Brand Name: Rexulti®

Generic Name: Brexpiprazole

Manufacturer: Otsuka America Pharmaceuticals Inc

Drug Class: Second Generation (Atypical) Antipsychotic

Uses:

Labeled Uses[1,2,3,4]: Major depressive disorder (given In combination), Schizophrenia
Unlabeled Uses[1,2,3,4]: N/A

Mechanism of Action[1,2,3,4]: The exact mechanism of action brexpiprazole is unknown. However, it may exert its therapeutic effects through partial antagonism of serotonergic 5-HT-1A receptors and dopaminergic D2 receptors, as well as antagonism of serotonin 5-HT-2A activity. This medication is also a partial agonist of D-3 receptors and an antagonist of 1A, a1B, a1D, a2C alpha receptors, 5-HT2B, 5-HT7, histamine H-1, and muscarinic M-1 receptors.

Pharmacokinetics[1,2,3,4]:

Absorption:

Tmax	Within 4 hours
V_d	1.56 L/kg
$t_{½}$	91 hours
Clearance	19.8mL/hr/kg
Protein binding	>99%
Bioavailability	95%

Metabolism: Brexpiprazole metabolism is primarily mediated by CYP3A4 and CYP2D6. Its major metabolite, DM-3411, is inactive. At steady state, DM-3411 represents 23% to 48% of brexpiprazole exposure in plasma.

Elimination: Brexpiprazole is primarily excreted by the feces, as 46% of a single dose. It is also excreted by the urine, as 25% of a single dose.

Efficacy:

Kane JM, Skuban A, Ouyang J, Hobart M, Pfister S, McQuade RD, Nyilas M, Carson WH, Sanchez R, Eriksson H. A multicenter, randomized, double-blind, controlled phase 3 trial of fixed-dose brexpiprazole for the treatment of adults with acute schizophrenia. Schizophr Res. 2015 May;164(1-3):127-35. doi: 10.1016/j.schres.2015.01.038. Epub 2015 Feb 12.

Study Design: Randomized, double-blind, placebo-controlled phase 3 study

Description of Study: *Methods:* Six-hundred seventy-four patients with a diagnosis of schizophrenia experiencing an acute exacerbation of psychotic symptoms were randomized (2:3:3:3) into four treatment groups: 1 mg, 2 mg or 4 mg of brexpiprazole or placebo. The study consisted of a pre-treatment screening phase of ≤14 days, a 6-week double-blind treatment period, and a 30-day follow-up phase. All doses of trial medication were administered orally, once daily. The primary endpoint was change from baseline to week 6 in Positive and Negative Syndrome Scale (PANSS) Total Score. The key secondary endpoint was changed from baseline at week 6 in Clinical Global Impressions—Severity (CGI-S). Response was defined as mean reduction from baseline in PANSS total score ≥30%, or CGI-I score of 1 (very much improved) or 2 (much improved). The primary efficacy endpoint was analyzed using mixed model for repeated measures analysis. Differences between the average effect of brexpiprazole 2 and 4 mg versus placebo were tested first at a significance level of 0.05. Of the 674 and 657 patients were included in the safety and efficacy samples, respectively. *Outcome Results:* In total, 458/674 patients (68.0%) completed the study. For the primary efficacy endpoint, the average effect of brexpiprazole 2 mg and 4 mg was statistically significant compared with placebo (LS mean difference −4.78, p = 0.0093). Brexpiprazole 4 mg showed statistically significant improvement versus placebo (treatment difference: -6.47, p=0.0022) for the primary endpoint. Improvement compared with placebo was also seen for the key secondary endpoint (treatment difference: -0.38, p=0.0015), and on multiple secondary efficacy outcomes. Brexpiprazole 1 and 2mg also showed numerical improvements versus placebo, although p>0.05. The most common treatment-emergent adverse events were headache, insomnia, agitation; incidences of akathisia were lower in brexpiprazole treatment groups (4.2%-6.5%) versus placebo (7.1%).

Limitations: This study was sponsored by Otsuka Pharmaceutical Development and Commercialization, Inc., the manufacturer of brexpiprazole. One of the authors is a consultant for Otsuka Pharmaceuticals and eight of the authors are employees of this company. The medication was compared to placebo, when an active comparator medication could have provided more clear insight into the efficacy of this medication. The brexpiprazole 2 mg assignment group had a slightly higher percentage of men and lower percentage of women compared to the other treatment groups. This study only had 68% of patients complete the study: 67.5% of patients in the 1 mg treatment groups, 69.4% of patients in the 2 mg treatment group, 70.7% of patients in the 4 mg treatment group, and 64.1% of patients in the placebo group completed. The most frequent reasons for

discontinuation across treatment groups were withdrawal of consent (12.5%), lack of efficacy (9.8%) and AEs (8.5%). Patients were only followed for six-weeks.

Conclusion: Brexpiprazole 4 mg is an efficacious and well tolerated treatment for acute schizophrenia in adults. Further research is needed to establish long-term efficacy as well as comparative efficacy in regard to other atypical antipsychotics.

Correll CU, Skuban A, Ouyang J, Hobart M, Pfister S, McQuade RD, Nyilas M, Carson WH, Sanchez R, Eriksson H. Efficacy and Safety of Brexpiprazole for the Treatment of Acute Schizophrenia: A 6-Week Randomized, Double-Blind, Placebo-Controlled Trial. Am J Psychiatry. 2015 Sep 1;172(9):870-80. doi: 10.1176/appi.ajp.2015.14101275. Epub 2015 Apr 16.

Study Design: Randomized, double-blind, placebo-controlled phase 3 study

Description of Study: *Methods:* six hundred thirty-six patients with schizophrenia experiencing an acute exacerbation were randomly assigned to daily brexpiprazole at a dosage of 0.25, 2, 4 mg or placebo (1:2:2:2) for 6 weeks. The study consisted of a 14-day screening phase, a 6-week double blind treatment phase, and a 30-day follow-up phase. In the groups receiving 2 or 4 mg of brexpiprazole, dosing began at 1 mg/day and was titrated to 2 mg on day 5 and 4 mg on day 8. The primary endpoint was change at 6-weeks in Positive and Negative Syndrome Scale total score. The key secondary endpoint was change in Clinical Global Impressions Scale (CGI) severity score. The primary efficacy endpoint was analyzed using a mixed model for repeated measures. Differences between effect of 2 and 4 mg of brexpiprazole versus placebo was assessed for statistically significant (p=0.05), comparisons for each individual dosage versus placebo. *Outcome Results:* In total, 623/636 patients were included in the efficacy population. Overall, 410 patients completed the study. For the primary efficacy endpoint, the average effect of brexpiprazole 2 mg and 4 mg was statistically significant compared in PANSS score with placebo (p = 0.0001). The average effect of the 2- and 4-mg brexpiprazole dosages, compared with placebo in CGI severity score were statistically significant (p=0.0006). Treatment emergent adverse events were lower in the three brexpiprazole groups (48.9% - 56.7%) than in the placebo group (62.0%).

Limitations: There was no active comparator in this study. The brexpiprazole 0.25 mg/day treatment arm had a higher percentage of Caucasian patient participants while the 2 mg/day treatment group had a higher percentage of Asian patient participants in regard to other treatment groups. There was a high percentage of patients who did not complete this study. Only 410/636 (64.5%) of patients completed the study: 56/90 (62.2%) patients, 124/182 (68.1%) patients, and 121/180 (67.2%) patients in the 0.25-, 2-, and 4-mg brexpiprazole groups respectively, compared with 109 of 184 (59.2%) in the placebo group. The study duration only lasted for six-weeks.

Conclusion: Brexpiprazole 2 mg and 4 mg given once daily were superior compared to placebo in reducing PANSS score. This medication was well tolerated by patients and is safe for use in the treatment of acute schizophrenia. Further research is needed to establish

long-term efficacy as well as comparative efficacy in regard to other atypical antipsychotics.

Thase ME, Youakim JM, Skuban A, Hobart M, Zhang P, McQuade RD, et al. Adjunctive brexiprazole 1 and 3 mg for patients with major depressive disorder following inadequate response to antidepressants. J Clin Psychiatry. 2015 Sep; 76(9):1232-40.

Study Design: Randomized, double-blind, placebo-controlled phase 3 study

Description of Study: *Methods:* Six-hundred seventy-seven patients who were still depressed despite 1 -3 antidepressant options were randomized (1:1:1) to three treatment groups, either: brexpiprazole 1 mg, 3 mg, or placebo for six weeks adjunctive antidepressant therapy. The dose was titrated over two to three weeks. The study consisted of a pre-treatment screening phase of an 8-week single-blind treatment phase (either escitalopram, fluoxetine, paroxetine, sertraline, duloxetine, or venlafaxine), a 6-week double-blind treatment period, and a 30-day follow-up phase. The primary endpoint was change from baseline at week 6 in Montgomery-Asberg Depression Rating Scale (MADRS). The key secondary efficacy end point was change in Sheehan Disability Scale mean score. The primary efficacy endpoint was analyzed using a mixed-model repeated-measures analysis. Differences between the average effect of brexpiprazole 2 and 4 mg versus placebo were tested first at a significance level of 0.025. Of the 677 and 669 patients were included in the efficacy population. *Outcome Results:* In total, 634/677 patients (93.0%) completed the study. For the primary efficacy endpoint, brexpiprazole 3 mg (n =213) showed a greater improvement in MADRS total score versus placebo (n =203; −8.29 vs −6.33; P = .0079), whereas brexpiprazole 1 mg did not (P = .0737). The brexpiprazole groups showed comparable improvement in SDS mean score versus placebo (least squares [LS] mean difference: [1 mg] −0.49, P = .0158; [3 mg] −0.48, P = .0191). The most common treatment-emergent adverse events in brexpiprazole 1-mg, 3-mg, and placebo groups, respectively were: akathisia (4.4%, 13.5%, 2.3%), headache (9.3%, 6.1%, 7.7%), and weight increase (6.6%, 5.7%, 0.9%).

Limitations: This study was sponsored by Otsuka Pharmaceutical Development and Commercialization, Inc., the manufacturer of brexpiprazole. One of the authors received grants Otsuka Pharmaceuticals and eight of the authors are employees of this company. The medication was compared to placebo, when an active comparator medication could have provided more clear insight into the efficacy of this medication. Difference between duration of current major depressive disorder episode was different between placebo and brexpiprazole, respectively 16.9 months versus 18.7 months. Patients were only followed for six-weeks.

Conclusion: Brexpiprazole 3 mg demonstrated efficacy versus placebo as adjunctive antidepressant therapy in patients who remain depressed despite one to three prior antidepressants. Both doses of brexpiprazole were well tolerated. Further research is needed to establish long-term efficacy as well as comparative efficacy

Contraindications[1,2,3,4]:

Hypersensitivity reactions: to brexpiprazole or any component of its formulation

Precautions[1,2,3,4]:

Adverse Event Related Concerns:

Blood dyscrasias: Leukopenia, neutropenia, and agranulocytosis (sometimes fatal) have been reported in clinical trials with antipsychotic use; presence of risk factors (eg, preexisting low WBC/ANC or history of drug-induced leuko-/neutropenia) should prompt periodic blood count assessment. Discontinue therapy at first signs of blood dyscrasias or if absolute neutrophil count <1,000/mm3.

Cerebrovascular effects: An increased incidence of cerebrovascular effects (eg, transient ischemic attack, stroke), including fatalities, has been reported in placebo-controlled trials of antipsychotics for the unapproved use in elderly patients with dementia-related psychosis.

CNS depression (impaired cognitive and motor skills): May cause CNS depression, which may impair physical or mental abilities; patients must be cautioned about performing tasks that require mental alertness (eg, operating machinery, driving). Given the primary CNS effects of brexpiprazole, caution should be used during co-administration with other CNS depressants and alcohol.

Dyslipidemia: Has been reported with atypical antipsychotics; risk profile may differ between agents. In clinical trials, the incidence of hypertriglyceridemia observed with brexpiprazole was greater than observed with placebo, while changes in fasting total cholesterol, LDL, and HDL were similar.

Esophageal dysmotility/aspiration: Antipsychotic use has been associated with esophageal dysmotility and aspiration; use with caution in patients at risk for aspiration pneumonia.

Extrapyramidal symptoms: May cause extrapyramidal symptoms (EPS), including pseudo-parkinsonism, acute dystonic reactions, akathisia, and tardive dyskinesia (risk of these reactions is generally much lower relative to typical/conventional antipsychotics). The risk of developing these disorders and the likelihood that it will become irreversible are believed to increase as the duration of treatment and total cumulative dose increase. Use with caution in patients with Parkinson disease.

Impulse control disorders: Has been associated with compulsive behaviors and/or loss of impulse control, which has manifested as pathological gambling, uncontrolled sexual urges, uncontrolled spending, binge or compulsive eating, and/or other intense urges. Prior history of impulse control issues may be at increased risk. Dose reduction or discontinuation have been reported to reverse these behaviors in most, but not all, cases.

Metabolic Changes: Hyperglycemia or diabetes, dyslipidemia, hyperprolactinemia, and weight gain may occur during therapy. Metabolic changes may increase cardiovascular or cerebrovascular risk over time. Metabolic changes are of particular concern patients with pre-existing risk factors, such as obesity, diabetes mellitus, or hyperlipidemia, but may occur in patients without these pre-existing conditions.

Neuroleptic malignant syndrome (NMS): Use may be associated with neuroleptic malignant syndrome (NMS); monitor for mental status changes, fever, muscle rigidity, and/or autonomic instability.

Orthostatic Hypotension: Increased risk for falls due to somnolence, orthostatic hypotension and motor or sensory instability. Complete fall risk assessments at baseline and periodically during treatment in patients with diseases or on medications that may also increase fall risk.

Suicidal ideation [US Boxed Warning]**:** In patients who exhibit changes in symptoms, worsening of depression, suicidality, or other unusual changes in mood or behaviors, a decision should be made to change or discontinue treatment. Closely monitor patients for clinical worsening and suicidality particularly during the initial 1 to 2 months of therapy or during periods of dosage adjustments (increases or decreases). If discontinuing, the medication should be tapered as rapidly as possible, with the knowledge abrupt discontinuation also cause adverse symptoms.

Temperature regulation: Antipsychotic use has been associated with impaired core body temperature regulation; caution with strenuous exercise, heat exposure, dehydration, and concomitant medication possessing anticholinergic effects.

Disease Related Concerns:

Dementia: [US Boxed Warning]: Elderly patients with dementia-related psychosis treated with antipsychotics are at an increased risk of death compared to placebo. Most deaths appeared to be either cardiovascular (eg, heart failure, sudden death) or infectious (eg, pneumonia) in nature. Brexpiprazole is not approved for the treatment of dementia-related psychosis.

Seizures: should be used cautiously in patients with seizures, a history of seizure disorder, or with conditions that potentially lower the seizure threshold.

Allergy Related Concerns:

Lactose Allergy: Tablets may contain lactose; avoid use in patients with galactose intolerance or glucose-galactose malabsorption.

Other Therapy Concerns:

Discontinuation of therapy: When discontinuing antipsychotic therapy, guidelines recommend *gradually tapering* antipsychotics to avoid physical withdrawal symptoms, including anorexia, anxiety, diaphoresis, diarrhea, dizziness, dyskinesia, headache, myalgia, nausea, paresthesia, restlessness, tremulousness, and vomiting. The risk of withdrawal symptoms is highest following abrupt discontinuation of highly anti-cholinergic or dopaminergic antipsychotics.

Adverse Effects[1,2,3,4]:

Occurring in >10% of patients

Endocrine metabolic:

Hyperglycemia (9% to 10%)

Increased serum triglycerides (Short-term: 5% to 13%; long-term: 13% to 17%)

Weight gain (Short-term: 2% to 11%; long-term: 20% to 30%)

Neurologic:

Akathisia (4% to 14%, dose related)

Occurring in >1% to <10% of patients

Neurologic:

Abnormal dreams (≥1%)

Anxiety (2% to 4%)

Extrapyramidal movements excluding akathisia (5% to 6%)

Dizziness (2% to 5%)

Drowsiness (4% to 6%)

Fatigue (3% to 5%)

Headache (4% to 9%)

Insomnia (≥1%)

Restlessness (2% to 4%; dose-related)

Sedation (2% to 3%)

Cardiovascular:

Cerebrovascular accident

Orthostatic hypotension (0.1% to 0.4%)

Syncope (0.1%)

Transient ischemic attack

Dermatologic:

Hyperhidrosis (≥1%)

Endocrine metabolic:

Diabetic ketoacidosis

Decreased cortisol (3% to 4%)

Increased serum prolactin (≥1%)

Gastrointestinal:

Dyspepsia (3% to 6%)

Increased appetite (major depressive disorder: 3%)

Constipation (2% to 3%)
Diarrhea (2%)
Abdominal pain (≥1%)
Flatulence (≥1%)
Nausea (≥1%)
Sialorrhea (≥1%)
Xerostomia (≥1%)

Genitourinary:

Urinary tract infection (≥1%)

Hematologic:

Agranulocytosis

Neurologic:

Seizure
Tremor (2% to 5%)
Increased creatine phosphokinase (2% to 4%)
Myalgia (≥1%)

Psychiatric:

At risk for suicide

Respiratory:

Nasopharyngitis (3% to 7%)

Miscellaneous:

Neuroleptic malignant syndrome
Blurred Vision (≥1%)

Drug Interactions[1,2,3,4]:

CYP2D6 Inhibitors (Moderate): May increase the serum concentration of Brexpiprazole. Management: If brexpiprazole is to be used together with both a moderate CYP2D6 inhibitor and a strong or moderate CYP3A4 inhibitor, the brexpiprazole dose should be reduced to 25% of the usual dose. Risk C: Monitor therapy

CYP2D6 Inhibitors (Strong): May increase the serum concentration of Brexpiprazole. Management: Reduce brexpiprazole dose to 50% of usual with a strong CYP2D6 inhibitor; this recommendation does not apply if treating major depressive disorder. Reduce to 25% of usual if used with both a strong CYP2D6 inhibitor and a CYP3A4 inhibitor. Risk D: Consider therapy modification.
For adjunct treatment in major depression, the dosage was not adjusted for strong CYP2D6 inhibitors (e.g., paroxetine, fluoxetine) in clinical trials, therefore, CYP considerations are already factored into general dosing recommendations and brexpiprazole may be administered without adjustments in patients with major depression.

CYP3A4 Inducers (Moderate): May decrease the serum concentration of CYP3A4 Substrates (High risk with Inducers). Risk C: Monitor therapy

CYP3A4 Inducers (Strong): May decrease the serum concentration of Brexpiprazole. Management: If brexpiprazole is used together with a strong CYP3A4 inducer, the brexpiprazole dose should gradually be doubled over the course of 1 to 2 weeks. Risk D: Consider therapy modification

CYP3A4 Inhibitors (Moderate): May increase the serum concentration of Brexpiprazole. Management: The brexpiprazole dose should be reduced to 25% of usual if used together with both a moderate CYP3A4 inhibitor and a strong or moderate CYP2D6 inhibitor, or if a moderate CYP3A4 inhibitor is used in a CYP2D6 poor metabolizer. Risk C: Monitor therapy

CYP3A4 Inhibitors (Strong): May increase the serum concentration of Brexpiprazole. Management: Reduce brexpiprazole dose to 50% of usual with a strong CYP3A4 inhibitor; reduce to 25% of usual if used with both a moderate CYP3A4 inhibitor and a CYP2D6 inhibitor, or if a strong CYP3A4 inhibitor is used in a CYP2D6 poor metabolizer. Risk D: Consider therapy modification

Avoid concomitant administration of brepiprazole with the following medications, as they are contraindicated:

Amisulpride
: May enhance the adverse/toxic effect of Amisulpride

Azelastine (Nasal)
: May enhance the CNS depressant effect of Azelastine

Bromperidol
: May enhance the CNS depressant effect

Conivaptan
: May increase the serum concentration of CYP3A4 Substrates

Fusidic Acid (Systemic)
: May increase the serum concentration of CYP3A4 Substrates

Idelalisib
: May increase the serum concentration of CYP3A4 Substrates

Metoclopramide
: May enhance the adverse/toxic effect of Antipsychotic Agents

Orphenadrine
: May enhance the CNS depressant effect of Orphenadrine

Oxomemazine
: May enhance the CNS depressant effect

Paraldehyde
: May enhance the CNS depressant effect of Paraldehyde

Piribedil
: May diminish the therapeutic effect of Piribedil

Sulpiride
: May enhance the adverse/toxic effect of Sulpiride

Thalidomide
: May enhance the CNS depressant effect of Thalidomide

Dosing/Administration[1,2,3,4]:

Adult Dosing

Schizophrenia: Initially, 1 mg by mouth once daily. On Day 5, increase to 2 mg by mouth once daily. On Day 8, may increase to 4 mg based on response/ tolerability. Recommended dose range is 2 to 4 mg/day (max dose of 4 mg/day.)
Adjunctive Treatment of Major Depression: Initially, 0.5 to 1 mg by mouth once daily. After titration to 1 mg/day, increase to the target dose of 2 mg by mouth once daily. Titrate dosage at weekly intervals based on response and tolerability. Maximum dose of 3 mg/day.

Pediatrics

Safety and efficacy have not been established. May increase the risk for suicidal thoughts and behaviors in pediatric patients. Newborns exposed to antipsychotic drugs during the third trimester are at risk for withdrawal symptoms.

Elderly

Clinical studies did not include any patients 65 years of age or older. In general, initiate treatment at the low end of the dosage range, to account for a greater frequency of decreased hepatic, renal, and cardiac function, concomitant diseases, and polypharmacy. Maximum dosage 4 mg per day.

Renal impairment

CrCl 60 mL/minute or more: No dosage adjustments are needed.
CrCl less than 60 mL/minute: including end-stage renal disease (ESRD): The maximum recommended dose is 2 mg PO once daily for major depression and 3 mg PO once daily for schizophrenia.

Hepatic impairment

Mild hepatic impairment: No dosage adjustments are needed.
Moderate to severe hepatic impairment (Child-Pugh score 7 or more): The maximum recommended dosage is 2 mg PO once daily for major depression and 3 mg PO once daily for schizophrenia

Use in special circumstances:

Overdose: No documented cases of overdose have occurred to dictate what threshold this would occur and what would need to be done in this occurrence

Conclusion:

Brexpiprazole is an effective therapy for patients with schizophrenia and as an adjunctive therapy for patients with major depression disorder. Additional studies need to be conducted to evaluate the long-term efficacy of this medication, as well as trials to compare this medications efficacy to other atypical antipsychotics. Brexpiprazole is safe to use with many medications to treat major depressive disorder; compatibility should be confirmed before initiation. The side effects and adverse events of the drug appear to be minimal. With its tolerability and effectiveness in the management of schizophrenia and major depressive disorder, brexpiprazole appears to be another clinically useful atypical antipsychotic agent.

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