin. While you are taking REXULTI your healthcare professional will also check your weight, blood sugar and blood pressure regularly.

Driving and Using Machines
REXULTI may make you feel drowsy. Do not drive a car, operate machinery, or do other dangerous activities until you know how REXULTI affects you.

Low Blood Pressure
Some people may faint, or get lightheaded and dizzy, especially when getting up from a lying or sitting position. This is more likely to happen if you are elderly and also at the start of treatment or when you increase the dose. This will usually pass on its own but if it does not, tell your healthcare professional.

Dehydration and Overheating
It is important not to become too hot or dehydrated while you are taking REXULTI.
- Do not exercise too much.
- In hot weather, stay inside in a cool place if possible.
- Stay out of the sun.
- Do not wear too much clothing or heavy clothing.
- Drink plenty of water.

Effects in Newborns
Babies born to mothers taking REXULTI while they are pregnant can have had serious health problems. Sometimes, the problems may resolve on their own. Be prepared to get immediate medical help for your baby if they:
- have trouble breathing.
- are overly sleepy.
- have muscle stiffness or floppy muscles (like a rag doll).
- are shaking.
- are having trouble feeding.

Tell your healthcare professional about all the medicines you take, including any drugs, vitamins, minerals, natural supplements or alternative medicines.

The following may interact with REXULTI:

- Drugs used to treat HIV infection and AIDS, such as indinavir, lopinavir/ritonavir, nelfinavir, ritonavir and saquinavir.
- Antibiotics used to treat bacterial infections, such as erythromycin, clarithromycin, azithromycin, tacrolimus, moxifloxacin, levofloxacin, ciprofloxacin and rifampin.
- Pentamidine, an antimicrobial drug used to treat infections in people with weakened immune systems.
- Drugs used to treat malaria, such as quinine and chloroquine.
- Drugs used to treat fungal infections, such as amphotericin B, itraconazole, fluconazole, voriconazole and ketoconazole.
- Domperidone often used to increase production of breast milk.
- Drugs used to prevent nausea and vomiting, such as ondansetron.
- Chemotherapy drugs used to treat cancer, such as sunitinib, nilotinib, ceritinib, vandetanib, vorinostat and arsenic trioxide.
- Drugs used to treat breathing problems like asthma and COPD, such as salmeterol and formoterol.
- Antidepressant drugs such as bupropion, fluoxetine, citalopram, venlafaxine, amitriptyline, imipramine, maprotiline and paroxetine.
- Drugs used to treat heart problems such as quinidine, procainamide, disopyramide, amiodarone, sotalol, ibutilide, dronedarone, flecainide and propafenone.
- Anti-seizure drugs such as carbamazepine and phenytoin.
- Diuretics or “water pills”.
- Laxatives and enemas.
- Antacid drugs, such as proton pump inhibitors.
- Opioids such as methadone.
- Other antipsychotic drugs such as chlorpromazine, pimozide, haloperidol, droperidol, ziprasidone and risperidone.
- Drugs used to lower blood pressure.
- St John’s wort, an herbal product used to treat depression.
- Alcohol. You should not drink alcohol with taking REXULTI.
- Grapefruit or grapefruit juice. Do not eat grapefruit or drink grapefruit juice while taking REXULTI.

How to take REXULTI:

- Take REXULTI exactly as your healthcare professional tells you to take it.
- Your healthcare professional has decided on the best dosage for you. Your healthcare professional may change your dose depending on how you respond and other medications you are taking.
- Do not change your dose or stop taking REXULTI without speaking to your healthcare professional.
- REXULTI can be taken with or without food.

Usual adult dose

The usual starting dose of REXULTI in schizophrenia is 1 mg per day.

The usual dose of REXULTI in schizophrenia is 2-4 mg per day.

Overdose:

If you think you have taken too much REXULTI, contact your healthcare professional, hospital emergency department or regional Poison Control Centre immediately, even if there are no symptoms.

Missed Dose:
You should not miss a dose of REXULTI. If you miss a dose, take the missed dose as soon as you remember. If you are close to your next dose, just skip the missed dose and take your next dose at your regular time. Do not take 2 doses of REXULTI at the same time. If you are not sure about your dosing, call your healthcare professional.

What are possible side effects from using REXULTI?
These are not all the possible side effects you may feel when taking REXULTI. If you experience any side effects not listed here, contact your healthcare professional.

Common side effects may include:

- diarrhea
- indigestion, stomach pain
- dry mouth
- weight gain
- dizziness
- difficulty staying still or restlessness
- shakiness (tremor)
- back pain, muscle pain
- sleepiness, drowsiness
- rash

If you have high levels of prolactin (measured with a blood test) and a condition called hypogonadism you may be at an increased risk of breaking a bone due to osteoporosis. This occurs in both men and women.

Serious side effects and what to do about them			
Symptom / effect	Talk to your healthcare professional		Stop taking drug and get immediate medical help
	Only if severe	In all cases	
UNCOMMON **Allergic Reaction:** rash, hives, swelling of the face, lips, tongue or throat, difficulty swallowing or breathing			√
Tardive Dyskinesia: muscle twitching or unusual movement of the face or tongue		√	
Stroke and Transient Ischemic Attacks: sudden weakness or numbness of the face, arms, or legs and speech or vision problems			√
Seizure: loss of consciousness with uncontrollable shaking			√
Blood Clots: swelling, pain and redness in an arm or leg that is warm to touch. You may develop sudden chest pain, difficulty breathing and heart palpitations		√	
Increased blood sugar: frequent urination, thirst, and hunger	√		
Decreased White Blood Cells: infections, fatigue, fever, aches, pains, and flu-like symptoms		√	
Dysphagia: tightness of the throat, difficulty swallowing or breathing which may lead to choking		√	
Low Blood Pressure: dizziness, fainting, lightheadedness May occur when you go from lying or sitting to standing up.	√		
Neuroleptic Malignant Syndrome: severe muscle stiffness or inflexibility with high fever, rapid or irregular heartbeat, sweating, state of confusion or reduced consciousness			√
Priapism: long-lasting (greater than 4 hours in duration) and painful erection of the penis			√
New or worsening constipation		√	
Rhabdomyolysis: very dark ("tea coloured") urine, muscle tenderness and/or aching			√

If you have a troublesome symptom or side effect that is not listed here or becomes bad enough to interfere with your daily activities, talk to your healthcare professional.

Reporting Side Effects
You can help improve the safe use of health products for Canadians by reporting serious and unexpected side effects to Health Canada. Your report may help to identify new side effects and change the product safety information.
3 ways to report:
- Online at MedEffect (www.healthcanada.gc.ca/medeffect);
- By calling 1-866-234-2345 (toll-free);
- By completing a Consumer Side Effect Reporting Form and sending it by:
  - Fax to 1-866-678-6789 (toll-free), or
  - Mail to: Canada Vigilance Program
    Health Canada, Postal Locator 1908C
    Ottawa, ON
    K1A 0K9

    Postage paid labels and the Consumer Side Effect Reporting Form are available at MedEffect (www.healthcanada.gc.ca/medeffect).

NOTE: Contact your healthcare professional if you need information about how to manage your side effects. The Canada Vigilance Program does not provide medical advice.

Storage:
Store REXULTI at room temperature, between 15 and 30 °C.

Keep out of reach and sight of children.

If you want more information about REXULTI:
- Talk to your healthcare professional.
- Find the full product monograph that is prepared for healthcare professionals and includes this Patient Medication Information by visiting the Health Canada website (www.healthcanada.gc.ca); the manufacturer's website www.otsukacanada.com, or by calling 1-877-341-9245.

This leaflet was prepared by Otsuka Pharmaceutical Co., Ltd.

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