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Fax

To:	John McCall, RPh	From:	OPDC MedInfo 240-683-3235
Fax:	1-888-656-6822	Pages:	18
Phone:		Date:	October 14, 2016
Re:	REXULTI® (brexpiprazole) Request Forms	cc:	

☐ Urgent x For Review ☐ Please Comment ☐ Please Reply ☐ Please Recycle

Please find attached the submission request forms for REXULTI.

If you have further questions or require additional information, please feel free to contact your Managed Market Liaison, Dr. Samantha Sweeney at 619-518-0757.

Otsuka Pharmaceutical Development & Commercialization, Inc.

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Otsuka Pharmaceutical Development & Commercialization, Inc.
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State of Alaska Department of Health and Social Services, Division of Health Care Services
Submission Request Form for Pharmaceutical Manufacturers

Fax this request to: 1-888-656-6822 ATTN: John McCall, R.Ph.

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Members of the Pharmacy and Therapeutics (P&T) Committee have requested that all clinical information, questions, or comments about the Preferred Drug List (PDL) be sent directly to Magellan Medicaid Administration. Manufacturers and other interested parties have been requested not to contact the members directly. Written comments on the PDL from all interested parties should be submitted to Erin Narus, PharmD, R.Ph. at the State of Alaska.

Note: Manufacturers submitting comments are requested to do so through their Product Manager using this form. This form constitutes a request for ***NEW*** information pertaining to peer-reviewed literature including off-label peer-reviewed studies.

Contact Information

MANUFACTURER NAME: Otsuka Pharmaceutical Development & Commercialization, In

DATE: 10 - 17 - 2016

PRODUCT MANAGER'S NAME: Samantha Sweeney, PharmD, MBA

TITLE: Managed Market Liaison

ADDRESS: 508 Carnegie Center Drive

CITY: Princeton

STATE: NJ

ZIP CODE: 08540

PHONE NUMBER: 619 - 518 - 0757

FAX NUMBER: - -

PRODUCT: REXULTI® (brexpiprazole)

Clinical Rationale Request for Consideration (If additional space is required, use Clinical Rationale Continuation Page).

INDICATIONS AND USAGE (Prescribing Information)
REXULTI is an atypical antipsychotic indicated for use as an adjunctive therapy to antidepressants for the treatment of major depressive disorder (MDD) and the treatment of schizophrenia.

MECHANISM OF ACTION (Prescribing Information; Maeda, 2014; Citrome, 2015)
The mechanism of action of REXULTI in the treatment of MDD or schizophrenia is unknown. However, the efficacy of REXULTI may be mediated through a combination of partial agonist activity at serotonin 5-HT1A and dopamine D2 receptors, and antagonist activity at serotonin 5-HT2A receptors. REXULTI is a distinct chemical entity that is not an isomer or metabolite of any compound (Maeda, 2014) . In addition to the aforementioned pharmacologic activities, REXULTI exerts antagonistic activity at adrenergic alpha1B and alpha2C receptors (Citrome, 2015).

EFFICACY AND SAFETY
Adjunctive Therapy to Antidepressants in Adults with Major Depressive Disorder (Prescribing Information)
The efficacy of REXULTI in the adjunctive treatment of MDD was evaluated in two 6-week, double-blind, placebo- controlled, fixed-dose trials of adult patients meeting DSM-IV-TR criteria for MDD, with or without symptoms of anxiety, who had an inadequate response to prior antidepressant therapy (ADT; 1 to 3 courses) in the current episode and who had also demonstrated an inadequate response throughout the 8 weeks of prospective antidepressant treatment (with escitalopram, fluoxetine, paroxetinparoxetine controlled-release, sertraline, duloxetine delayed release, or venlafaxine extended release). Inadequate resporesponse during the prospective antidepressant treatment phase was defined as having persistent symptoms without substantial improvement throughout the course of treatment. Patients in Study 228 (hereafter "Study 1") were randomized to REXULTI 2 mg once a day or placebo. Patients in Study 227 (hereafter "Study 2") were randomized to REXULTI 1 or 3 mg once a day or placebo. For patients randomized to REXULTI, all patients initiated treatment at 0.5 mg once daily during Week 1. At Week 2, the

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Clinical Rationale Request for Consideration (If additional space is required, use Clinical Rationale Continuation Page).

REXULTI dosage was increased to 1 mg in all treatment groups, and either maintained at 1 mg or increased to 2 mg or 3 mg once daily, based on treatment assignment, from Week 3 onwards. The dosages were then maintained for the 4 remaining weeks. The primary endpoint was change from baseline to Week 6 in the Montgomery-Asberg Depression Rating Scale (MADRS), a 10-item clinician-related scale used to assess the degree of depressive symptomatology, with 0 representing no symptoms, and 60 representing worst symptoms. At randomization, the mean MADRS total score was 27. In Studies 1 and 2, REXULTI (+ ADT) 2 mg/day and 3 mg/day were superior to placebo + ADT in reducing mean MADRS total scores. The most common adverse reactions associated with REXULTI, reported in ≥5% of patients and at least twice the rate of placebo, were weight increase and akathisia.

Acute, Short-Term Studies in Schizophrenia (Prescribing Information)
The efficacy of REXULTI in the treatment of adults with schizophrenia was demonstrated in two 6-week, randomized, double-blind, placebo-controlled, fixed-dose clinical trials in patients who met DSM-IV-TR criteria for schizophrenia. In both studies, Study 231 (hereafter "Study 3") and Study 230 (hereafter "Study 4"), patients were randomized to REXULTI 2 or 4 mg once per day or placebo. Patients in the REXULTI groups initiated treatment at 1 mg once daily on Days 1 to 4. The REXULTI dosage was increased to 2 mg on Days 5 to 7. The dosage was then either maintained at 2 mg once daily or increased to 4 mg once daily, depending on treatment assignment, for the 5 remaining weeks. The primary efficacy endpoint of both trials was the change from baseline to Week 6 in the Positive and Negative Syndrome Scale (PANSS) Total Score. The PANSS is a 30-item scale that measures positive symptoms of schizophrenia (7 items), negative symptoms of schizophrenia (7 items), and general psychopathology (16 items), each rated on a scale of 1 (absent) to 7 (extreme); the total PANSS scores range from 30 (best) to 210 (worst). In Study 3, REXULTI at both 2 mg/day and 4 mg/day was superior to placebo on the PANSS Total Score. In Study 4, REXULTI 4 mg/day was superior to placebo on the PANSS total score. Examination of population subgroups based on age, gender and race did not suggest differential responsiveness. The most common adverse reaction associated with REXULTI, reported in ≥4% of patients and at least twice the rate of placebo, was weight increase.

52-Week Maintenance Treatment (Fleischhacker, 2016)
Fleischhacker et al conducted a 52-week, randomized, double-blind, placebo-controlled study to evaluate the efficacy and safety of REXULTI as maintenance treatment in adults with schizophrenia (n=202 randomized). Patients with acute exacerbation of schizophrenia were cross titrated from current antipsychotic treatment(s) to REXULTI over 1-4 weeks, prior to entering a 12-36 week single-blind stabilization phase on REXULTI 1-4 mg/day. Patients progressed to the double-blind maintenance phase if they met a set of criteria for stability for 12 consecutive weeks. This study showed a beneficial effect of REXULTI relative to placebo on the primary endpoint of time to exacerbation of psychotic symptoms / impending relapse (log-rank test: hazard ratio=0.292, p<0.0001). Significantly fewer patients relapsed in the REXULTI group compared with placebo (13.5% vs 38.5%, p<0.0001). During the stabilization phase, 8.8% of patients were withdrawn due to adverse events. During the maintenance treatment phase, the withdrawal rates due to adverse events were 5.2% and 11.5% in the REXULTI and placebo groups, respectively.

Comparative Data
Citrome et al (2016) conducted an open-label, exploratory study evaluating the effects of REXULTI and aripiprazole on efficacy, cognitive functioning, and safety in hospitalized patients with acute, relapsing schizophrenia. The efficacy endpoints evaluated included a change from baseline to Week 6 in the following outcomes: Positive and Negative Syndrome Scale (PANSS) Total Score, Clinical Global Impression-Severity (CGI-S) Scale, Clinical Global Impression-Improvement (CGI-I) Scale, PANSS responders, the Specific Level of Functioning (SLOF), Barratt Impulsiveness Scale (BIS-11) total score, and Cogstate computerized cognitive test battery scores. Aripiprazole was included as a positive control to confirm assay sensitivity in this study. A total of 97 patients were randomized to receive either REXULTI (n=64) or aripiprazole (n=33). Patients received flexible doses of REXULTI 1 to 4 mg/day (target dose: 3 mg/day) or aripiprazole 10 to 20 mg/day (target dose:15 mg/day) for 6 weeks. A reduction in symptoms of schizophrenia as assessed by the PANSS Total Score was observed from baseline to Week 6 in patients treated with REXULTI or aripiprazole (- 22.9 vs -19.4, respectively). A modest improvement in impulsivity was observed with REXULTI, but not with aripiprazole (BIS-11: -2.7 vs 0.1). REXULTI demonstrated slightly greater numerical improvement compared to aripiprazole in CGI-S, SLOF, CGI-I, and response rate. No changes were noted in Cogstate scores for either treatment. At least one treatment-emergent adverse event (TEAE) was reported in approximately 60% of patients in both treatment groups. Akathisia was reported more

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Clinical Rationale Continuation Page (Use only if needed).

frequently in patients treated with aripiprazole (21.2%) compared to REXULTI (9.4%). Other TEAEs were similar between the two drugs. In patients treated with REXULTI and aripiprazole, mean body weight increased by 4.3 kg and 3.8 kg, respectively at Week 6 (observed cases).

COST EFFECTIVENESS DATA

In a poster publication by Aigbogun et al (2015), a decision analytic model evaluated a hypothetical cohort of patients with schizophrenia initiating treatment with REXULTI 1–4 mg or lurasidone 40–80 mg over a 1-year period. At 6 months, patients remained on initial treatment or discontinued due to relapse, adverse events (AEs), or for other reasons. Data were obtained from comparable long-term maintenance/acute trials and product labeling. Placebo-adjusted relative risks were used to estimate treatment efficacy. Costs included treatment and drug costs. Primary outcomes were incremental cost per relapse and hospitalizations avoided with REXULTI. Results of the model indicated that the use of REXULTI was a dominant strategy (e.g., less costly and more effective) compared to lurasidone for the treatment of adults with schizophrenia. In addition, per patient, REXULTI treatment resulted in fewer relapses and hospitalizations, lower total cost of treatment, and higher quality of life (as estimated by health state utilities), compared to lurasidone. Sensitivity analyses suggested that discontinuation rates due to relapse for both treatments and the daily cost of REXULTI were major drivers of the incremental cost-effectiveness ratios (ICERs).

OPEN-LABEL, EXPLORATORY STUDIES

Major Depressive Disorder (MDD): Anxiety Symptoms (Davis, 2016)

Anxiety symptoms are common in patients with MDD, and studies have shown that anxiety symptoms in patients with MDD are associated with more severe depression, poorer course, greater impairment in functioning, and worse health-related quality of life, suggesting that anxiety symptoms in MDD are an indicator for more difficult-to-treat patients. Davis et al (2016) conducted an exploratory study to examine the effects of adjunctive REXULTI in patients with MDD and anxiety symptoms with an inadequate response to current antidepressant treatment (ADT). Patients received open-label ADT + REXULTI (1 to 3 mg/day, target dose 2 mg/day) for 6 weeks. Efficacy endpoints included a change from baseline to Week 6 in Montgomery-Asberg Depression Rating Scale (MADRS), Hamilton Anxiety Rating Scale (HAM-A) total score and Kellner Symptoms Questionnaire (KSQ) anxiety subscale score. A total of 32/37 (86.5%) patients completed 6 weeks of REXULTI + ADT treatment. Improvements were observed in the mean change in MADRS total score from baseline to Week 6 in patients treated with REXULTI + ADT (least squares [LS] mean change: -19.6, P<0.0001) and in HAM-A total score (LS mean change: -17.8, P<0.0001). In addition, a reduction in the KSQ anxiety subscale score (LS mean change: -5.2, P value not reported) was also observed. Activating treatment-emergent adverse events (TEAEs) occurring in ≥5% of patients included akathisia (5.4%), restlessness (5.4%), and insomnia (5.4%). There were no discontinuations due to TEAEs.

Major Depressive Disorder (MDD): Irritability Symptoms (Fava, 2016)

Irritability and anger attacks are common in MDD, affecting about one-third to half of the patients. Irritability in MDD is associated with greater severity, earlier age at onset, higher rates of comorbid anxiety and impulse-control disorders, increased incidence of suicidality, greater chronicity, fatigue, and self-blame during episodes, and general disability. Fava et al (2016) conducted an open-label, flexible-dose, exploratory study evaluating the effect of adjunctive REXULTI on irritability symptoms in 54 adult patients with MDD. Patients with an inadequate response to their current antidepressant treatment (ADT) received adjunctive REXULTI (target dose: 3mg), in addition to their current ADT (at the same dose) for 6 weeks. REXULTI was discontinued following the 6-week treatment period, and patients continued on their current ADT for 4 weeks. Clinically relevant improvements were seen at week 6 in Sheehan Irritability Scale (SIS) total score, SIS item 1 (irritable mood) score, Kellner Symptom Questionnaire (KSQ) total, anger-hostility subscale, and IDS-C30 item 6 (irritable mood). A total of 50 (92.6%) patients completed 6 weeks of REXULTI treatment. Irritability symptoms improved at week 6 and worsened after REXULTI discontinuation as assessed at week 10. Treatment-emergent adverse events (TEAEs) occurring in ≥5% of patients included akathisia (20.4%), headache (11.1%), dry mouth (7.4%), fatigue (7.4%), increased appetite (7.4%), insomnia (7.4%), diarrhea (5.6%), dizziness (5.6%), fall (5.6%), somnolence (5.6%), and weight increased (5.6%).

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Major Depressive Disorder (MDD): Young Adults in School or Work (Weisler, 2016)
Patients with MDD experience a wide range of physical, cognitive, and emotional symptoms, which can impair multiple domains of patient functioning including their ability to function socially, maintain family relations, and perform productively in a work environment. Weisler et al (2016) conducted an open-label, flexible-dose, exploratory study evaluating the effects of REXULTI in young adults (18 to 35 years) with MDD and also in school or working. A total of 47 patients who experienced an inadequate response to current ADT received REXULTI 1-3 mg/day (target dose, 2 mg/d) adjunctive to the same stable dose of ADT for 12 weeks. Least squares (LS) mean change from baseline on the Montgomery-Asberg Depression Rating Scale (MADRS) at week 12 showed significant improvement in depressive symptoms with adjunctive REXULTI treatment (MADRS total score, -18.1 [p<0.0001]). Significant improvements were seen in functioning (work/school, social life, and home responsibilities) as evidenced by reductions from baseline in Sheehan Disability Scale Score (SDS; LS mean change -11.2 [p<0.0001]) and Work Limitations Questionnaire (WLQ; p<0.0001). Changes from baseline in additional measures supported improvements in patient functioning and depressive symptoms. The most common adverse events were headache (21.3%), weight increase (17.0%), and somnolence (17.0%); reported rates of akathisia were low (6.4%). Clinically relevant increases in weight (≥7%) occurred in 10.5% of patients.

Major Depressive Disorder (MDD): Chronobiologic Parameters of SleepSleep Disturbances (Krystal, 2016)
Sleep complaints are reported in a large percentage of patients with MDD and predicts poorer clinical outcomes. Additionally, sleep disturbance is an independent risk factor for suicidal ideation and completed suicide. Krystal et al (2016) evaluated the effects of adjunctive treatment with REXULTI in adult patients (n=44) with MDD and inadequate response to antidepressant treatment (ADT) and sleep disturbances in an exploratory, open-label, flexible-dose (1-3 mg/d), 8-week study. Polysomnography (PSG) and Consensus Sleep Diary for Morning showed improvements in sleep efficiency, total sleep time, sleep onset latency, wake-time after sleep onset and latency to persistent sleep. Additionally, insomnia severity, daytime sleepiness and morning sleepiness improved as measured by multiple sleep scales. Depressive symptoms improved, which was seen to be dependent on sleep as assessed by the Insomnia Severity Index. Treatment-emergent adverse events (TEAEs) occurring in ≥ 5% of patients included nausea (13.6%), sedation (13.6%), headache (11.4%), somnolence (9.1%), upper respiratory tract infection (9.1%), weight increased (9.1%) and fatigue (6.8%).

Schizophrenia: Early Episode (Malla, 2016)
The first 5 years following a first psychotic episode are widely recognized as the critical period for optimal long term outcomes. It has been proposed that longer durations of untreated psychosis are associated with reductions in the volume of gray matter within defined regions of the brain, leading to speculation that untreated psychosis may have a neurotoxic effect. Malla et al (2016) investigated the effects of flexibly dosed REXULTI (up to 4 mg/d) in the improvement of adult (18-35 years old; first episode ≤5 years before the time of study) outpatients with early-episode schizophrenia in an exploratory, open-label, 16-week study (n=49). The primary endpoint of mean change in PANSS Total Score from baseline to Week 16 showed significant improvement (least square mean change: -10.2, p<0.0001), which was further supported by changes in Clinical Global Impression-Severity of Illness (CGI-S) and Clinical Global Impression-Improvement (CGI-I) scores. Additionally, significant improvements were noted for social function as measured by Personal and Social Performance (PSP) and Specific Level of Functioning (SLOF) scales and for sleep as seen in the Pittsburgh Sleep Quality Index (PSQI). Treatment-emergent adverse events (TEAEs) occurring in ≥ 5% of patients included insomnia (14.3%), somnolence (8.2%), nausea (6.1%), sedation (6.1%) and weight increased (6.1%).

SAFETY (Prescribing Information)
For the complete BOXED WARNING and additional information, please refer to the FULL PRESCRIBING INFORMATION for REXULTI, which is available at www.Rexulti.com.
(1) Increased Mortality in Elderly Patients with Dementia-Related Psychosis. Elderly patients with dementia-related psychosis

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ACTION TO BE TAKEN: _____ **DATE:** __ __ - __ __ - __ __ __ __

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treated with antipsychotic drugs are at an increased risk of death. REXULTI is not approved for the treatment of patients with dementia-related psychosis; (2) Suicidal Thoughts and Behaviors. Antidepressants increased the risk of suicidal thoughts and behaviors in patients aged 24 years and younger in short- term studies. Monitor closely for clinical worsening and for emergence of suicidal thoughts and behaviors. The safety and efficacy of REXULTI have not been established in pediatric patients

DOSAGE AND ADMINISTRATION (Prescribing Information)
Adjunctive Treatment of Major Depressive Disorder: The recommended starting dosage for REXULTI as adjunctive treatment for MDD is 0.5 mg or 1 mg once daily, taken orally with or without food. Titrate to 1 mg once daily, then up to the target dosage of 2 mg once daily. Dosage increases should occur at weekly intervals based on the patient's clinical response and tolerability. The maximum recommended daily dosage is 3 mg. Periodically reassess to determine the continued need and appropriate dosage for treatment.

Treatment of Schizophrenia: The recommended starting dosage for REXULTI in schizophrenia 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. 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. Periodically reassess to determine the continued need and appropriate dosage for treatment.

References:

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HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use REXULTI® safely and effectively. See full prescribing information for REXULTI.

REXULTI® (brexpiprazole) tablets, for oral use
Initial U.S. Approval: 2015

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

See full prescribing information for complete boxed warning.

- **Elderly patients with dementia-related psychosis treated with antipsychotic drugs are at increased risk of death. REXULTI is not approved for the treatment of patients with dementia-related psychosis (5.1).**
- **Antidepressants increase the risk of suicidal thoughts and behaviors in patients aged 24 years and younger. Monitor for clinical worsening and emergence of suicidal thoughts and behaviors (5.2).**
- **Safety and effectiveness of REXULTI have not been established in pediatric patients (8.4).**

INDICATIONS AND USAGE

REXULTI is an atypical antipsychotic indicated for:

- Use as an adjunctive therapy to antidepressants for the treatment of major depressive disorder (MDD) (1,14.1)
- Treatment of schizophrenia (1,14.2)

DOSAGE AND ADMINISTRATION

- Administer REXULTI once daily with or without food (2.1, 2.2, 12.3)

Indication	Starting Dose	Recommended Dose	Maximum Dose
MDD (2.1)	0.5 mg/day or 1 mg/day	2 mg/day	3 mg/day
Schizophrenia (2.2)	1 mg/day	2 to 4 mg/day	4 mg/day

- *Moderate to Severe Hepatic Impairment (Child-Pugh score ≥7):* Maximum recommended dosage is 2 mg once daily for patients with MDD and 3 mg once daily for patients with schizophrenia (2.3)
- *Moderate, Severe or End-Stage Renal Impairment (CLcr<60 mL/minute):* Maximum recommended dosage is 2 mg once daily for patients with MDD and 3 mg once daily for patients with schizophrenia (2.4)
- *Known CYP2D6 Poor Metabolizers:* Reduce the usual dosage by half (2.5)

DOSAGE FORMS AND STRENGTHS

Tablets: 0.25 mg, 0.5 mg, 1 mg, 2 mg, 3 mg, and 4 mg (3)

CONTRAINDICATIONS

Known hypersensitivity to REXULTI or any of its components (4)

WARNINGS AND PRECAUTIONS

- *Cerebrovascular Adverse Reactions in Elderly Patients with Dementia-Related Psychosis:* Increased incidence of cerebrovascular adverse reactions (e.g. stroke, transient ischemic attack) (5.3)
- *Neuroleptic Malignant Syndrome:* Manage with immediate discontinuation and close monitoring (5.4)
- *Tardive Dyskinesia:* Discontinue if clinically appropriate (5.5)
- *Metabolic Changes:* Monitor for hyperglycemia/diabetes mellitus, dyslipidemia and weight gain (5.6)
- *Leukopenia, Neutropenia, and Agranulocytosis:* Perform complete blood counts (CBC) in patients with pre-existing low white blood cell count (WBC) or history of leukopenia or neutropenia. Consider discontinuing REXULTI if a clinically significant decline in WBC occurs in absence of other causative factors (5.7)
- *Orthostatic Hypotension and Syncope:* Monitor heart rate and blood pressure and warn patients with known cardiovascular or cerebrovascular disease, and risk of dehydration or syncope (5.8)
- *Seizures:* Use cautiously in patients with a history of seizures or with conditions that lower the seizure threshold (5.9)

ADVERSE REACTIONS

Most common adverse reactions were (6.1):
MDD: Weight increased and akathisia (≥5% and at least twice the rate for placebo)
Schizophrenia: Weight increased (≥4% and at least twice the rate for placebo)

To report SUSPECTED ADVERSE REACTIONS, contact Otsuka America Pharmaceutical, Inc. at 1-800-438-9927 or FDA at 1-800-FDA-1088 *(www.fda.gov/medwatch).*

DRUG INTERACTIONS

Factors	*Dosage Adjustments for REXULTI (2.5)*
Strong CYP2D6* or CYP3A4 Inhibitors	Administer half of usual dose
Strong/moderate CYP2D6 with Strong/ moderate CYP3A4 Inhibitors	Administer a quarter of usual dose
Known CYP2D6 Poor Metabolizers taking strong/moderate CYP3A4 Inhibitors	Administer a quarter of usual dose
Strong CYP3A4 Inducers	Double the usual dose and further adjust based on clinical response

** REXULTI may be administered without dosage adjustment in patients with MDD when administered with strong CYP2D6 inhibitors (e.g., paroxetine, fluoxetine).*

USE IN SPECIFIC POPULATIONS

Pregnancy: May cause extrapyramidal and/or withdrawal symptoms in neonates with third trimester exposure (8.1)

See 17 for PATIENT COUNSELING INFORMATION and Medication Guide

Revised: 08/2016

FULL PRESCRIBING INFORMATION: CONTENTS*

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REXULTI® (brexpiprazole)

FULL PRESCRIBING INFORMATION

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

Increased Mortality in Elderly Patients with Dementia-Related Psychosis

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

Suicidal Thoughts and Behaviors

Antidepressants increased the risk of suicidal thoughts and behaviors in patients aged 24 years and younger in short-term studies. Monitor closely for clinical worsening and for emergence of suicidal thoughts and behaviors. The safety and efficacy of REXULTI have not been established in pediatric patients *[see Warnings and Precautions (5.2), Use in Specific Populations (8.4)]*.

1 INDICATIONS AND USAGE

REXULTI is indicated for:

- Adjunctive treatment of major depressive disorder (MDD) *[see Clinical Studies (14.1)]*.
- Treatment of schizophrenia *[see Clinical Studies (14.2)]*.

2 DOSAGE AND ADMINISTRATION

2.1 Adjunctive Treatment of Major Depressive Disorder

The recommended starting dosage for REXULTI as adjunctive treatment is 0.5 mg or 1 mg once daily, taken orally with or without food *[see Clinical Pharmacology (12.3)]*.

Titrate to 1 mg once daily, then up to the target dosage of 2 mg once daily. Dosage increases should occur at weekly intervals based on the patient's clinical response and tolerability. The maximum recommended daily dosage is 3 mg. Periodically reassess to determine the continued need and appropriate dosage for treatment.

2.2 Treatment of Schizophrenia

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

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

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

2.4 Dosage Adjustments for Renal Impairment

For patients with moderate, severe or end-stage renal impairment (creatinine clearance Cl_{cr}<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 *[see Use in Specific Populations (8.6), Clinical Pharmacology (12.3)]*.

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

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

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

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

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

3 DOSAGE FORMS AND STRENGTHS

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

Table 2: REXULTI Tablet Strengths and Identifying Features

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

4 CONTRAINDICATIONS

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

5 WARNINGS AND PRECAUTIONS

5.1 Increased Mortality in Elderly Patients with Dementia-Related Psychosis

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

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

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

In pooled analyses of placebo-controlled trials of antidepressant drugs (SSRIs and other antidepressant classes) that included approximately 77,000 adult patients, and over 4,400 pediatric patients, the incidence of suicidal thoughts and behaviors in patients 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 behaviors per 1000 patients treated are provided in Table 3.

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

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

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

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

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

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

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

5.4 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.

Clinical manifestations of NMS are hyperpyrexia, muscle rigidity, altered mental status and evidence of autonomic instability. Additional signs may include elevated creatinine phosphokinase, myoglobinuria (rhabdomyolysis), and acute renal failure.

If NMS is suspected, immediately discontinue REXULTI and provide intensive symptomatic treatment and monitoring.

5.5 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.

5.6 Metabolic Changes

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

Hyperglycemia and Diabetes Mellitus

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

Major Depressive Disorder

In the 6-week, placebo-controlled, fixed-dose clinical trials in 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 patients with normal baseline fasting glucose experienced a shift to high while taking REXULTI+Antidepressant (ADT); 25% of subjects with borderline fasting glucose experienced shifts to high. Combined, 9% of subjects with normal or borderline fasting glucose experienced shifts to high fasting glucose during the long-term depression studies.

Schizophrenia

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

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

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 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			
	Placebo	**1 mg/day**	**2 mg/day**	**3 mg/day**
Triglycerides				
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 subjects who had a measurement at baseline and at least one post-baseline result.
n=the number of subjects with shift.

In the long-term, open-label 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 subjects with normal or borderline fasting triglycerides experienced shifts to very high fasting triglycerides during the long-term depression studies.

Schizophrenia

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

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

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 n=407	1 mg/day n=225	2 mg/day n=187	3 mg/day 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% (8/407)*	5% (11/225)*	5% (9/187)*	2% (5/228)*

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

In the long-term, open-label 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

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 patients with schizophrenia.

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

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

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

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

5.7 Leukopenia, Neutropenia, and Agranulocytosis

Leukopenia and neutropenia have been reported during treatment with antipsychotic agents. Agranulocytosis (including fatal cases) has been reported with other agents in this class.

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

Monitor patients with clinically significant neutropenia for fever or other symptoms or signs of infection and treat promptly if such symptoms or signs occur. Discontinue REXULTI in patients with absolute neutrophil count <1000/mm^3 and follow their WBC until recovery.

5.8 Orthostatic Hypotension and Syncope

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

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

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

5.9 Seizures

Like other antipsychotic drugs, REXULTI may cause seizures. This risk is greatest in patients with a history of seizures or with conditions that lower the seizure threshold. Conditions that lower the seizure threshold may be more prevalent in older patients.

5.10 Body Temperature Dysregulation

Atypical antipsychotics may disrupt the body's ability to reduce core body temperature. Strenuous exercise, exposure to extreme heat, dehydration, and anticholinergic medications may contribute to an elevation in core body temperature; use REXULTI with caution in patients who may experience these conditions.

5.11 Dysphagia

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

5.12 Potential for Cognitive and Motor Impairment

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

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

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

6 ADVERSE REACTIONS

The following adverse reactions are discussed in more detail in other sections of the labeling:

- Increased Mortality in Elderly Patients with Dementia-Related Psychosis *[see Boxed Warning, Warnings and Precautions (5.1)]*
- Suicidal Thoughts and Behaviors in Adolescents and Young Adults *[see Boxed Warning, Warnings and Precautions (5.2)]*

REXULTI® (brexpiprazole)

- Cerebrovascular Adverse Reactions Including Stroke in Elderly Patients with Dementia-Related Psychosis *[see Warnings and Precautions (5.3)]*
- Neuroleptic Malignant Syndrome (NMS) *[see Warnings and Precautions (5.4)]*
- Tardive Dyskinesia *[see Warnings and Precautions (5.5)]*
- Metabolic Changes *[see Warnings and Precautions (5.6)]*
- Leukopenia, Neutropenia, and Agranulocytosis *[see Warnings and Precautions (5.7)]*
- Orthostatic Hypotension and Syncope *[see Warnings and Precautions (5.8)]*
- Seizures *[see Warnings and Precautions (5.9)]*
- Body Temperature Dysregulation *[see Warnings and Precautions (5.10)]*
- Dysphagia *[see Warnings and Precautions (5.11)]*
- Potential for Cognitive and Motor Impairment *[see Warnings and Precautions (5.12)]*

6.1 Clinical Trials Experience

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

Major Depressive Disorder

The safety of REXULTI was evaluated 1,054 patients (18 to 65 years of age) diagnosed with MDD who participated in two 6-week, placebo-controlled, fixed-dose clinical trials in patients with major depressive disorder in which REXULTI was administered at doses of 1 mg to 3 mg daily as adjunctive treatment to continued antidepressant therapy; patients in the placebo group continued to receive antidepressant therapy *[see Clinical Studies (14.1)]*.

Adverse Reactions Reported as Reasons for Discontinuation of Treatment

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

Common Adverse Reactions

Adverse reactions associated with the adjunctive use of REXULTI (incidence of 2% or greater and adjunctive REXULTI incidence greater than adjunctive placebo) that occurred during acute therapy (up to 6-weeks in patients with MDD) are shown in Table 8.

Table 8: Adverse Reactions in Pooled 6-Week, Placebo-Controlled, Fixed-Dose MDD Trials (Studies 1 and 2)*

	Placebo (N=411)	REXULTI			
		1 mg/day (N=226)	2 mg/day (N=188)	3 mg/day (N=228)	All REXULTI (N=643)
Gastrointestinal Disorders					
Constipation	1%	3%	2%	1%	2%
General Disorders and Administration Site Conditions					
Fatigue	2%	3%	2%	5%	3%
Infections and Infestations					
Nasopharyngitis	2%	7%	1%	3%	4%
Investigations					
Weight Increased	2%	7%	8%	6%	7%
Blood Cortisol Decreased	1%	4%	0%	3%	2%
Metabolism and Nutrition					
Increased Appetite	2%	3%	3%	2%	3%
Nervous System Disorders					
Akathisia	2%	4%	7%	14%	9%
Headache	6%	9%	4%	6%	7%
Somnolence	0.5%	4%	4%	6%	5%
Tremor	2%	4%	2%	5%	4%
Dizziness	1%	1%	5%	2%	3%
Psychiatric Disorders					
Anxiety	1%	2%	4%	4%	3%
Restlessness	0%	2%	3%	4%	3%

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

Dose-Related Adverse Reactions in the MDD trials

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

Schizophrenia

The safety of REXULTI was evaluated in 652 patients (18 to 65 years of age) diagnosed with schizophrenia who participated in two 6-week, placebo-controlled, fixed-dose clinical trials in which REXULTI was administered at daily doses of 1 mg, 2 mg and 4 mg *[see Clinical Studies (14.2)]*.

Common Adverse Reactions

Adverse reactions associated with REXULTI (incidence of 2% or greater and REXULTI incidence greater than placebo) during short-term (up to 6-weeks) trials in patients with schizophrenia are shown in Table 9.

Table 9: Adverse Reactions in Pooled 6-Week, Placebo-Controlled, Fixed-Dose Schizophrenia Trials (Studies 3 and 4)*

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

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

Extrapyramidal Symptoms

Major Depressive Disorder

The incidence of reported EPS-related adverse reactions, excluding akathisia, was 6% for REXULTI+ADT-treated patients versus 3% for placebo+ADT-treated patients. The incidence of akathisia events for REXULTI+ADT-treated patients was 9% versus 2% for placebo+ADT-treated patients.

In the 6-week, placebo-controlled MDD studies, data was objectively collected on the Simpson Angus Rating Scale (SAS) for extrapyramidal symptoms (EPS), the Barnes Akathisia Rating Scale (BARS) for akathisia and the Abnormal Involuntary Movement Score (AIMS) for dyskinesia. The mean change from baseline at last visit for REXULTI+ADT-treated patients for the SAS, BARS and AIMS was comparable to placebo treated patients. The percentage of patients who shifted from normal to abnormal was greater in REXULTI+ADT-treated patients versus placebo+ADT for the BARS (4% versus 0.6%) and the SAS (4% versus 3%).

Schizophrenia

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

In the 6-week, placebo-controlled, fixed-dose schizophrenia studies, data was objectively collected on the Simpson Angus Rating Scale (SAS) for extrapyramidal symptoms (EPS), the Barnes Akathisia Rating Scale (BARS) for akathisia and the Abnormal Involuntary Movement Scale (AIMS) for dyskinesia. The mean change from baseline at last visit for REXULTI-treated patients for the SAS, BARS and AIMS was comparable to placebo-treated patients. The percentage of patients who shifted from normal to abnormal was greater in REXULTI-treated patients versus placebo for the BARS (2% versus 1%) and the SAS (7% versus 5%).

Dystonia

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

Other Adverse Reactions Observed During the Premarketing Evaluation of REXULTI

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

Eye Disorders: Vision Blurred

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

Infections and Infestations: Urinary Tract Infection

Investigations: Blood Prolactin Increased

Musculoskeletal and Connective Tissue Disorders: Myalgia

Psychiatric Disorders: Abnormal Dreams, Insomnia

Skin and Subcutaneous Tissue Disorders: Hyperhidrosis

7 DRUG INTERACTIONS

7.1 Drugs Having Clinically Important Interactions with REXULTI

Table 10: Clinically Important Drug Interactions with REXULTI

Strong CYP3A4 Inhibitors	
Clinical Impact:	Concomitant use of REXULTI with strong CYP3A4 inhibitors increased the exposure of brexpiprazole compared to the use of REXULTI alone *[see Clinical Pharmacology (12.3)]*
Intervention:	With concomitant use of REXULTI with a strong CYP3A4 inhibitor, reduce the REXULTI dosage *[see Dosage and Administration (2.5)]*
Examples:	itraconazole, clarithromycin, ketoconazole
Strong CYP2D6 Inhibitors*	
Clinical Impact:	Concomitant use of REXULTI with strong CYP2D6 inhibitors increased the exposure of brexpiprazole compared to the use of REXULTI alone *[see Clinical Pharmacology (12.3)]*
Intervention:	With concomitant use of REXULTI with a strong CYP2D6 inhibitor, reduce the REXULTI dosage *[see Dosage and Administration (2.5)]*
Examples:	paroxetine, fluoxetine, quinidine
Both CYP3A4 Inhibitors and CYP2D6 Inhibitors	
Clinical Impact:	Concomitant use of REXULTI with 1) a strong CYP3A4 inhibitor and a strong CYP2D6 inhibitor; or 2) a moderate CYP3A4 inhibitor and a strong CYP2D6 inhibitor; or 3) a strong CYP3A4 inhibitor and a moderate CYP2D6 inhibitor; or 4) a moderate CYP3A4 inhibitor and a moderate CYP2D6 inhibitor, increased the exposure of brexpiprazole compared to the use of REXULTI alone *[see Clinical Pharmacology (12.3)]*
Intervention:	With concomitant use of REXULTI with 1) a strong CYP3A4 inhibitor and a strong CYP2D6 inhibitor; or 2) a moderate CYP3A4 inhibitor and a strong CYP2D6 inhibitor; or 3) a strong CYP3A4 inhibitor and a moderate CYP2D6 inhibitor; or 4) a moderate CYP3A4 inhibitor and a moderate CYP2D6 inhibitor, decrease the REXULTI dosage *[see Dosage and Administration (2.5)]*
Examples:	1) itraconazole + quinidine 2) fluconazole + paroxetine 3) itraconazole + duloxetine 4) fluconazole + duloxetine
Strong CYP3A4 Inducers	
Clinical Impact:	Concomitant use of REXULTI and a strong CYP3A4 inducer decreased the exposure of brexpiprazole compared to the use of REXULTI alone *[see Clinical Pharmacology (12.3)]*
Intervention:	With concomitant use of REXULTI with a strong CYP3A4 inducer, increase the REXULTI dosage *[see Dosage and Administration (2.5)]*
Examples:	rifampin, St. John's wort

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

7.2 Drugs Having No Clinically Important Interactions with REXULTI

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

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Exposure Registry

There is a pregnancy exposure registry that monitors pregnancy outcomes in women exposed to REXULTI during pregnancy. For more information contact the National Pregnancy Registry for Atypical Antipsychotics at 1-866-961-2388 or visit http://womensmentalhealth.org/clinical-and-research-programs/pregnancyregistry/.

Risk Summary

Adequate and well-controlled studies have not been conducted with REXULTI in pregnant women to inform drug-associated risks. However, neonates whose mothers are exposed to antipsychotic drugs, like REXULTI, during the third trimester of pregnancy are at risk for extrapyramidal and/or withdrawal symptoms. In animal reproduction studies, no teratogenicity was observed with oral administration of brexpiprazole to pregnant rats and rabbits during organogenesis at doses up to 73 and 146 times, respectively, of maximum recommended human dose (MRHD) of 4 mg/day on a mg/m² basis. However, when pregnant rats were administered brexpiprazole during the period of organogenesis through lactation, the number of perinatal deaths of pups was increased at 73 times the MRHD *[see Data]*. The background risk of major birth defects and miscarriage for the indicated population(s) is unknown. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2-4% and 15-20%, respectively.

Clinical Considerations

Fetal/Neonatal Adverse Reactions

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

Data

Animal Data

Pregnant rats were treated with oral doses of 3, 10, and 30 mg/kg/day (7.3, 24, and 73 times the MRHD on a mg/m² basis) of brexpiprazole during the period of organogenesis. Brexpiprazole was not teratogenic and did not cause adverse developmental effects at doses up to 73 times the MRHD.

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

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

8.2 Lactation

Risk Summary

Lactation studies have not been conducted to assess the presence of brexpiprazole in human milk, the effects of brexpiprazole on the breastfed infant, or the effects of brexpiprazole on milk production. Brexpiprazole is present in rat milk. The development and health benefits of breastfeeding should be considered along with the mother's clinical need for REXULTI and any potential adverse effects on the breastfed infant from REXULTI or from the underlying maternal condition.

8.4 Pediatric Use

Safety and effectiveness in pediatric patients have not been established. Antidepressants increased the risk of suicidal thoughts and behaviors in pediatric patients *[see Boxed Warning, Warnings and Precautions (5.2)]*.

8.5 Geriatric Use

Clinical studies of the efficacy of REXULTI did not include any patients aged 65 or older to determine whether they respond differently from younger patients. 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.

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 subjects (70 to 85 years old, N=11) with MDD were comparable to those observed in adults subjects 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 *[see Boxed Warning, Warnings and Precautions (5.1)]*.

8.6 CYP2D6 Poor Metabolizers

Dosage adjustment is recommended in known CYP2D6 poor metabolizers, because these patients have higher brexpiprazole concentrations than normal metabolizers of CYP2D6. Approximately 8% of Caucasians and 3–8% of Black/African Americans cannot metabolize CYP2D6 substrates and are classified as poor metabolizers (PM) *[see Dosage and Administration (2.5), Clinical Pharmacology (12.3)]*.

8.7 Hepatic Impairment

Reduce the maximum recommended dosage in patients with moderate to severe hepatic impairment (Child-Pugh score ≥7). Patients with moderate to severe hepatic impairment (Child-Pugh score ≥7) generally had higher exposure to brexpiprazole than patients with normal hepatic function *[see Clinical Pharmacology (12.3)]*. Greater exposure may increase the risk of REXULTI-associated adverse reactions *[see Dosage and Administration (2.3)]*.

8.8 Renal Impairment

Reduce the maximum recommended dosage in patients with moderate, severe, or end-stage renal impairment (CLcr<60 mL/minute). Patients with impaired renal function (CLcr<60 mL/minute) had higher exposure to brexpiprazole than patients with normal renal function *[see Clinical Pharmacology (12.3)]*. Greater exposure may increase the risk of REXULTI-associated adverse reactions *[see Dosage and Administration (2.4)]*.

8.9 Other Specific Populations

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

9 DRUG ABUSE AND DEPENDENCE

9.1 Controlled Substance

REXULTI is not a controlled substance.

9.2 Abuse

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

9.3 Dependence

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

10 OVERDOSAGE

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

Consult a Certified Poison Control Center **(1-800-222-1222 or www.poison.org)** for up-to-date guidance and advice regarding a REXULTI overdosage. Management of overdose should concentrate on supportive therapy, maintaining an adequate airway, oxygenation and ventilation, and management of symptoms. Close medical supervision and monitoring should continue until the patient recovers.

Charcoal

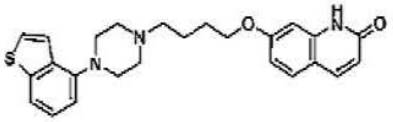
Oral activated charcoal and sorbitol (50 g/240 mL), administered one hour after ingesting oral brexpiprazole, decreased brexpiprazole C_{max} and area under the curve (AUC) by approximately 5% to 23% and 31% to 39% respectively; however, there is insufficient information available on the therapeutic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

Hemodialysis

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

11 DESCRIPTION

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



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

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

The mechanism of action of brexpiprazole in the treatment of 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.

12.2 Pharmacodynamics

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

Cardiac Electrophysiology

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

12.3 Pharmacokinetics

Absorption

After single dose administration of REXULTI tablets, the peak plasma brexpiprazole concentrations occurred within 4 hours after administration; and the absolute oral bioavailability was 95%. Brexpiprazole steady-state concentrations were attained within 10-12 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 MDR1 (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

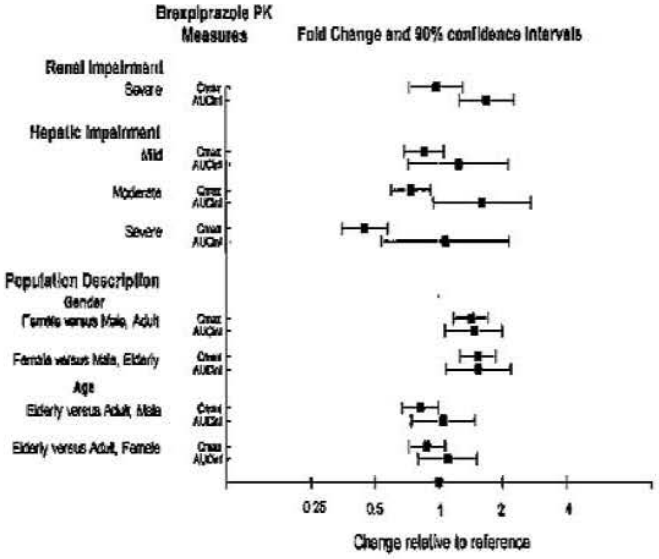
Following a single oral dose of [^{14}C]-labeled brexpiprazole, approximately 25% and 46% of the administered radioactivity was recovered in the urine and feces, respectively. Less than 1% of unchanged brexpiprazole was excreted in the urine and approximately 14% of the oral dose was recovered unchanged 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.

REXULTI® (brexpiprazole)

Studies in Specific Populations

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

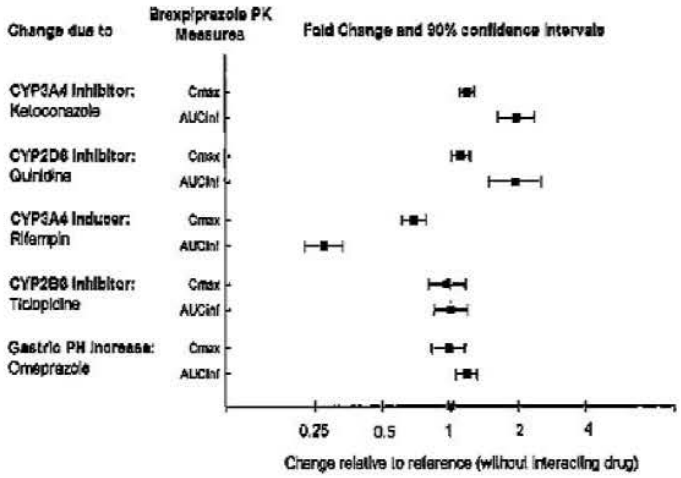
Figure 1: Effects of Intrinsic Factors on Brexpiprazole Pharmacokinetics



Drug Interaction Studies

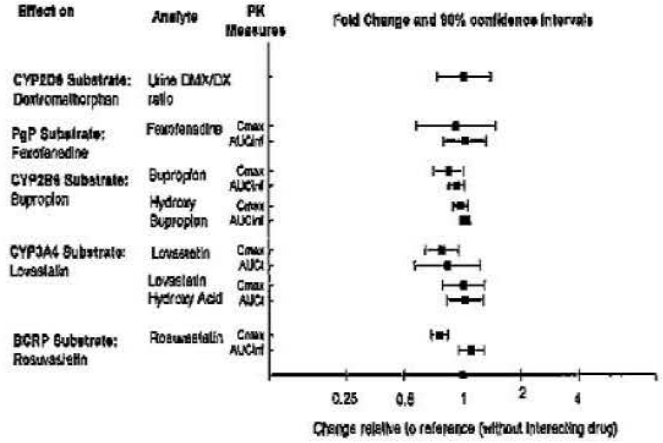
Effects of other drugs on the exposures of brexpiprazole are summarized in Figure 2. Based on simulation, a 5.1-fold increase in AUC values at steady-state is expected when extensive metabolizers of CYP2D6 are administered with both strong CYP2D6 and CYP3A4 inhibitors. A 4.8-fold increase in mean AUC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

Figure 2: The Effects of Other Drugs on Brexpiprazole Pharmacokinetics



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

Figure 3: The Effects of REXULTI on Pharmacokinetics of Other Drugs



13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenesis

Lifetime carcinogenicity studies were conducted in ICR mice and SD rats. Brexpiprazole was administered orally for two years to male and female mice at doses of 0.75, 2 and 5 mg/kg/day (0.9 to 6.1 times the oral MRHD of 4 mg/day based on mg/m² body surface area) and to male and female rats at doses of 1, 3, and 10 mg/kg and 3, 10, and 30 mg/kg/day, respectively (2.4 to 24 and 7.3 to 73 times the oral MRHD, males and females). In female mice, the incidence of mammary gland adenocarcinoma was increased at all doses and the incidence of adenosquamous carcinoma was increased at 2.4 and 6.1 times the MRHD. No increase in the incidence of tumors was observed in male mice. In the rat study, brexpiprazole was not carcinogenic in either sex at doses up to 73 times the MRHD.

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

Mutagenesis

Brexpiprazole was not mutagenic when tested in the *in vitro* bacterial reverse mutation assay (Ames test). Brexpiprazole was negative for clastogenic activity in the *in vivo* micronucleus assay in rats, and was not genotoxic in the *in vivo/in vitro* unscheduled DNA synthesis assay in rats. *In vitro* with mammalian cells brexpiprazole was clastogenic but only at doses that induced cytotoxicity. Based on a weight of evidence, brexpiprazole is not considered to present a genotoxic risk to humans.

Impairment of Fertility

Female rats were treated with oral doses of 0.3, 3 or 30 mg/kg/day (0.7, 7.3, and 73 times the oral MRHD on a mg/m² basis) prior to mating with untreated males and continuing through conception and implantation. Estrus cycle irregularities and decreased fertility were observed at 3 and 30 mg/kg/day. Prolonged duration of pairing and increased preimplantation losses were observed at 30 mg/kg/day.

Male rats were treated with oral doses of 3, 10, or 100 mg/kg/day (7.3, 24 and 240 times the oral MRHD on a mg/m² basis) for 63 days prior to mating with untreated females and throughout the 14 days of mating. No differences were observed in the duration of mating or fertility indices in males at any dose of brexpiprazole.

14 CLINICAL STUDIES

14.1 Adjunctive Treatment of Major Depressive Disorder

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

Patients in Study 228 (hereafter "Study 1") were randomized to REXULTI 2 mg once a day or placebo. Patients in Study 227 (hereafter "Study 2") were randomized to REXULTI 1 or 3 mg once a day or placebo. For patients randomized to REXULTI, all patients initiated treatment at 0.5 mg once daily during Week 1. At Week 2, the REXULTI dosage was increased to 1 mg in all treatment groups, and either maintained at 1 mg or increased to 2 mg or 3 mg once daily, based on treatment assignment, from Week 3 onwards. The dosages were then maintained for the 4 remaining weeks.

REXULTI® (brexpiprazole)

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

At randomization, the mean MADRS total score was 27. In Studies 1 and 2, REXULTI [+ antidepressant (ADT)] 2 mg/day and 3 mg/day were superior to placebo + ADT in reducing mean MADRS total scores. Results from the primary efficacy parameters for both fixed dose trials are shown below in Table 11. Figure 4 below shows the time course of response based on the primary efficacy measure (MADRS) in Study 1.

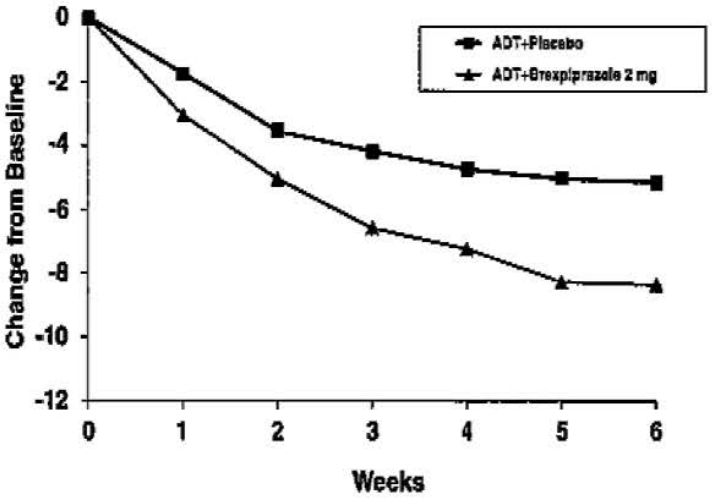
Table 11: Summary of Efficacy Results for Studies 1 and 2 for the Adjunctive Treatment of MDD

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

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

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

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



14.2 Schizophrenia

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

In both studies, Study 231 (hereafter "Study 3") and Study 230 (hereafter "Study 4"), patients were randomized to REXULTI 2 or 4 mg once per day or placebo. Patients in the REXULTI groups initiated treatment at 1 mg once daily on Days 1 to 4. The REXULTI dosage was increased to 2 mg on Days 5 to 7. The dosage was then either maintained at 2 mg once daily or increased to 4 mg once daily, depending on treatment assignment, for the 5 remaining weeks.

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

In Study 3, REXULTI at both 2 mg/day and 4 mg/day was superior to placebo on the PANSS total score. In Study 4, REXULTI 4 mg/day was superior to placebo on the PANSS total score (Table 12). Figure 5 shows the time course of response based on the primary efficacy measure (change from baseline in PANSS total score) in Study 3.

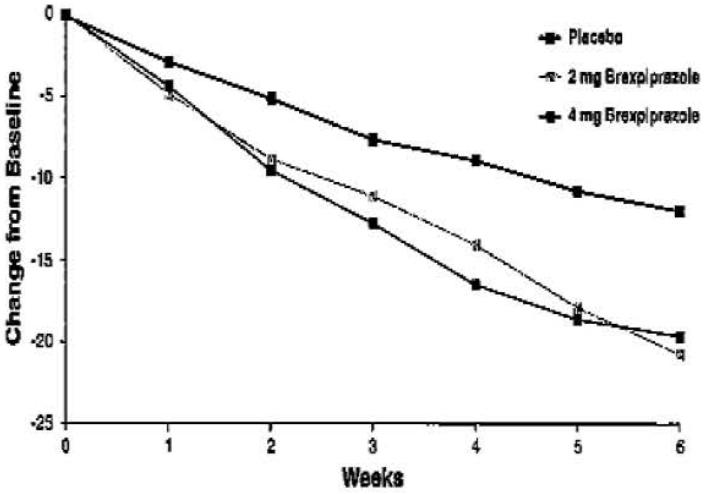
Examination of population subgroups based on age, gender and race did not suggest differential responsiveness.

Table 12: Summary of Efficacy Results for Studies in Schizophrenia

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

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

Figure 5: Change from Baseline in PANSS Total Score by Study Visit (Week) in Patients with Schizophrenia in Study 3



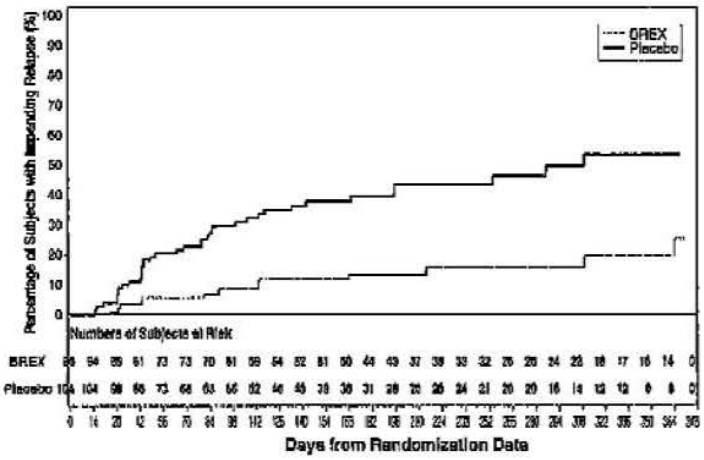
The safety and efficacy of REXULTI as maintenance treatment in adults with schizophrenia aged 18 to 65 years were demonstrated in the maintenance phase of a randomized withdrawal trial (Study 331-10-232, hereafter "Study 5"). Patients were stabilized for at least 12 weeks on 1 to 4 mg/day of REXULTI (N=202). They were then randomized in the double-blind treatment phase to either continue REXULTI at their achieved stable dose (N=97), or to switch to placebo (N=105).

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

REXULTI® (brexpiprazole)

A pre-specified interim analysis demonstrated a statistically significantly longer time to relapse in patients randomized to the REXULTI group compared to placebo-treated patients. The trial was subsequently terminated early because maintenance of efficacy had been demonstrated. The Kaplan-Meier curves of the cumulative proportion of patients with relapse during the double-blind treatment phase for REXULTI and placebo groups are shown in Figure 6. The key secondary endpoint, the proportion of subjects who met the criteria for impending relapse, was statistically significantly lower in REXULTI-treated patients compared with placebo group.

Figure 6: Kaplan Meier Estimation of Percent Impending Relapse in Study 5



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

16 HOW SUPPLIED/STORAGE AND HANDLING

16.1 How Supplied

REXULTI (brexpiprazole) tablets have markings on one side, and are available in the following strengths and package configurations (see Table 13):

Table 13: Package Configuration for REXULTI Tablets

Tablet Strength	Tablet Color/Shape	Tablet Markings	Pack Size	NDC Code
0.25 mg	light brown round, shallow convex; bevel-edged	"BRX" and "0.25"	Bottle of 30	59148-035-13
0.5 mg	light orange round, shallow convex; bevel-edged	"BRX" and "0.5"	Bottle of 30	59148-036-13
1 mg	light yellow round, shallow convex; bevel-edged	"BRX" and "1"	Bottle of 30	59148-037-13
2 mg	light green round, shallow convex; bevel-edged	"BRX" and "2"	Bottle of 30	59148-038-13
3 mg	light purple round, shallow convex; bevel-edged	"BRX" and "3"	Bottle of 30	59148-039-13
4 mg	white round, shallow convex; bevel-edged	"BRX" and "4"	Bottle of 30	59148-040-13

16.2 Storage

Store REXULTI tablets at 20°C to 25°C (68°F to 77°F); excursions permitted to 15°C to 30°C (59°F to 86°F) *[see USP Controlled Room Temperature]*.

17 PATIENT COUNSELING INFORMATION

Advise the patient or caregiver to read the FDA-approved patient labeling (Medication Guide).

Suicidal Thoughts and Behaviors

Advise patients and caregivers to look for the emergence of suicidality, especially early during treatment and when the dosage is adjusted up or down and instruct them to report such symptoms to the healthcare provider *[see Box Warning, Warnings and Precautions (5.2)]*.

Dosage and Administration

Advise patients that REXULTI can be taken with or without food. Advise patients regarding importance of following dosage escalation instructions *[see Dosage and Administration (2.1), (2.2)]*.

Neuroleptic Malignant Syndrome (NMS)

Counsel patients about a potentially fatal adverse reaction – Neuroleptic Malignant Syndrome (NMS) that has been reported in association with administration of antipsychotic drugs. Advise patients to contact a health care provider or report to the emergency room if they experience signs or symptoms of NMS *[see Warnings and Precautions (5.4)]*.

Tardive Dyskinesia

Counsel patients on the signs and symptoms of tardive dyskinesia and to contact their health care provider if these abnormal movements occur *[see Warnings and Precautions (5.5)]*.

Metabolic Changes

Educate patients about the risk of metabolic changes, how to recognize symptoms of hyperglycemia and diabetes mellitus, and the need for specific monitoring, including blood glucose, lipids, and weight *[see Warnings and Precautions (5.6)]*.

Leukopenia, Neutropenia and Agranulocytosis

Advise patients with a pre-existing low WBC or a history of drug induced leukopenia/neutropenia that they should have their CBC monitored while taking REXULTI *[see Warnings and Precautions (5.7)]*.

Orthostatic Hypotension and Syncope

Educate patients about the risk of orthostatic hypotension and syncope especially early in treatment, and also at times of re-initiating treatment or increases in dosage *[see Warnings and Precautions (5.8)]*.

Heat Exposure and Dehydration

Counsel patients regarding appropriate care in avoiding overheating and dehydration *[see Warnings and Precautions (5.10)]*.

Interference with Cognitive and Motor Performance

Caution patients about performing activities requiring mental alertness, such as operating hazardous machinery or operating a motor vehicle, until they are reasonably certain that REXULTI therapy does not adversely affect their ability to engage in such activities *[see Warnings and Precautions (5.12)]*.

Concomitant Medications

Advise patients to inform their health care providers of any changes to their current prescription or over-the-counter medications because there is a potential for clinically significant interactions *[see Drug Interactions (7.1)]*.

Pregnancy

Advise patients that third trimester use of REXULTI may cause extrapyramidal and/or withdrawal symptoms in a neonate and to notify their healthcare provider with a known or suspected pregnancy. Advise patients that there is a pregnancy exposure registry that monitors pregnancy outcomes in women exposed to REXULTI during pregnancy *[see Use in Specific Populations (8.1)]*.

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

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MEDICATION GUIDE
REXULTI® (REX-ul-TE)
(brexpiprazole)
Tablets

What is the most important information I should know about REXULTI?

REXULTI may cause serious side effects, including:

- **Increased risk of death in elderly people with dementia-related psychosis.** Medicines like REXULTI can raise the risk of death in elderly who have lost touch with reality (psychosis) due to confusion and memory loss (dementia). REXULTI is not approved for the treatment of patients with dementia-related psychosis.
- **Risk of suicidal thoughts or actions.** Antidepressant medicines, depression and other serious mental illnesses, may cause suicidal thoughts or actions. REXULTI is not approved for the treatment of people younger than 18 years of age.
  - **Antidepressant medicines may increase suicidal thoughts or actions in some children, teenagers, or young adults within the first few months of treatment.**
  - **Depression and other serious mental illnesses are the most important causes of suicidal thoughts or actions. Some people may have a particularly high risk of having suicidal thoughts or actions.** These include people who have (or have a family history of) bipolar illness (also called manic-depressive illness) or suicidal thoughts or actions.
  - **How can I watch for and try to prevent suicidal thoughts and actions in myself or a family member?**
    - Pay close attention to any changes, especially sudden changes, in mood, behaviors, thoughts, or feelings. This is very important when an antidepressant medicine is started or when the dose is changed.
    - Call the healthcare provider right away to report new or sudden changes in mood, behavior, thoughts, or feelings.
    - Keep all follow-up visits with the healthcare provider as scheduled. Call the healthcare provider between visits as needed, especially if you have concerns about symptoms.

Call a healthcare provider right away if you or your family member has any of the following symptoms, especially if they are new, worse, or worry you:

- thoughts about suicide or dying
- new or worsening depression
- feeling very agitated or restless
- panic attacks
- new or worsening irritability
- an extreme increase in activity or talking (mania)
- attempts to commit suicide
- new or worsening anxiety
- acting on dangerous impulses
- trouble sleeping (insomnia)
- acting aggressive, being angry, or violent
- other unusual changes in behavior or mood

What else do I need to know about antidepressant medicines?

- **Never stop an antidepressant medicine without first talking to your healthcare provider.** Stopping an antidepressant medicine suddenly can cause other symptoms.
- **Antidepressants are medicines used to treat depression and other illnesses.** It is important to discuss all the risks of treating depression and also the risks of not treating it. Patients and their families or other caregivers should discuss all treatment choices with the healthcare provider, not just the use of antidepressants.
- **Antidepressant medicines have other side effects.** Talk to the healthcare provider about the possible side effects of the medicine prescribed for you or your family member.
- **Antidepressant medicines can interact with other medicines.** Know all of the medicines that you or your family member takes. Keep a list of all medicines (including prescription medicines, non-prescription medicines, vitamins and herbal supplements) to show the healthcare provider. Do not start new medicines without first checking with your healthcare provider.

What is REXULTI?

REXULTI is a prescription medicine used to treat:

- Major depressive disorder (MDD): REXULTI is used with antidepressant medicines, when your healthcare provider determines that an antidepressant alone is not enough to treat your depression.
- Schizophrenia

It is not known if REXULTI is safe and effective in people under 18 years of age.

Who should not take REXULTI?

Do not take REXULTI if you are allergic to brexpiprazole or any of the ingredients in REXULTI. See the end of this Medication Guide for a complete list of ingredients in REXULTI.

What should I tell my healthcare provider before taking REXULTI?

Before taking REXULTI, tell your healthcare provider if you:

- have diabetes or high blood sugar or a family history of diabetes or high blood sugar. Your healthcare provider should check your blood sugar before you start REXULTI and during your treatment.
- have high levels of cholesterol, triglycerides, LDL-cholesterol, or low levels of HDL cholesterol
- have or had seizures (convulsions)
- have or had low or high blood pressure
- have or had heart problems or a stroke
- have or had a low white blood cell count
- 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, talk to your healthcare provider about registering with the National Pregnancy Registry for Atypical Antipsychotics. You can register by calling 1-866-961-2388 or visit http://womensmentalhealth.org/clinical-and-research-programs/pregnancyregistry/
- are breastfeeding or plan to breastfeed. It is not known if REXULTI passes into your breast milk. You and your healthcare provider should decide if you will take REXULTI or breastfeed.

Tell your healthcare provider about all the medicines you take or recently have taken, including prescription medicines, over-the-counter medicines, vitamins and herbal supplements.

REXULTI® (brexpiprazole)

REXULTI and other medicines may affect each other causing possible serious side effects. REXULTI may affect the way other medicines work, and other medicines may affect how REXULTI works.

Your healthcare provider can tell you if it is safe to take REXULTI with your other medicines. **Do not** start or stop any medicines while taking REXULTI without talking to your healthcare provider first.

Know the medicines you take. Keep a list of your medicines to show your healthcare provider and pharmacist when you get a new medicine.

How should I take REXULTI?

- Take REXULTI exactly as your healthcare provider tells you to take it. **Do not** change the dose or stop taking REXULTI yourself.
- REXULTI can be taken with or without food.
- 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 provider.**
- If you take too much REXULTI, call your healthcare provider or Poison Control Center at **1-800-222-1222** right away, or go to the nearest hospital emergency room.

What should I avoid while taking REXULTI?

- **Do not** drive a car, operate machinery, or do other dangerous activities until you know how REXULTI affects you. REXULTI may make you feel drowsy.
- Avoid getting over-heated or dehydrated while taking REXULTI.
  - **Do not** over-exercise.
  - Stay out of the sun. **Do not** wear too much or heavy clothing.
  - In hot weather, stay inside in a cool place if possible.
  - Drink plenty of water.

What are the possible side effects of REXULTI?

See "What is the most important information I should know about REXULTI?"

REXULTI may cause serious side effects, including:

- **Stroke in elderly people (cerebrovascular problems) that can lead to death.**
- **Neuroleptic Malignant Syndrome (NMS):** Tell your healthcare provider right away if you have **some or all** of the following symptoms: high fever, stiff muscles, confusion, sweating, changes in pulse, heart rate, and blood pressure. These may be symptoms of a rare and serious condition that can lead to death. Call your healthcare provider right away if you have any of these symptoms.
- **Uncontrolled body movements (tardive dyskinesia):** REXULTI may cause movements that you cannot control in your face, tongue or other body parts. Tardive dyskinesia may not go away, even if you stop taking REXULTI. Tardive dyskinesia may also start after you stop taking REXULTI.
- **Problems with your metabolism such as:**
  - **high blood sugar (hyperglycemia):** Increases in blood sugar can happen in some people who take REXULTI. Extremely high blood sugar can lead to coma or death. If you have diabetes or risk factors for diabetes (such as being overweight or having a family history of diabetes), your healthcare provider should check your blood sugar before you start taking REXULTI and during your treatment.

    Call your healthcare provider if you have any of these symptoms of high blood sugar while taking REXULTI:
    - feel very thirsty
    - feel very hungry
    - feel sick to your stomach
    - feel weak or tired
    - need to urinate more than usual
    - feel confused, or your breath smells fruity
  - **Increased fat levels (cholesterol and triglycerides) in your blood.**
  - **weight gain:** You and your healthcare provider should check your weight regularly.
- **Low white blood cell count**
- **Decreased blood pressure (orthostatic hypotension).** You may feel lightheaded or faint when you rise too quickly from a sitting or lying position.
- **Seizures** (convulsions)
- **Problems controlling your body temperature so that you feel too warm.** See **"What should I avoid while taking REXULTI?"**
- **Difficulty swallowing that can cause food or liquid to get into your lungs.**

The **most common side effects** of REXULTI include weight gain and an inner sense of restlessness such as feeling like you need to move.

These are not all the possible side effects of REXULTI. For more information, ask your healthcare provider or pharmacist.

Call your doctor for medical advice about side effects. **You may report side effects to FDA at 1-800-FDA-1088.**

How should I store REXULTI?

Store REXULTI at room temperature, between 68°F to 77°F (20°C to 25°C).

Keep REXULTI and all medicines out of the reach of children.

General information about the safe and effective use of REXULTI.

Medicines are sometimes prescribed for purposes other than those listed in a Medication Guide. Do not use REXULTI for a condition for which it was not prescribed. Do not give REXULTI to other people, even if they have the same symptoms you have. It may harm them.

This Medication Guide summarizes the most important information about REXULTI. If you would like more information, talk with your healthcare provider. You can ask your pharmacist or healthcare provider for information about REXULTI that is written for healthcare professionals. **For more information about REXULTI, go to [www.REXULTI.com] or call 1-800-441-6763.**

What are the ingredients in REXULTI?

Active ingredient: brexpiprazole

Inactive ingredients: lactose monohydrate, corn starch, microcrystalline cellulose, hydroxypropyl cellulose, low-substituted hydroxypropyl cellulose, magnesium stearate, hypromellose, and talc.

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