

Brexpiprazole (REXULTI®)**National Drug Monograph****March 2016****VA Pharmacy Benefits Management Services, Medical Advisory Panel, and VISN Pharmacist Executives**

The purpose of VA PBM Services drug monographs is to provide a focused drug review for making formulary decisions. Updates will be made when new clinical data warrant additional formulary discussion. Documents will be placed in the Archive section when the information is deemed to be no longer current.

FDA Approval Information¹

Description/Mechanism of Action	Brexpiprazole is a novel second generation antipsychotic (SGA) used in the treatment of schizophrenia and the adjunctive treatment of major depressive disorder (MDD). It has partial agonist activity at 5-HT _{1A} and D ₂ neuroreceptors and antagonist activity at 5-HT _{2A} and alpha _{1/2} receptors.
Indication(s) Under Review in this document (may include off label)	<ul style="list-style-type: none"> • Use as an adjunctive therapy to antidepressants for the treatment of major depressive disorder (MDD) • Treatment of schizophrenia
Dosage Form(s) Under Review	Tablets: 0.25 mg, 0.5 mg, 1 mg, 2 mg, 3 mg, and 4 mg
REMS	<input type="checkbox"/> REMS <input checked="" type="checkbox"/> No REMS <input type="checkbox"/> Postmarketing Requirements <i>See Other Considerations for additional REMS information</i>
Pregnancy	<ul style="list-style-type: none"> • May cause extrapyramidal symptoms (EPS) and/or withdrawal symptoms in neonates with third trimester exposure. • Health care providers are encouraged to enroll women exposed to brexpiprazole during pregnancy in the National Pregnancy Registry for Atypical Antipsychotics. Contact information in prescribing information. <p><i>Also see Use in Specific Populations from prescribing information</i></p>

Executive Summary¹⁻⁴

Efficacy	<ul style="list-style-type: none"> • Adjunctive Treatment of Major Depressive Disorder <ul style="list-style-type: none"> ○ Primary endpoint was change from baseline to Week 6 in the Montgomery-Asberg Depression Rating Scale (MADRS). Brexpiprazole 2 mg +antidepressant (ADT) displayed greater improvement when compared to placebo +ADT to placebo. Brexpiprazole has not been compared to other medications used for adjunctive treatment of MDD (other SGAs, liothyronine, lithium, etc.) • Treatment of Schizophrenia <ul style="list-style-type: none"> ○ Primary endpoint was change from baseline to Week 6 in the Positive and Negative Syndrome Scale (PANSS) total score. Brexpiprazole 4mg/day displayed greater improvement when compared to placebo. There are a number of approved SGAs for treatment of schizophrenia. Brexpiprazole has not been directly compared with them.
Safety	<ul style="list-style-type: none"> • Boxed Warnings: Increased Mortality in Elderly Patients with Dementia-Related Psychosis, Suicidal Thoughts and Behaviors • Safety of brexpiprazole is available from clinical trials of 6 weeks' duration. • Safety results were similar to the known safety profile of SGAs as a class; no unique safety concerns were identified.

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<p>Projected Place in Therapy</p>	<ul style="list-style-type: none"> • Partial response to antidepressants is common in MDD. To date, only two other SGAs are FDA approved for adjunctive treatment - quetiapine XR and aripiprazole. Olanzapine/fluoxetine (Symbyax®) has been FDA approved for treatment-resistant MDD. Several other agents including SGAs, lithium, and liothyronine have been studied for off-label use. Brexpiprazole may be considered in those who have failed or have a contraindication to other adjunctive treatment options. • Schizophrenia is a chronic, severe, and disabling mental disorder. There are a number of SGAs approved for treatment of schizophrenia, but individual patient response cannot be predicted. Trials of different antipsychotics are often required before an effective treatment can be identified. Based on VA PBM recommendations for treatment of schizophrenia, two first line agents (haloperidol, loxapine, perphenazine, quetiapine, and risperidone) must be trialed and clozapine should be offered before considering an alternative formulary antipsychotic (aripiprazole, olanzapine, ziprasidone). Due to the numerous formulary antipsychotics available in this treatment algorithm, brexpiprazole should be reserved for patients who have previously experienced a therapeutic response and tolerated the medication.
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Background

<p>Purpose for review</p>	<p>Recent FDA approval Issues to be determined:</p> <ul style="list-style-type: none"> • Review and compare therapeutic alternatives to brexpiprazole, including evaluation of mechanism of action (MOA), side effects, and dosing. Review evidence to support use of brexpiprazole for the treatment of schizophrenia and as adjunctive treatment of major depressive disorder. • Review the safety of brexpiprazole. • Identify brexpiprazole’s place in therapy relative to formulary and non-formulary alternatives.
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<p>Other therapeutic options</p>	<ul style="list-style-type: none"> • Adjunctive Treatment of Major Depressive Disorder <ul style="list-style-type: none"> ○ The Veteran Affairs (VA)/Department of Defense (DoD) Clinical Practice Guideline (CPG) for Management of MDD suggests several options including nonpharmacological interventions (e.g. psychotherapy or electroconvulsive therapy) or addition of a second pharmacologic agent as outlined below. • Treatment of Schizophrenia <ul style="list-style-type: none"> ○ The VA Pharmacy Benefits Management (PBM) services published recommendations to guide selection of antipsychotic treatment of schizophrenia. ○ Several antipsychotics are available as outlined below.
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Formulary Alternatives for Adjunctive Treatment of MDD	Other Considerations
Bupropion ³	Usual dosing: <ul style="list-style-type: none"> • IR: 200 to 450 mg by mouth daily in divided doses • ER: 150-450 mg by mouth once daily • SR: 100 mg by mouth twice daily to 200 mg by mouth twice daily
Buspirone ³	Usual dosing: 7.5 mg by mouth twice daily to maximum dose of 60 mg/day (in divided doses)
Liothyronine ^{3,5}	Usual dosing: 25mcg-50 mcg by mouth daily

	Serum T3 and TSH levels should be drawn as clinically indicated.
Lithium ^{3,6}	Usual dosing: 300 to 900 mg by mouth as a single or in divided doses daily
	Lithium levels should be drawn as clinically indicated.
Aripiprazole ^{3,7}	FDA indication for adjunctive treatment of MDD.
	Usual dosing: 2 to 15 mg by mouth daily
Olanzapine ^{3,7}	FDA indication for treatment-resistant depression as a combination with fluoxetine (Symbyax ^{®6})
	Usual dosing
	<ul style="list-style-type: none"> Olanzapine in combination with non-fluoxetine antidepressant: Olanzapine 5-20 mg by mouth daily Olanzapine/fluoxetine (Symbyax[®]): Olanzapine 6-18 mg/fluoxetine 25 to 50 mg by mouth daily
	Additional comments:
	<ul style="list-style-type: none"> Symbyax[®] is nonformulary. Olanzapine and fluoxetine are available as separate formulary agents, although they are not available in the strengths that are approved for Symbyax[®].
Risperidone ^{3,7}	Usual dosing: 0.5 to 3 mg by mouth daily
Quetiapine ^{3,7}	XR formulation is not on the VA National Formulary but has FDA indication for adjunctive treatment of MDD.
	Regular release formulation has been studied for off-label use for adjunctive treatment of MDD
	Usual dosing:
	<ul style="list-style-type: none"> XR: 50 to 300 mg by mouth daily IR: 400 mg by mouth daily (studied with venlafaxine 225mg daily)⁸
Ziprasidone ^{3,7,9}	Usual dosing: 40 to 80 mg by mouth twice daily
	Must be taken with food for optimal absorption.

Formulary Alternatives for Treatment of Schizophrenia

Other Considerations

First-Generation Antipsychotics

Haloperidol ⁴	Usual dosing: 0.5 to 5 mg by mouth two or three times daily
Loxapine ⁴	Usual dosing: 60 to 100 mg by mouth per day in divided doses
Perphenazine ⁴	Usual dosing: 8 to 64 mg by mouth per day in divided doses
Chlorpromazine ¹⁰	Usual dosing: 200 mg – 800 mg by mouth in divided doses for outpatients
Fluphenazine ¹¹	Usual dosing: 1 to 5 mg by mouth daily for maintenance after symptoms are controlled
Thiothixene ¹²	Usual dosing: 20 to 30 mg by mouth per day in divided doses
Molindone ¹³	Usual dosing: starting dose is 50 to 75 mg by mouth daily; increase based on response to a maximum of 225 mg daily

Second-Generation Antipsychotics

Quetiapine ⁴	Usual dosing: <ul style="list-style-type: none"> IR: 400 to 800 mg by mouth per day (once daily or in divided doses) ER: 400 to 800 mg by mouth once daily
Risperidone ⁴	Usual dosing: 2 to 8 mg by mouth per day (once daily or in 2 divided doses)
Clozapine ⁴	Usual dosing: 300 to 450 mg by mouth per day (in 2-3 divided doses)
	Additional comments: <ul style="list-style-type: none"> Typically reserved for treatment resistant patients due to risk of agranulocytosis, strict laboratory monitoring, and required enrollment in the Clozapine REMS program.
Aripiprazole ⁴	Usual dosing: 10 to 30 mg by mouth daily
Olanzapine ⁴	Usual dosing: 10 to 20 mg by mouth daily
Ziprasidone ^{4,9}	Usual dosing: 20 to 80 mg by mouth twice daily
	Must be taken with food for optimal absorption.
Non-formulary Alternatives for Treatment of Schizophrenia	Other Considerations
Lurasidone ¹⁴	Usual dosing: 40 to 160 mg by mouth daily
	Must be taken with food (at least 350 calories).
	Formulary restricted to depressive episodes associated with bipolar disorder
Paliperidone ¹⁵	Usual dosing: 6 to 12 mg by mouth daily
Iloperidone ¹⁶	Usual dosing: 6 to 12 mg by mouth twice daily
Asenapine ¹⁷	Usual dosing: 5 to 10 mg sublingually twice daily
Cariprazine ¹⁸	Usual dosing: 1.5 to 6 mg by mouth daily

Efficacy (FDA Approved Indications)

Literature Search Summary

A literature search was performed on PubMed (1966 to December 2015) using the search terms <brexpiprazole> and <Rexulti>. The search was limited to studies performed in humans and published in the English language. The U.S. National Institutes of Health clinical trials registry was searched for relevant clinical trials. All randomized controlled trials published in peer-reviewed journals were included. FDA medical transcripts were also utilized in this review.

Review of Efficacy

Efficacy Measures

Montgomery-Asberg Depression Rating Scale (MADRS)

Ten-item clinician-administered scale used to measure the severity of depressive symptoms. Includes items related to apparent and reported sadness, inner tension, reduced sleep or appetite, concentration difficulties, lassitude, inability to feel, pessimistic thoughts and suicidal thoughts.

- o 0-6 = normal/symptoms absent
- o 7-19 = mild depression
- o 20-34 = moderate depression
- o >34 = severe depression
- o "Response" = reduction in MADRS score by ≥50% from baseline
- o "Remission" = MADRS score ≤10

Sheehan Disability Scale (SDS)

Self-administered questionnaire that includes three 10-point visual analog scales; produces a global functional impairment score that ranges from 0 (unimpaired) to 30 (highly impaired).

Positive and Negative Symptom Scale for Schizophrenia (PANSS)

A validated 30-item rating scale developed to assess individuals with schizophrenia and is also used in research settings as a primary efficacy measure. The PANSS is an adaptation of earlier scales including the Brief Psychiatric Rating Scale (BPRS) to assess the positive and negative symptoms of schizophrenia. Each item is rated by physician observation and scored from 1 to 7 (1 = absent, 7 = extreme).

Clinical Global Impressions – Severity (CGI-S)

A three-item scale that measures the severity of illness, global improvement, and therapeutic response. The CGI-S is a subscale of the CGI scale the measures severity of illness. Severity of illness is rated on a 7-point spectrum (1 = normal, 7 = among the most severely ill patients).

Adjunctive Treatment of Major Depressive Disorder¹⁹⁻²⁰

Quality of the Evidence – Moderate

Two pivotal clinical trials (331-10-227¹⁹, 331-10-228²⁰) were reviewed by the FDA to support approval of brexpiprazole for adjunctive treatment to ADT for those with MDD. Both studies were Phase 3, multinational, randomized, double-blind, and placebo-controlled. Study 331-10-228 evaluated brexpiprazole 2mg+ADT and placebo+ADT. Study 331-10-227 compared brexpiprazole 1mg/day+ADT, brexpiprazole 3mg/day+ADT, and placebo+ADT. Both studies used the same study design, as discussed below, followed by the results of each trial and a discussion of efficacy.

- Subjects were randomized to receive brexpiprazole+ADT or placebo+ADT.
 - ADT options: escitalopram, fluoxetine, paroxetine CR, sertraline, duloxetine, venlafaxine XR
 - Strict concomitant medication regulations were implemented, including guidelines for anticholinergic use for management of EPS and sleep aid restrictions.
- Trial design consisted of a screening phase, a single-blind prospective treatment phase (Phase A) and a double-blind randomization phase (Phase B).
 - Screening period: 7-28 days to establish eligibility.
 - Phase A: Subjects received a single-blind placebo plus an investigator-determined, open-label ADT for 8 weeks.
 - Phase B: Subjects with incomplete response (defined as <50% reduction in 17-item Hamilton Depression Rating Scale (HDRS-17) total score from baseline) at the end of Phase A were assigned to receive placebo+ADT or brexpiprazole +ADT for six weeks.
- The primary outcome efficacy measure was change in MADRS Total Score from the end of Phase A (Week 8 visit) to the end of Phase B (Week 14) between the brexpiprazole+ADT arm and the placebo+ADT arm, estimated as the difference between the Least Squares (LS) means.
- The key secondary endpoint was the change in SDS Mean Score from the end of Phase A (Week 8 visit) to the end of Phase B (Week 14 visit) between the brexpiprazole+ADT arm and the placebo+ADT arm. In order for this endpoint to be evaluable, the pre-specified protocol stated that significance must be found for the primary endpoint.
- Key inclusion and exclusion criteria were consistent in both trials. Outpatient subjects ages 18-65 years diagnosed with a single or recurrent nonpsychotic episode of MDD of at least 8 weeks' duration based on DSM-IV-TR criteria, inadequate response to an adequate trial of between 1 and 3 ADTs and HDRS-17 score ≥ 18 during the screening period were included. Subjects were excluded for the following reasons: treatment during the current episode with adjunctive antipsychotics; initiating or changing psychotherapy; electroconvulsive therapy (ECT); hospitalization during the current episode; occurrence of hallucinations or delusions during the current episode; current diagnosis of other psychiatric or serious medical condition; serious risk of suicide; substance abuse or dependence; previous inadequate response to ECT; previous vagus nerve stimulation or deep brain stimulation; exclusionary laboratory test values or electrocardiogram (ECG) results.

- Mean age across all trials was ~44 years with ~30% male and ~70% female subjects. Race and ethnicity did not differ significantly across treatment arms and had the following breakdown: ~80% Caucasian, ~1% Asian, ~12% Black/African American, ~1% Native American/Alaskan, ~1% other.

Results:

- Protocol Amendment:
 - The randomization criterion was redefined to classify incomplete responders as those who did not meet criteria over the entire course of Phase A, and not solely at the end of Phase A.
 - This protocol amendment was applied to both pivotal trials.
- Trial 331-10-227¹⁹
 - Primary Endpoint: Change in MADRS Total Score at Week 14 (end of Phase B)
 - The 3mg/day and 1 mg/day brexpiprazole+ADT group showed numerical improvement compared with the placebo+ADT group (LS mean difference -1.52, p=0.0327 and LS mean difference -1.19, p=0.0925, respectively); however, the p-value did not meet the pre-specified threshold of 0.025 for statistical significance. Based on the pre-specified statistical plan, this is a negative trial.
 - With removal of 42 subjects who did not meet criteria for randomization based on an amendment to the protocol, the results for the 1mg/day brexpiprazole+ADT group and placebo+ADT group were essentially unchanged. The LS mean difference for the 3 mg/day brexpiprazole+ADT group was slightly larger before amendment compared to after amendment (before -1.19 versus after -1.95), and the p-value met the Hochberg threshold (p=0.0079).
 - FDA statistician recommended the sample without amendment be used for the primary analysis to maintain integrity of the intention-to-treat design. Results before Amendment 3 and after the Amendment 3 are provided in Table 1 below.
 - Key Secondary Endpoint: Change in SDS Mean Score at Week 14
 - Both brexpiprazole+ADT dose groups showed greater improvement (P<0.05) than placebo+ADT group; however because neither dose showed statistical significance for the primary endpoint, this key secondary endpoint was not evaluable.
- Trial 331-10-228²⁰
 - Primary Endpoint: Change in MADRS Total Score at Week 14
 - Mean reduction from baseline to week 6 in MADRS total score was greater for brexpiprazole compared with placebo
 - Results prior to Amendment 3: LS mean = -8.27 vs -5.15; LS mean difference = -3.12 [95% CI, -4.70 to -1.54], P=0.0001
 - Results after Amendment 3: LS mean = -8.36 vs -5.15; LS mean difference = -3.21 [95% CI, -4.87 to -1.54], P=0.0002
 - Key Secondary Endpoint: Change in SDS Mean Score at Week 14
 - Brexpiprazole+ADT showed greater improvement (p<0.05) than placebo +ADT, with a LS means difference of -0.45 (p=0.0349).
 - Despite statistical significance, the magnitude of improvement was quite small; clinical relevance of this degree of change is questionable.

Trial	331-10-228 ²⁰	331-10-227 ¹⁹
Trial Phase	3	
Design	Phase A: Single-blind placebo+ADT Phase B: Double-blind, placebo-controlled+ADT	
Treatment Duration	Phase A: 8 weeks; Phase B: 6 weeks	
Patient Disposition at end of Phase A (ADT+placebo)	Included (n=379) Excluded (n=477) Did not meet randomization criteria (n=331) Lost to follow-up (n=16) Adverse events (n=19) Met withdrawal criteria (n=16) Withdrawn by investigator (n=5) Withdrew consent (n=34)	Included (n=667) Excluded (n=255) Withdrew consent (n=74) Adverse events (n=60) Met withdrawal criteria (n=45) Protocol deviation (n=39) Lost to follow up (n=27) Withdrawn by investigator (n=10)

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	Protocol deviation (n=24) Did not take ADT (n=2)	
Dosing Schedule	Fixed	
Phase B Treatment Groups (+ADT)	2 mg/day (n=188) Placebo (n=191)	1 mg/day (n=226) 3 mg/day (n=230) Placebo (n=221)
Randomization Ratio	1:1	1:1:1
Primary Endpoint: Change in MADRS Total Score End of Phase B	Baseline MADRS Total Score at end of Phase A	
	2 mg/day: 26.61 (5.79) Placebo: 27.14 (5.60)	1 mg/day: 26.7 (5.6) 3 mg/day: 26.4 (5.2) Placebo: 26.3 (5.3)
	LS Mean Difference Versus Placebo prior to Amendment 3 (p-value)	
	-3.12 (0.001)	1mg/day: -1.19 (0.0925) 3mg/day: -1.52 (0.0327)
	LS Mean Difference Versus Placebo after Amendment 3 (p-value)	
	-3.21 (0.0001)	1 mg/day: -1.3 (0.0737) 3 mg/day: -1.95 (0.0079)
Key Secondary Endpoint: Change in SDS Mean Score End of Phase B	Baseline SDS Mean Score (SD)	
	2 mg/day: 6 (2.0) Placebo: 6.3 (2.1)	1 mg/day: 5.9 (2.0) 3 mg/day: 5.7 (2.2) Placebo: 5.6 (1.9)
	LS Mean Difference Versus Placebo (p-value)	
	-0.45 (0.0372)	Not Evaluable
% MADRS Responders ^a : (LS Mean [95% CI]; p-value).	2 mg/day: 23.5 (1.63 [1.1, 2.44]; 0.17) Placebo: 14.7	1 mg/day: 23.1 (1.53 [1.06, 2.2]; 0.25) 3 mg/day: 22.1 (1.51 [1.03, 2.21]; 0.326) Placebo: 15.1%
% MADRS Remitters ^b (LS Mean [95% CI]; p-value).	2 mg/day: 14.4 (1.68 [0.98, 2.86]; 0.058) Placebo: 8.4	1 mg/day: 15.1 (1.3 [0.81, 2.07]; 0.28) 3 mg/day: 13.7 (1.19 [0.74, 1.92]; 0.46) Placebo: 11.9

^aMADRS Responders: Defined as patients having $\geq 50\%$ reduction from the end of Phase A in MADRS Total Score

^bMADRS Remitters: Defined as MADRS total score ≤ 10 and $\geq 50\%$ reduction in MADRS total score from baseline

Discussion

- Brexpiprazole's approval as adjunctive treatment of MDD was based on one positive trial (331-10-228)²⁰ and supportive evidence from other trials (including 331-10-227)¹⁹ that were not positive based on the pre-specified plan in the original protocol.
- Improvement of the MADRS was observed in those receiving brexpiprazole 2mg/day.
- Neither 1mg/day nor 3mg/day showed a statistically significant improvement in MADRS prior to application of Protocol Amendment 3. Exclusion of subjects per this amendment resulted in a positive study. The FDA conducted a number of alternative analyses, which consistently resulted in statistically significant improvement of the brexpiprazole 3mg/day treatment group vs. placebo.
- Evidence supports a target dose of brexpiprazole 2mg/day and maximum dose of brexpiprazole 3mg/day in combination with ADT for adjunctive treatment of MDD.

Treatment of Schizophrenia²¹⁻²²

Quality of the Evidence – High

The FDA approval of brexpiprazole as a treatment for schizophrenia was based on two pivotal 6-week, Phase 3, multinational, randomized, double-blind, placebo-controlled trials (331-10-230²¹, 331-10-231²²) and one Phase 2 trial²³ designed to assess the efficacy, safety, and tolerability of brexpiprazole versus placebo for the treatment of hospitalized adults with schizophrenia (Phase 2 trial not discussed in this monograph). A summary of two pivotal Phase 3 trials is provided here. Study 331-10-231 evaluated 3 fixed doses of brexpiprazole (0.25, 2, and 4 mg/day) versus placebo. Study 331-10-230 compared brexpiprazole 1, 2, and 4mg/day to placebo. The same study design was used in both pivotal trials and is outlined below, followed by a summary of results for each individual trial and a short discussion.

- Hospitalized subjects with a DSM-IV-TR diagnosis of schizophrenia were randomized to receive brexpiprazole or placebo for treatment of a current acute relapse of schizophrenia. Hospitalization was continued for the entire 6-week double-blind treatment period. Subjects that completed all trial visits were offered entry into an open-label rollover trial. Those who did not enter the open-label rollover trial were contacted 30 days after the last dose of trial medication for follow-up on safety outcomes.
- The primary efficacy outcome measure was change from baseline to Week 6 in the Positive and Negative Syndrome Scale (PANSS) Total Score.
- The key secondary efficacy outcome measure was change from baseline to Week 6 in the Clinical Global Impression-Severity (CGI-S score). The pre-specified protocol stated that analysis of this measure was to proceed only if the primary outcome measure was significant.
- Key inclusion and exclusion criteria were consistent in both trials. Subjects were between the ages of 18 and 65. This age restriction was implemented to minimize second generation antipsychotic exposure to subjects that may have dementia-related psychosis rather than schizophrenia. Subjects were also required to score ≥ 40 on the Brief Psychiatric Rating Scale (BPRS) with a score of ≥ 4 on items evaluating specific psychotic symptoms, CGS-S score ≥ 4 , and have a stable living environment when not in the hospital. Subjects were excluded if they were considered resistant/refractory to antipsychotic treatment, had a history of failure to respond to clozapine or response to clozapine treatment only, or were hospitalized for more than 21 days for the current episode.
- Prohibited medications included antipsychotics, antidepressants, mood stabilizers, varenicline, benzodiazepines (except per rescue therapy protocol), CYP2D6 inhibitors, and CYP3A4 inhibitors and inducers.
- Mean age across all trials was ~39 years with ~60% male and ~40% female subjects. Race and ethnicity did not differ significantly across treatment arms but had the following breakdown: ~65% Caucasian, ~23% Black/African American, ~9% other.

Results

- Protocol Amendment
 - The analysis of data for multiple comparisons was changed from the Hochberg procedure to the Average Effect model.
 - FDA requested presentation of efficacy results using both the Average Effect method and the original Hochberg procedure to verify there was no difference in the conclusion.
 - Protocol amendment was applied to both pivotal studies.
- Study 331-10-230²¹:
 - Primary Endpoint: Change from baseline to Week 6 in PANSS Total Score
 - Brexpiprazole 4 mg/day (LS mean difference=-6.5, p=0.002) showed greater improvement when compared with placebo. Brexpiprazole 2 mg/day (LS mean difference=-3.1, p=0.14) showed a greater numerical improvement but did not show superiority to placebo.
 - Conclusions are consistent when analyzed with both Hochberg procedure and the Average Effect method.
 - Key Secondary Endpoint: Change from baseline to Week 6 in CGI-S score
 - Analysis was unable to proceed because only brexpiprazole 4 mg/day met statistical significance. Thus, results would be considered exploratory.
 - Improvement was superior for the brexpiprazole 4 mg/day group (LS mean difference-0.38, p=0.002) compared with placebo. Numerical improvement was observed in the brexpiprazole 2 mg/day (LS mean difference-0.19, p=0.127) and brexpiprazole 1 mg/day (LS mean difference-0.10, p=0.445) groups when compared with placebo, but this data was not statistically evaluable.
- Study 331-10-231²³:
 - Primary Endpoint: Change from baseline to Week 6 in PANSS Total Score
 - Superiority was found for brexpiprazole 4 mg/day (LS mean difference-7.64, p=0.0006) and 2 mg/day (LS mean difference-8.72, p<0.0001) when compared to placebo. Statistical significance was not found in the group receiving brexpiprazole 0.25 mg/day (LS mean difference-2.89, p=0.291) when compared to placebo.

- Conclusions are consistent when analyzed with both Hochberg procedure and the Average Effect method.
- Key Secondary Endpoint: Change from baseline to Week 6 in CGI-S score
 - Superiority was found for brexpiprazole 4mg/day (LS mean difference-0.38, p=0.0012) and brexpiprazole 2mg/day (LS mean difference-0.33, p=0.0056) when compared to placebo.
 - Conclusions are consistent when analyzed with both Hochberg procedure and the Average Effect method.

Table 2: Summary of Pivotal Trials to Support Use of Brexpiprazole in Treatment of Schizophrenia		
Trial	331-10-231 ²³	331-10-230 ²²
Trial Phase	3	
Design	Multinational, randomized, double-blind, placebo-controlled	
Treatment Duration	6 weeks	
Dosing Schedule	Fixed	
Treatment Groups	4 mg/day, N=180 2 mg/day, N=182 0.25 mg/day, N=90 Placebo, N=184	4 mg/day, N=184 2 mg/day, N=186 1 mg/day, N=120 Placebo, N=184
Randomization Ratio	2:2:1:2	3:3:2:3
Primary Endpoint: Change from baseline to Week 6 in PANSS Total Score	Baseline Mean PANSS Total Score (SD)	
	4 mg/day: 94.9 (12.2) 2 mg/day: 95.9 (13.7) 0.25 mg/day: 93.4 (11.7) Placebo: 95.9 (11.5)	4 mg/day: 95.1 (12.5) 2 mg/day: 96.3 (12.8) 1 mg/day: 93.3 (12.8) Placebo: 94.8 (13)
	LS Mean Difference Compared to Placebo (p-value)	
	4 mg/day: -7.64 (0.0006) 2 mg/day: -8.72 (<0.0001) 0.25 mg/day: -2.89, (0.291)	4 mg/day: -6.47 (0.002) 2 mg/day: -3.08 (0.14) 1 mg/day: -3.37 (0.1588)
Key Secondary Endpoint: CGI-S Score from baseline to Week 6	Baseline Mean CGI-S Score (SD)	
	4 mg/day: 4.8 (0.6) 2 mg/day: 4.9 (0.6) 0.25 mg/day: 4.9 (0.6) Placebo: 4.8 (0.7)	4 mg/day: 4.9 (0.6) 2 mg/day: 5 (0.7) 1 mg/day: 4.9 (0.7) Placebo: 4.9 (0.6)
	LS Mean Difference Compared to Placebo (p-value)	
	4 mg/day: -0.38 (0.0012) 2 mg/day: -0.33 (0.0056) 0.25 mg/day: -0.03 (0.85)	4 mg/day: -0.38 (0.002) 2 mg/day: -0.19 (0.127) 1 mg/day: -0.10 (0.445)
% Response Rates (RR [95% CI]; p-value).	4 mg/day: 46.1 (1.48 [1.14, 1.91]; 0.004) 2 mg/day: 47.8 (1.59 [1.23, 2.05]; 0.0004) 0.25 mg/day: 39.1 (1.27 [0.92, 1.76]; 0.16) Placebo: 30.3	4 mg/day: 49.7 (1.54 [1.2, 2]; 0.0006) 2 mg/day: 38.6% (1.22 [0.92, 1.62]; 0.168) 1 mg/day: 43.6% (1.35 [1.02, 1.79]; 0.43) Placebo: 31.7%

^aResponse defined as mean change from baseline in PANSS total score of $\geq 30\%$

Discussion

- In both 6-week studies, brexpiprazole 4mg/day showed statistically greater improvement on PANSS when compared to placebo for treatment of schizophrenia.
- Brexpiprazole 2mg/day demonstrated statistically greater improvement on PANSS in 40% of the participants when compared to placebo in one trial, but statistical significance was not able to be replicated. Pooled data across the two pivotal Phase 3 trials supports clinical efficacy at 2mg/day.
- Since lowest effective dose should be used, efficacy data supports inclusion of both brexpiprazole 2mg/day and brexpiprazole 4mg/day dosing for treatment of schizophrenia.

Potential Off-Label Use

- Treatment of agitation associated with Alzheimer's Disease^{24, 25, 26}
- Attention-deficit/hyperactivity disorder²⁷
- Posttraumatic stress disorder²⁷
- Treatment of bipolar disorder

Safety

(for more detailed information refer to the product package insert)

	Comments
Boxed Warning	<ul style="list-style-type: none"> Elderly patients with dementia-related psychosis treated with antipsychotic drugs are at an increased risk of death. Brexpiprazole is not approved for the treatment of patients with dementia-related psychosis. 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. Safety and effectiveness of brexpiprazole have not been established in pediatric patients.
Contraindications	<ul style="list-style-type: none"> Known hypersensitivity to brexpiprazole or any of its components
Warnings/Precautions	<ul style="list-style-type: none"> <i>Cerebrovascular Adverse Reactions in Elderly Patients with Dementia-Related Psychosis:</i> Increased incidence of cerebrovascular adverse reactions (i.e., stroke, transient ischemic stroke) <i>Neuroleptic Malignant Syndrome:</i> Manage with immediate discontinuation and close monitoring. Symptoms may include muscle cramps, tremors, fever, unstable blood pressure, and altered mental status. <i>Tardive Dyskinesia:</i> Discontinue if clinically appropriate <i>Metabolic Changes:</i> Monitor for hyperglycemia/ diabetes mellitus, dyslipidemia, and weight gain <i>Leukopenia, Neutropenia, and Agranulocytosis:</i> Perform complete blood counts (CBC) in patients with pre-existing low white blood cell count (WBC) or history of leukopenia or neutropenia. <i>Orthostatic Hypotension and Syncope:</i> Monitor heart rate and blood pressure and warn patients with known cardiovascular or cerebrovascular disease, and risk of dehydration or syncope <i>Seizures:</i> Use cautiously in patients with a history of seizures or with conditions that lower the seizure threshold

Safety Considerations

- Although there are no long-term trials available, the safety of brexpiprazole is likely to be similar to agents in the second-generation antipsychotic drug class.
- Boxed warnings: increased mortality in elderly patients with dementia-related psychosis; increased risk of suicidality.
- Weight gain and metabolic abnormalities appear to be moderate when compared to other second-generation antipsychotics. The safety profile appeared to be similar to aripiprazole (akathisia, insomnia, anxiety) although a significant portion of the subjects also experienced fatigue and somnolence.

Adverse Reactions

Common adverse reactions (Incidence \geq 5%)	<ul style="list-style-type: none"> At least one treatment emergent adverse event (TEAE) was reported in 76% subjects (3413 out of 4472) who received brexpiprazole in phase 2/3 MDD, schizophrenia, and ADHD trials. A total of 233 out of 4,472 subjects (5.2%) who received brexpiprazole in the phase 2/3 MDD, schizophrenia, and ADHD trials reported TEAEs that were classified as serious. TEAE's occurring in \geq5% of subjects were: weight gain (16.2%), insomnia (10.1%), headache (9.8%), akathisia (9.4%), somnolence (6.6%), fatigue (6.0%), anxiety (5.7%), increased appetite (5.4%). 4.7% of subjects treated for MDD in all brexpiprazole+ADT groups experienced \geq7% weight gain in short term trials. 10.1% of subjects with schizophrenia in all brexpiprazole 2-4mg/day groups
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	from the U.S. had experienced weight gain. 1.7% of non-U.S. subjects experienced weight gain.
Death/Serious adverse reactions	<ul style="list-style-type: none"> • 13 deaths as of the data cutoff date of January 13, 2014. • Of these 13 deaths, 3 were male subjects and 10 were female subjects. • 12 deaths did not appear to be related to brexiprazole. The causes of these deaths were reported as follows: two completed suicides, pulmonary embolism, metastatic malignant melanoma, gastric ulcer perforation, peritonitis, unknown, septic shock, cardiac failure, asphyxia, coronary artery disease, and stroke • One death by completed suicide was assessed as “possibly related” to brexiprazole.
Discontinuations due to adverse reactions	A total of 3% of brexiprazole-treated patients (compared to 1% of placebo-treated patients) discontinued use due to adverse reactions.

Drug Interactions

Drug-Drug Interactions²⁸

- Brexiprazole is a substrate of CYP3A4 and 2D6
- Brexiprazole – Strong CYP3A4 Inducers: Concurrent use may result in decreased brexiprazole exposure
 - Phenytoin, carbamazepine, rifampin, St. John’s wort
 - Double the usual dose and further adjust based on clinical response
- Brexiprazole – Strong CYP2D6 Inhibitors: Concurrent use may result in increased brexiprazole exposure
 - Quinidine, bupropion, fluoxetine, paroxetine
 - Administer half of usual dose
 - Brexiprazole may be administered without dosage adjustments in patients with MDD when administered with strong CYP2D6 inhibitors (e.g., paroxetine, fluoxetine)
- Brexiprazole – Moderate CYP2D6 Inhibitors: Concurrent use may result in increased brexiprazole exposure
 - Terbinafine, cinacalcet, duloxetine, dronedarone, sertraline
- Brexiprazole – Strong CYP3A4 Inhibitors: Concurrent use may result in increased brexiprazole exposure
 - Ketoconazole, clarithromycin, nefazodone, ritonavir
 - Administer half of usual dose
- Brexiprazole – Moderate CYP3A4 Inhibitors: Concurrent use may result in increased brexiprazole exposure
 - Erythromycin, verapamil, aprepitant, imatinib, dronedarone
- Administer a quarter of usual dose when brexiprazole is used in the following scenarios:
 - In combination with strong/moderate CYP2D6 and strong/moderate CYP3A4 inhibitors
 - Known CYP2D6 poor metabolizers taking strong/moderate CYP3A4 inhibitors

Risk Evaluation

As of January 21, 2016

Look-alike/sound-alike error potentials	NME Drug Name	Lexi-Comp	First DataBank	ISMP	Clinical Judgment
	Brexiprazole 0.25, 0.5, 1, 2 mg tabs	None	None	None	Aripiprazole Omeprazole Lansoprazole Rabeprazole Betaxolol
	Rexulti®	None	None	None	Rituximab Raudixin

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- (Lexi-Comp, First Databank, and ISMP Confused Drug Name List)

Dosing and Administration

Indication	Starting Dose	Recommended Dose	Maximum Dose
MDD	0.5 mg/day or 1 mg/day	2 mg/day	3 mg/day
Schizophrenia	1mg/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 3mg once daily for patients with schizophrenia
- *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
- *Known CYP2D6 Poor Metabolizers:* Reduce the usual dosage by half

Special Populations (Adults)

	Comments
Elderly	<ul style="list-style-type: none"> • Subjects exhibited similar pharmacokinetic parameters (C_{max} and AUC) as adult (18 to 45 years) subjects. Persons >65 years of age were not eligible for the clinical trials for either indication.
Pregnancy	<ul style="list-style-type: none"> • Adequate and well-controlled studies have not been conducted. • Adverse events were observed in some animal reproduction studies. • Extrapyramidal and/or withdrawal symptoms have been reported in neonates whose mothers have been exposed to antipsychotic drugs like brexpiprazole during the third trimester of pregnancy. • Health care providers are encouraged to enroll women exposed to brexpiprazole during pregnancy in the National Pregnancy Registry for Atypical Antipsychotics. Contact information in prescribing information.
Lactation	<ul style="list-style-type: none"> • Lactation studies have not been conducted to assess 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.
CYP2D6 Poor Metabolizers	<ul style="list-style-type: none"> • Adjustment is recommended in known CYP2D6 poor metabolizers, because these patients may have higher brexpiprazole concentrations than normal metabolizers. • Approximately 8% of Caucasians and 3-8% of Black/African Americans cannot metabolize CYP2D6 substrates and are classified as poor metabolizers.
Renal Impairment	<ul style="list-style-type: none"> • Reduce the maximum recommended dosage in patients with moderate, severe, or end-stage renal impairment (CrCl <60mL/minute)
Hepatic Impairment	<ul style="list-style-type: none"> • Reduce the maximum recommended dosage in patients with moderate to severe hepatic impairment (Child-Pugh score ≥ 7)
Pharmacogenetics/genomics	<ul style="list-style-type: none"> • Genetic testing may be considered <ul style="list-style-type: none"> ○ Cytochrome P450, Family 2, Subfamily D, Polypeptide 6

Projected Place in Therapy

Adjunctive Treatment of Major Depressive Disorder

- Major depressive disorder is one of the most common mental disorders.²⁹ In 2013, an estimated 15.7 million adults in the US had at least one major depressive episode in the past year. This represents 6.7% of all US adults.
- MDD is a serious, debilitating chronic illness and potentially fatal disease (e.g., due to suicide).²⁹
- Fewer than 30% of patients achieve complete remission with a selective serotonin reuptake inhibitor (SSRI).²⁹
- The DSM-V³⁰ provides guidelines for diagnosis, although most trials to date used DSM-IV criteria. The American Psychiatric Association (APA)³¹ provides guidelines for treatment of MDD. Additionally, the VA/DoD provides Clinical Practice Guidelines³ for management of MDD.
- The APA guidelines³¹ recommend an adequate trial (defined as 4-6 weeks) of an antidepressant (SSRI, SNRI, mirtazapine, etc.) and define remission of MDD as at least 3 weeks of the absence of both sad mood and reduced interest, and no more than three remaining symptoms of the major depressive episode.
- For those who do not achieve remission, the APA recommends maximizing the initial treatment, changing to other treatments, or augmenting and combining treatments.
- Brexiprazole has not been added to the guidelines at the time of this review, but the APA does recommend adding a second-generation antipsychotic.
- The VA/DoD Clinical Practice Guidelines³ recommend augmentation for patients who do not achieve remission after an adequate 8-12 week trial of two different antidepressants. Augmentation can include psychotherapy, combination medication treatment, or ECT.
- Based on the evidence available to date, brexiprazole 2 mg/day has been shown to be effective. Although brexiprazole 3 mg/day did not prove to be statistically significant in the trials, its use is reasonable for those who do not have adequate response to brexiprazole 2 mg/day.¹⁹⁻²⁰
- Many alternatives to brexiprazole are available. To date, only two other SGAs are FDA approved for adjunctive treatment - quetiapine XR and aripiprazole. Olanzapine/fluoxetine (Symbyax®) has been FDA approved for treatment-resistant MDD. Agents including other SGAs (risperidone, ziprasidone), buspirone, bupropion, lithium, and liothyronine have been studied for off-label use.
- Brexiprazole should be reserved for patients who previously had a therapeutic response and tolerated the medication.

Treatment of Schizophrenia

- Schizophrenia is a chronic, severe, and disabling mental disorder characterized by deficits in thought processes, perceptions, and emotional responsiveness.³²
- According to the National Institute of Mental Health, schizophrenia occurs in an estimated 1.1% of the US adult population.³²
- The DSM-V³⁰ provides guidelines for diagnosis of schizophrenia, although most trials to date used DSM-IV criteria. The American Psychiatric Association (APA) has published guidelines for the treatment of schizophrenia.³³ Additionally, the VA PBM has published recommendations for antipsychotic selection in schizophrenia.⁴
- The APA³³ recommends that selection of an antipsychotic for the treatment of schizophrenia be based on clinical circumstances such as potential risks and benefits of the medication, patient's previous experience with antipsychotics, and preferred route of medication administration.
- The VA PBM⁴ recommends a trial of two first line agents (haloperidol, loxapine, perphenazine, quetiapine, and risperidone) and an offer of clozapine before considering an alternative formulary antipsychotic (aripiprazole, olanzapine, ziprasidone).
- Based on VA PBM recommendations for treatment of schizophrenia, brexiprazole should be reserved for patients who previously had a therapeutic response and tolerated the medication.

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Appendix A: GRADEing the Evidence

Designations of Quality

Quality of evidence designation Description

High	Evidence includes consistent results from well-designed, well-conducted studies in representative populations that directly assess effects on health outcomes (2 consistent, higher-quality randomized controlled trials or multiple, consistent observational studies with no significant methodological flaws showing large effects).
Moderate	Evidence is sufficient to determine effects on health outcomes, but the number, quality, size, or consistency of included studies; generalizability to routine practice; or indirect nature of the evidence on health outcomes (1 higher-quality trial with > 100 participants; 2 higher-quality trials with some inconsistency; 2 consistent, lower-quality trials; or multiple, consistent observational studies with no significant methodological flaws showing at least moderate effects) limits the strength of the evidence.
Low	Evidence is insufficient to assess effects on health outcomes because of limited number or power of studies, large and unexplained inconsistency between higher-quality studies, important flaws in study design or conduct, gaps in the chain of evidence, or lack of information on important health outcomes.

Please refer to Qaseem A, et al. The development of clinical practice guidelines and guidance statements of the American College of Physicians: Summary of Methods. *Ann Intern Med* 2010;153:194-199.