Brexpiprazole for schizophrenia and as adjunct for major depressive disorder

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Brexpiprazole, FDA-approved in July 2015 to treat schizophrenia and as an adjunct for major depressive disorder (MDD) (Table 1), has shown efficacy in 2 phase-III acute trials for each indication. Although brexpiprazole is a dopamine D2 partial agonist, it differs from aripiprazole, the other available D2 partial agonist, because it is more potent at serotonin 5-HT1A and 5-HT2A receptors and displays less intrinsic activity at D2 receptors, which could mean better tolerability.

Clinical implications
Schizophrenia is heterogeneous, and individual response and tolerability to antipsychotics vary greatly; therefore, new drug options are useful. For MDD, before the availability of brexpiprazole, only 3 antipsychotics were FDA-approved for adjunctive use with antidepressant therapy; brexpiprazole represents another agent for patients whose depressive symptoms persist after standard antidepressant treatment.

Variables that limit the use of antipsychotics include extrapyramidal symptoms (EPS), akathisia, sedation/somnolence, weight gain, metabolic abnormalities, and hyperprolactinemia. If post-marketing studies and clinical experience confirm that brexpiprazole has an overall favorable side-effect profile regarding these tolerability obstacles, brexpiprazole would potentially have advantages over some other available agents, including aripiprazole.

### Table 1

<table>
<thead>
<tr>
<th>Fast facts about brexpiprazole</th>
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<tr>
<td><strong>Brand name:</strong> Rexulti</td>
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<tr>
<td><strong>Class:</strong> Atypical antipsychotic</td>
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<td><strong>Indications:</strong> Schizophrenia and adjunctive therapy for major depressive disorder</td>
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<td><strong>FDA approval date:</strong> July 10, 2015</td>
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<td><strong>Availability date:</strong> August 2015</td>
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<td><strong>Manufacturer:</strong> Otsuka America Pharmaceutical, Inc., and Lundbeck</td>
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<td><strong>Dosing forms:</strong> 0.25 mg, 0.5 mg, 1 mg, 2 mg, 3 mg, and 4 mg tablets</td>
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<td><strong>Recommended dosage:</strong> 2 to 4 mg/d (schizophrenia) and 2 mg/d (major depressive disorder)</td>
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How it works
In addition to a subnanomolar binding affinity (Ki < 1 nM) to dopamine D2 receptors as a partial agonist, brexpiprazole also exhibits similar binding affinities for serotonin 5-HT1A (partial agonist), 5-HT2A (antagonist), and adrenergic α1B (antagonist) and α2C (antagonist) receptors.

Brexpiprazole also has high affinity (Ki < 5 nM) for dopamine D3 (partial ago-
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nist), serotonin 5-HT2B (antagonist), and 5-HT7 (antagonist), and at adrenergic α1A (antagonist) and α1D (antagonist) receptors. Brexpiprazole has moderate affinity for histamine H1 receptors (Ki = 19 nM, antagonist), and low affinity for muscarinic M1 receptors (Ki > 1000 nM, antagonist).

Brexipirazole’s pharmacodynamic profile differs from other available antipsychotics, including aripiprazole. Whether this translates to meaningful differences in efficacy and tolerability will depend on the outcomes of specifically designed clinical trials as well as “real-world” experience. Animal models have suggested amelioration of schizophrenia-like behavior, depression-like behavior, and anxiety-like behavior with brexipirazole.6

Pharmacokinetics

At 91 hours, brexpiprazole’s half-life is relatively long; a steady-state concentration is attained in approximately 2 weeks.1 In the phase-III clinical trials, brexipirazole was titrated to target dosages, and therefore the product label recommends the same. Brexipirazole can be administered with or without food.

In a study of brexipirazole excretion, after a single oral dose of [14C]-labeled brexipirazole, approximately 25% and 46% of the administered radioactivity was recovered in urine and feces, respectively. Less than 1% of unchanged brexipirazole was excreted in the urine, and approximately 14% of the oral dose was recovered unchanged in the feces.

Exposure, as measured by maximum concentration and area under the concentration curve, is dose proportional.

Metabolism of brexipirazole is mediated principally by cytochrome P450 (CYP) 3A4 and CYP2D6. Based on in vitro data, brexipirazole shows little or no inhibition of CYP450 isozymes.

Efficacy

FDA approval for brexipirazole for schizophrenia and for adjunctive use in MDD was based on 4 phase-III pivotal acute clinical trials conducted in adults, 2 studies each for each disorder.14 These studies are described in Table 2.2-5

Schizophrenia. The primary outcome measure for the acute schizophrenia trials was change on the Positive and Negative Syndrome Scale (PANSS) total scores from baseline to 6-week endpoint. Statistically significant reductions in PANSS total score were observed for brexipirazole dosages of 2 mg/d and 4 mg/d in one study,7 and 4 mg/d in another study.3 Responder rates also were measured, with response defined as a reduction of ≥30% from baseline in PANSS total score or a Clinical Global Impressions-Improvement score of 1 (very much improved) or 2 (much improved).2,3 Pooling together the available data for the recommended target dosage of brexipirazole for schizophrenia (2 to 4 mg/d) from the 2 phase-III studies, 45.5% of patients responded to the drug, compared with 31% for the pooled placebo groups, yielding a number needed to treat (NNT) of 7 (95% CI, 5-12).6

Although not described in product labeling, a phase-III 52-week maintenance study demonstrated brexipirazole’s efficacy in preventing exacerbation of psychotic symptoms and impending relapse in patients with schizophrenia.10 Time from randomization to exacerbation of psychotic symptoms or impending relapse showed a beneficial effect with brexipirazole compared with placebo (log-rank test: hazard ratio = 0.292, P < .0001). Significantly fewer patients in the brexipirazole group relapsed compared with placebo (13.5% vs 38.5%, P < .0001), resulting in a NNT of 4 (95% CI, 3-8).

Major depressive disorder. The primary outcome measure for the acute MDD studies was change in Montgomery-Åsberg Depression Rating Scale (MADRS) scores from baseline to 6-week endpoint of the randomized treatment phase. All patients were required to have a history of inadequate response to 1 to 3 treatment trials of standard
antidepressants for their current depressive episode. In addition, patients entered the randomized phase only if they had an inadequate response to antidepressant therapy during an 8-week prospective treatment trial of standard antidepressant treatment plus single-blind placebo.

Participants who responded adequately to the antidepressant in the prospective single-blind phase were not randomized, but instead continued on antidepressant treatment plus single-blind placebo for 6 weeks.

The phase-III studies showed positive results for brexpiprazole, 2 mg/d and 3 mg/d, with change in MADRS from baseline to endpoint superior to that observed with placebo.\textsuperscript{4,5}

When examining treatment response, defined as a reduction of ≥50% in MADRS total score from baseline, NNT vs placebo for response were 12 at all dosages tested, however, NNT vs placebo for remission (defined as MADRS total score ≤10 and ≥50% improvement from baseline) ranged from 17 to 31 and were not statistically significant.\textsuperscript{6}

When the results for brexpiprazole, 1 mg/d, 2 mg/d, and 3 mg/d, from the 2 phase-III trials are pooled together, 23.2% of the patients receiving brexpiprazole were responders, vs 14.5% for placebo, yielding a NNT of 12.

\begin{table}[h]
\centering
\caption{Pivotal randomized, double-blind, placebo-controlled phase-III trials of brexpiprazole}
\begin{tabular}{|l|c|c|c|c|}
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\textbf{ClinicalTrials.gov identifier} & \textbf{Length (weeks)} & \textbf{N} & \textbf{Brexpiprazole dosage (mg/d)} & \textbf{Comments} \\
\hline
Schizophrenia & & & & \\
NCT01396421 & 6 & 636 & 0.25, 2, 4 & • Published as Correll et al, 2015\textsuperscript{2} \\
& & & & • Positive study for brexpiprazole, 2 mg/d and 4 mg/d \\
& & & & • In groups receiving 2 or 4 mg of brexpiprazole, dosing began at 1 mg/d and was titrated to 2 mg/d on Day 5 and 4 mg/d on Day 8 \\
NCT01393613 & 6 & 674 & 1, 2, 4 & • Published as Kane et al, 2015\textsuperscript{3} \\
& & & & • Positive study for brexpiprazole, 4 mg/d \\
& & & & • In groups receiving 2 or 4 mg of brexpiprazole, dosing began at 1 mg/d and was titrated to 2 mg/d on Day 5 and 4 mg/d on Day 8 \\
& & & & \\
Major depressive disorder (adjunctive to antidepressant treatment) & & & & \\
NCT01360632 & 14 (randomized phase: 6 weeks) & 677 & 1, 3 & • Published as Thase et al, 2015\textsuperscript{4} \\
& & & & • Positive study for brexpiprazole, 3 mg/d \\
& & & & • Dosing of brexpiprazole was either 0.5 mg/d for the first week, followed by 1.0 mg/d for the remainder of the trial, or 0.5 mg/d for the first week, followed by 1 mg/d for the second week, followed by 3 mg/d for the remainder of the trial \\
NCT01360645 & 14 (randomized phase: 6 weeks) & 379 & 2 & • Published as Thase et al, 2015\textsuperscript{5} \\
& & & & • Positive study for brexpiprazole, 2 mg/d \\
& & & & • Dosing of brexpiprazole was 0.5 mg/d for the first week, followed by 1 mg/d for the second week, followed by 2 mg/d for the remainder of the trial \\
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(95% CI, 8-26); 14.4% of the brexpiprazole-treated patients met remission criteria, vs 9.6% for placebo, resulting in a NNT of 21 (95% CI, 12-138).6

Tolerability

Overall tolerability can be evaluated by examining the percentage of patients who discontinued the clinical trials because of an adverse event (AE). In the acute schizophrenia double-blind trials for the recommended dosage range of 2 to 4 mg, the discontinuation rates were lower overall for patients receiving brexpiprazole compared with placebo.2,3 In the acute MDD trials, 32.6% of brexpiprazole-treated patients and 10.7% of placebo-treated patients discontinued because of AEs,4,5 yielding a number needed to harm (NNH) of 53 (95% CI, 30-235).6

The most commonly encountered AEs for MDD (incidence ≥5% and at least twice the rate for placebo) were akathisia (8.6% vs 1.7% for brexpiprazole vs placebo, and dose-related) and weight gain (6.7% vs 1.9%),1 with NNH values of 15 (95% CI, 11-23), and 22 (95% CI, 15-42), respectively.6 The most commonly encountered AE for schizophrenia (incidence ≥4% and at least twice the rate for placebo) was weight gain (4% vs 2%),1 with a NNH of 50 (95% CI, 26-1773).6

Of note, rates of akathisia in the schizophrenia trials were 5.5% for brexpiprazole and 4.6% for placebo,1 yielding a non-statistically significant NNH of 112.6 In a 6-week exploratory study,11 the incidence of EPS-related AEs including akathisia was lower for brexpiprazole-treated patients (14.1%) compared with those receiving aripiprazole (30.3%), for a NNT advantage for brexpiprazole of 7 (not statistically significant).

Short-term weight gain appears modest; however, outliers with an increase of ≥7% of body weight were evident in open-label long-term safety studies.1,6 Effects on glucose and lipids were small. Minimal effects on prolactin were observed, and no clinically relevant effects on the QT interval were evident.

Contraindications

The only absolute contraindication for brexpiprazole is known hypersensitivity to brexpiprazole or any of its components. Reactions have included rash, facial swelling, urticaria, and anaphylaxis.1

As with all antipsychotics and antipsychotics with an indication for a depressive disorder:

- there is a bolded boxed warning in the product label regarding increased mortality in geriatric patients with dementia-related psychosis. Brexpiprazole is not approved for treating patients with dementia-related psychosis
- there is a bolded boxed warning in the product label about suicidal thoughts and behaviors in patients age ≤24. The safety and efficacy of brexpiprazole have not been established in pediatric patients.

Dosing

Schizophrenia. The recommended starting dosage for brexpiprazole for schizophrenia is 1 mg/d on Days 1 to 4. Brexpiprazole can be titrated to 2 mg/d on Day 5 through Day 7, then to 4 mg/d on Day 8 based on the patient’s response and ability to tolerate the medication. The recommended target dosage is 2 to 4 mg/d with a maximum recommended daily dosage of 4 mg.

Major depressive disorder. The recommended starting dosage for brexpiprazole as adjunctive treatment for MDD is 0.5 mg or 1 mg/d. Brexpiprazole can be titrated to 1 mg/d, then up to the target dosage of 2 mg/d, with dosage increases occurring at weekly intervals based on the patient’s clinical response and ability to tolerate the agent, with a maximum recommended dosage of 3 mg/d.

Other considerations. For patients with moderate to severe hepatic impairment, or moderate, severe, or end-stage renal impairment, the maximum recommended dosage is 3 mg/d for patients with schizophrenia, and 2 mg/d for patients with MDD.

Clinical Point

In schizophrenia trials, the discontinuation rates were lower for patients receiving brexpiprazole compared with placebo.
In general, dosage adjustments are recommended in patients who are known CYP2D6 poor metabolizers and in those taking concomitant CYP3A4 inhibitors or CYP2D6 inhibitors or strong CYP3A4 inducers:

- for strong CYP2D6 or CYP3A4 inhibitors, administer one-half the usual dosage
- for strong/moderate CYP2D6 with strong/moderate CYP3A4 inhibitors, administer a one-quarter of the usual dosage
- for known CYP2D6 poor metabolizers taking strong/moderate CYP3A4 inhibitors, also administer a one-quarter of the usual dosage
- for strong CYP3A4 inducers, double the usual dosage and further adjust based on clinical response.

In clinical trials for MDD, brexpiprazole dosage was not adjusted for strong CYP2D6 inhibitors (eg, paroxetine, fluoxetine). Therefore, CYP considerations are already factored into general dosing recommendations and brexpiprazole could be administered without dosage adjustment in patients with MDD; however, under these circumstances, it would be prudent to start brexpiprazole at 0.5 mg, which, although “on-label,” represents a low starting dosage. (Whenever 2 drugs are co-administered and 1 agent has the ability to disturb the metabolism of the other, using smaller increments to the target dosage and possibly waiting longer between dosage adjustments could help avoid potential drug–drug interactions.)

No dosage adjustment for brexpiprazole is required on the basis of sex, race or ethnicity, or smoking status. Although clinical studies did not include patients age ≥65, the product label recommends that in general, dose selection for a geriatric 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.

References

Related Resources

Drug Brand Names
Aripiprazole - Abilify
Brexpiprazole - Rexulti
Fluoxetine - Prozac
Paroxetine - Paxil

Bottom Line
Brexiprazole, an atypical antipsychotic, is FDA-approved for schizophrenia and as an adjunct to antidepressants in major depressive disorder. For both indications, brexpiprazole demonstrated positive results compared with placebo in phase-III trials. Brexpiprazole is more potent at serotonin 5-HT1A and 5-HT2A receptors and displays less intrinsic activity at D2 receptors than aripiprazole, which could mean that the drug may be better-tolerated.

6. Citrome L. Brexpiprazole for schizophrenia and as adjunct for major depressive disorder: a systematic review of the efficacy and safety profile for this newly approved antipsychotic—what is the number needed to treat, number needed to harm, and likelihood to be helped or harmed? Int J Clin Pract. 2015;69(9):978-997.


