Risperidone extended-release injectable suspension

Jonathan M. Meyer, MD

Oral antipsychotic nonadherence is a significant contributor to relapse in patients with schizophrenia spectrum disorders. Long-acting injectable (LAI) antipsychotics have been developed to provide sustained antipsychotic exposure, with evidence that use of LAIs significantly reduces hospitalization rates.[1] One limiting factor in transitioning patients to certain LAIs is the need for prolonged oral coverage at the onset of treatment for agents that cannot be loaded. Nonadherence with this bridging oral therapy places the patient at risk for symptom exacerbation until effective antipsychotic plasma levels are achieved from the LAI.[2] Although risperidone is one of the more widely used antipsychotics for treating schizophrenia, until recently the only available LAI preparation, risperidone microspheres (Risperdal Consta), required 3 weeks of oral coverage upon initiation.[3]

To obviate this need for extended oral bridging, a novel LAI form of risperidone was developed utilizing a proprietary subcutaneous injectable formulation that provides effective plasma active moiety levels within 1 week of the injection and sustained antipsychotic levels with monthly usage. Risperidone extended-release injectable suspension (investigational name RBP-7000, brand name Perseris) was approved on July 27, 2018 for the treatment of adults with schizophrenia (***Table 1***). The efficacy and safety of RBP-7000 was demonstrated in a pivotal 8-week, double-blind, placebo-controlled trial of adult patients age 18 to 55 with acute exacerbation of schizophrenia.[4]

Table 1

Fast facts about RBP-7000

Brand name: Perseris
Class: Long-acting injectable atypical antipsychotic (risperidone)
Indication: Adults with schizophrenia
Approval date: July 27, 2018
Availability date: September 1, 2018
Manufacturer: Indivior Inc., North Chesterfield, VA
Dosing forms: 90 mg and 120 mg by abdominal subcutaneous injection once monthly
Recommended dosage for schizophrenia: After establishing oral risperidone tolerability, 90 mg or 120 mg monthly, equivalent to 3 mg/d or 4 mg/d of oral risperidone, respectively. No oral coverage is needed at the onset of therapy, and no additional loading injections are required

Clinical implications

Oral medication nonadherence remains a significant public health issue for patients with schizophrenia, with an estimated 50% of patients failing to achieve 80% adherence even when enrolled in clinical trials specifically designed to track adherence.[5] Although LAI atypical antipsychotics

New formulation eliminates need for oral coverage when initiating treatment

Dr. Meyer is a Psychopharmacology Consultant, California Department of State Hospitals, Sacramento, California; Clinical Professor of Psychiatry, University of California, San Diego, La Jolla, California; and Deputy Editor of Current Psychiatry.

Disclosure

Dr. Meyer is a consultant to Acadia Pharmaceuticals, Alkermes, Allergan, Neurocrine, and Teva Pharmaceutical Industries, and a speaker for Acadia Pharmaceuticals, Alkermes, Allergan, Merck, Neurocrine, Otsuka America, Inc., Sunovion Pharmaceuticals, and Teva Pharmaceutical Industries.

Clinical Point

Effective drug levels are seen within the first week without the need for oral coverage

have been available since the approval of Risperdal Consta, the LAI form of risperidone, and both LAI forms of aripiprazole, were not designed to be loaded. A 1-day initiation regimen for aripiprazole lauroxil has been developed to avoid the need for 3 weeks of oral medication coverage,[6,7] but aripiprazole monohydrate and risperidone microspheres mandate oral bridging of 2 and 3 weeks, respectively.[2] Because one of the primary indications for LAI antipsychotic therapy is oral medication nonadherence, this prolonged period of oral coverage creates a risk for symptom exacerbation when the bridging period occurs outside of a controlled setting, as is common when patients are discharged from inpatient hospitalization.

One solution to this problem has its antecedents in the development of the Atrigel biodegradable injectable polymer, which was designed to deliver prolonged medication exposure after subcutaneous injection.[8] This biodegradable polymer drug delivery system suspends and dissolves the medication of interest (in this case, risperidone) in a poly DL-lactide-coglycolide gel and its biocompatible carrier.[9] The viscous liquid undergoes a phase transition upon contact with tissue fluids after subcutaneous injection, resulting in an implant that releases risperidone in a controlled manner as it is resorbed. Importantly, the kinetic parameters of RBP-7000 are such that effective drug levels are seen within the first week without the need for oral coverage.[10]

Use in adults with schizophrenia. After establishing tolerability with oral risperidone, the recommended doses are 90 mg or 120 mg monthly, which correspond to oral daily risperidone doses of 3 mg or 4 mg. RBP-7000 must be administered as a subcutaneous abdominal injection by a health care professional. It is recommended that the patient be in the supine position for the injection and that the injection sites be rotated monthly among 4 quadrants in the abdominal region. The injection volumes for the 90 mg and 120 mg doses are 0.6 mL and 0.8 mL, respectively.[10] As the gel implant becomes firmer, the patient will notice a lump for several weeks that will decrease in size over time. Patients should be advised not to rub or massage the injection site, and to be aware of the placement of any belts or clothing with waistbands.[10]

Pharmacologic profile, adverse reactions

Risperidone is an atypical antipsychotic that has been commercially available in the U.S. since December 29, 1993, and its adverse effect profile is well characterized. The most common adverse effects associated with risperidone include those related to dopamine D2 antagonism, metabolic adverse effects, and an increase in serum prolactin. In the 12-month long-term safety study of RBP-7000, 1-minute post-dose injection site pain scores (on a 100-point scale) were highest on Day 1 (mean of 25) and decreased over time with subsequent injections (14 to 16 following the last injection).[10]

How the Atrigel system works. The Atrigel system was developed in the late 1980s and consists of a solution of a resorbable polymer in a biocompatible carrier.[11] After *in vivo* administration (typically via subcutaneous injection), the polymer undergoes a phase change from a liquid to a formed implant (***Figure 1, page 29***). Being in liquid form, this system provides the advantage of placement by simple means, such as injection by syringes. The absorption rates of various polymers and the release rates for various drugs are tailored to the desired indication. Approved uses for Atrigel include the subgingival delivery of the antibiotic doxycycline for chronic adult periodontitis (approved September 1998), and the monthly subcutaneous injectable form of the anti-androgen leuprolide, which was approved in January 2002.[8,12] Release periods up to 4 months have been achieved with Atrigel; 1 month is the most often desired release period. The biodegradable

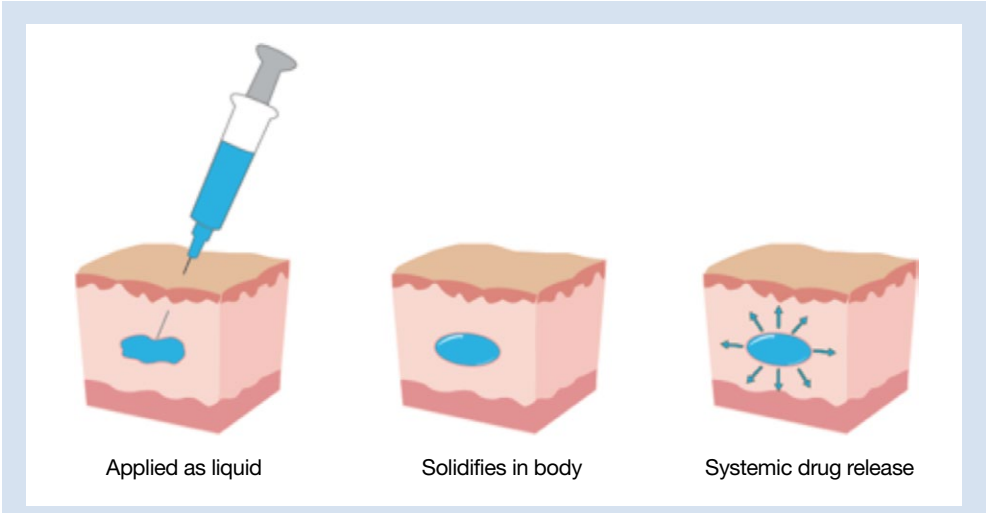
continued on page 29

Discuss this article at www.facebook.com/MDedgePsychiatry

continued from page 24

Figure 1

The Atrigel system



polymer used for RBP-7000 is designed to provide effective plasma drug levels during the first week of treatment, and sustained levels with a 1-month dosing interval. The small subcutaneous implant that is formed is gradually resorbed over the course of 1 month.

Pharmacokinetics. As with all LAI medications, the half-life with repeated dosing vastly exceeds that achieved with oral administration. Following oral administration, mean peak plasma levels of risperidone occur at 1 hour, and those for the active metabolite 9-OH risperidone occur at 3 hours.[13] Oral risperidone has a mean half-life of 3 hours, while the active metabolite 9-OH risperidone has a mean half-life of 21 hours.[14] Due to its longer half-life, the metabolite comprises 83% of the active drug levels at steady state.[14] Although risperidone is susceptible to interactions via cytochrome P450 (CYP) inhibitors and inducers, particularly CYP2D6 (***Table 2,***[10] ***page 30***), the pharmacokinetics of the combined total of risperidone and 9-OH risperidone levels (deemed the active moiety) are similar in CYP2D6 extensive and poor metabolizers, with an overall mean elimination half-life of approximately 20 hours.[13]

The kinetics for RBP-7000 are markedly different than those for oral risperidone (***Figure 2,***[15] ***page 31***). After a single subcutaneous injection, RBP-7000 shows 2 absorption peaks for risperidone. The first lower peak occurs with a T_{max} of 4 to 6 hours due to initial release of risperidone during the implant formation process; a second risperidone peak occurs after 10 to 14 days and is associated with slow release from the subcutaneous depot.[9,16,17] For both 9-OH risperidone levels and the total active moiety (risperidone plus 9-OH risperidone levels), the median T_{max} of the first peak ranges from 4 to 48 hours and the second peak ranges from 7 to 11 days. Following a single subcutaneous injection of RBP-7000, the apparent terminal half-life of risperidone ranges from 9 to 11 days, on average. The mean apparent terminal half-life of the active moiety ranges from 8 to 9 days.[9,16,17] Based on population pharmacokinetic modeling, the 90 mg and 120 mg doses of RBP-7000 are estimated to provide drug exposure equivalent to 3 mg/d and 4 mg/d of oral risperidone, respectively.[9,16,17]

continued

Clinical Point

The small subcutaneous implant that is formed is gradually resorbed over the course of 1 month

Table 2

RBP-7000 basic kinetic information

Factor	Description
Bioavailability	100%
Half-life of active moiety (combined risperidone + 9-OH risperidone levels)	9 to 11 days
Administration	Monthly
Adjustments for strong CYP2D6 inhibitors	When a strong CYP2D6 inhibitor is to be added, patients may be placed on the lowest dose (90 mg) of RBP-700 for 2 to 4 weeks before the CYP2D6 inhibitor is added to adjust for the expected increase in plasma concentrations of risperidone. Treatment with the 90-mg dose should be continued unless clinical judgment necessitates interruption of treatment with RBP-7000
Adjustments for strong CYP3A4 inducers	After initiation of therapy with carbamazepine or other known hepatic enzyme inducers, patients should be closely monitored during the first 4 to 8 weeks. In patients receiving 90 mg of RBP-7000, consider increasing the dose to 120 mg. In patients receiving 120 mg, additional oral risperidone therapy may need to be considered On discontinuation of strong CYP3A4 hepatic enzyme inducers, the dosage of RBP-7000 or any additional oral risperidone therapy should be re-evaluated and, if necessary, decreased to adjust for the expected increase in plasma concentration of risperidone. For patients treated with 90 mg, it is recommended to continue treatment with the 90-mg dose after stopping the inducer unless clinical judgment necessitates interruption of treatment with RBP-7000

CYP: cytochrome P450

Source: Reference 10

Clinical Point

The 90 mg and 120 mg doses may provide drug exposure equal to 3 mg/d and 4 mg/d of oral risperidone, respectively

Efficacy of RBP-7000 was established in an 8-week, double-blind, placebo-controlled trial of adult patients experiencing an acute exacerbation of schizophrenia (age 18 to 55).[4] Eligible participants had:

- An acute exacerbation of schizophrenia that occurred ≤8 weeks before the screening visit and would have benefited from psychiatric hospitalization or continued hospitalization
- Positive and Negative Syndrome Scale (PANSS) total score between 80 and 120 at visit 1 and a score of >4 on at least 2 of the following 4 items: hallucinatory behavior, delusions, conceptual disorganization, or suspiciousness/persecution
- The diagnosis of acute exacerbation of schizophrenia and PANSS total score were confirmed through an independent video-conference interview conducted by an experienced rater.

Participants were excluded if they:

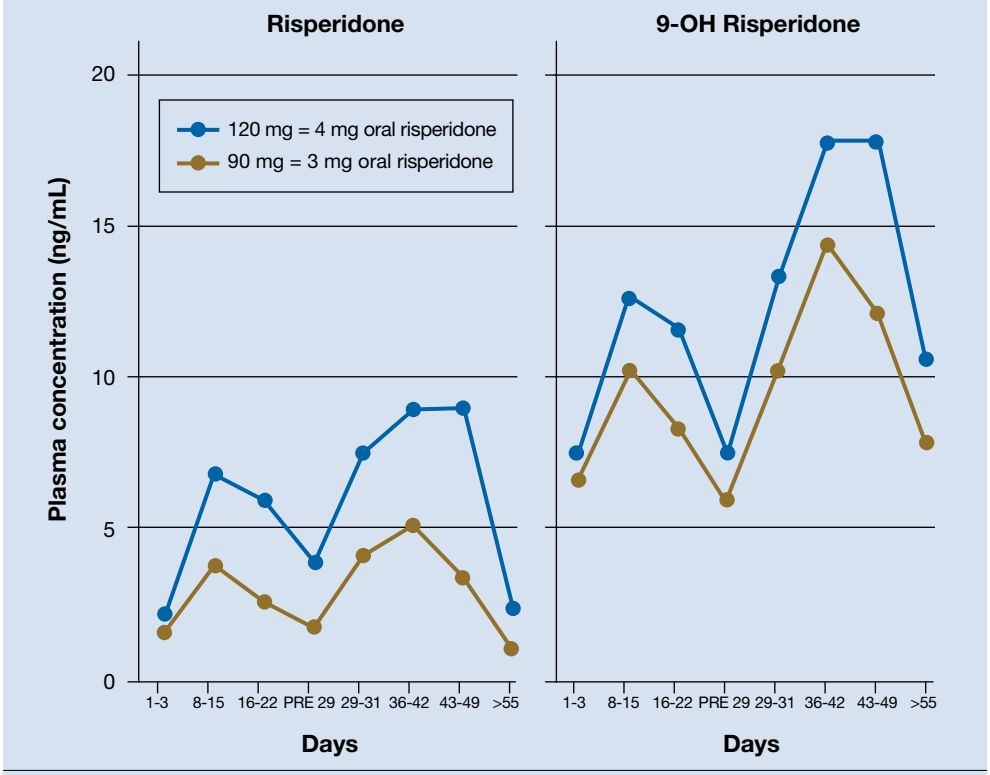
- Experienced a ≥20% improvement in PANSS total score between the initial screening visit and the first injection
- had been treated at any time with clozapine for treatment-resistant schizophrenia
- had met DSM-IV-TR criteria for substance dependence (with the exception of nicotine or caffeine) before screening.

During the initial screening visit, participants received a 0.25-mg tablet of oral risperidone on 2 consecutive days to assess the tolerability of risperidone.

Outcome. Participants were randomized in a 1:1:1 manner to placebo (n = 112) or 1

Figure 2

Kinetics of RBP-7000



Source: Reference 15

of 2 monthly doses of RBP-7000: 90 mg (n = 111) or 120 mg (n = 114). Using the least squares means of repeated-measures changes from baseline in PANSS total scores, there was a significant improvement in the difference in PANSS total scores from baseline to the end of the study compared with placebo: 90-mg RBP-7000, -6.148 points (95% confidence interval [CI], -9.982 to -2.314, P = .0004); 120-mg RBP-7000, -7.237 points (95% CI, -11.045 to -3.429, P < .0001). The absolute change from baseline in PANSS total score was -15.367 points for the 90-mg dose and -16.456 points for the 120-mg dose.[4] Completion rates across all 3 arms were comparable: placebo 70.6%, RBP-7000 90 mg 77.6%, and RBP-7000 120 mg 71.4%.

Tolerability. In the 8-week phase III efficacy trial of RBP-7000, adverse effects occurring with an incidence ≥5% and at least twice the rate of placebo were weight gain (placebo 3.4%, 90 mg 13.0%, 120 mg 12.8%) and sedation (placebo 0%, 90 mg 7.0%, 120 mg 7.7%).[10] Compared with baseline, participants had a mean weight gain at the end of the study of 2.83 kg in the placebo group, 5.15 kg in the 90-mg RBP-7000 group, and 4.69 kg in the 120-mg RBP-7000 group. There were no clinically significant differences at study endpoint in glucose and lipid parameters. Consistent with the known effects of risperidone, there were increases in mean prolactin levels during the 8-week study, the effects of which were greater for women. For men, mean prolactin levels from baseline to study end were: placebo: 9.8 ± 7.9 vs 9.9 ± 8.0 ng/mL; 90 mg: 8.9 ± 6.9 vs 22.4 ± 11.2 ng/mL; and 120 mg: 8.2 ± 5.2 vs 31.3 ± 14.8 ng/mL. For women, mean

Clinical Point

In clinical trials, significant improvement in PANSS total score occurred in patients receiving RBP-7000

Related Resource

- Carpenter J, Wong KK. Long-acting injectable antipsychotics: What to do about missed doses. Current Psychiatry. 2018; 17(7):10-12,14-19,56.

Drug Brand Names

Aripiprazole • Abilify
Carbamazepine • Carbatrol, Tegretol
Doxycycline • Atridox
Leuprolide acetate injectable suspension • Eligard
Paliperidone palmitate • Invega Sustenna
Risperidone • Risperdal
Risperidone extended-release injectable suspension • Perseris
Risperidone long-acting injection • Risperdal Consta

Clinical Point

There were increases in mean prolactin levels during the 8-week study, the effects of which were greater for women

prolactin levels from baseline to study end were: placebo: 12.8 ± 11.7 vs 10.4 ± 8.0 ng/mL; 90 mg: 7.7 ± 5.3 vs 60.3 ± 46.9 ng/mL; and 120 mg: 10.9 ± 8.6 vs 85.5 ± 55.1 ng/mL. In the pivotal study, discontinuations due to adverse events were low across all treatment groups: 2.5% for placebo vs 0% for 90 mg and 1.7% for 120 mg.[4] There was no single adverse reaction leading to discontinuation that occurred at a rate of ≥2% and greater than placebo in patients treated with RBP-7000.[10] There were no clinically relevant differences in mean changes from baseline in corrected QT, QRS, and PR intervals, and in heart rate. Similarly, in the 12-month, long-term safety study, there were no clinically relevant changes in mean electrocardiography interval values from baseline to post-dose assessments.[10]

Using a 100-point visual analog scale (VAS), injection site pain scores 1 minute after the first dose decreased from a mean of 27 to the range of 3 to 7 for scores obtained 30 to 60 minutes post-dose. In the 12-month long-term safety study, 1-minute post-dose injection site pain VAS scores were highest on Day 1 (mean of 25) and decreased over time with subsequent injections (14 to 16 following last injection).[10]

Clinical considerations

Unique properties. RBP-7000 uses the established Atrigel system to provide effective antipsychotic levels in the first week of treatment, without the need for bridging oral coverage or a second loading injection. The abdominal subcutaneous injection volume is relatively small (0.6 mL or 0.8 mL).

Why Rx? The reasons to prescribe RBP-7000 for adult patients with schizophrenia include:

- no oral coverage required at the initiation of treatment
- effective plasma active moiety levels are seen within the first week without the need for a second loading injection
- monthly injection schedule.

Dosing. The recommended dosage of RBP-7000 is 90 mg or 120 mg once monthly, equivalent to 3 mg/d or 4 mg/d of oral risperidone, respectively. Oral risperidone tolerability should be established before the first injection. No oral risperidone coverage is required. RBP-7000 has not been

Bottom Line

RBP-7000 (Perseris) is the second long-acting injectable (LAI) form of risperidone approved in the U.S. Unlike risperidone microspheres (Consta), RBP-7000 does not require any oral risperidone coverage at the beginning of therapy, provides effective drug levels within the first week of treatment with a single injection, and uses a monthly dosing interval. RBP-7000 does not require loading upon initiation. The monthly injection is <1 mL, is administered in abdominal subcutaneous tissue, and uses the Atrigel system.

studied in patients with renal or hepatic impairment and should be used with caution in these patients. Prior to initiating treatment in these patients, it is advised to carefully titrate up to at least 3 mg/d of oral risperidone. If a patient can tolerate 3 mg/d of oral risperidone and is psychiatrically stable, then the 90-mg dose of RBP-7000 can be considered.[10]

Contraindications. The only contraindications for RBP-7000 are known hypersensitivity to risperidone, paliperidone (9-OH risperidone), or other components of the injection.

Clinical Point

RBP-7000 has not been studied in patients with renal or hepatic impairment and should be used with caution in these patients

References

1. Kishimoto T, Hagi K, Nitta M, et al. Effectiveness of long-acting injectable vs oral antipsychotics in patients with schizophrenia: a meta-analysis of prospective and retrospective cohort studies. Schizophr Bull. 2018;44(3):603-619.
2. Meyer JM. Converting oral to long acting injectable antipsychotics: a guide for the perplexed. CNS Spectrums. 2017;22(S1):14-28.
3. Risperdal Consta [package insert]. Titusville, NJ: Janssen Pharmaceuticals, Inc; 2018.
4. Nasser AF, Henderson DC, Fava M, et al. Efficacy, safety, and tolerability of RBP-7000 once-monthly risperidone for the treatment of acute schizophrenia: an 8-week, randomized, double-blind, placebo-controlled, multicenter phase 3 study. J Clin Psychopharmacol. 2016;36(2):130-140.
5. Remington G, Teo C, Mann S, et al. Examining levels of antipsychotic adherence to better understand nonadherence. J Clin Psychopharmacol. 2013;33(2):261-263.
6. Hard ML, Wehr AY, Du Y, et al. Pharmacokinetic evaluation of a 1-day treatment initiation option for starting long-acting aripiprazole lauroxil for schizophrenia. J Clin Psychopharmacol. 2018;38(5):435-441.
7. Hard ML, Wehr AY, Sadler BM, et al. Population pharmacokinetic analysis and model-based simulations of aripiprazole for a 1-day initiation regimen for the long-acting antipsychotic aripiprazole lauroxil. Eur J Drug Metab Pharmacokinet. 2018;43(4):461-469.
8. Southard GL, Dunn RL, Garrett S. The drug delivery and biomaterial attributes of the ATRIGEL technology in the treatment of periodontal disease. Expert Opin Investig Drugs. 1998;7(9):1483-1491.
9. Gomeni R, Heidbreder C, Fudala PJ, Nasser AF. A model-based approach to characterize the population pharmacokinetics and the relationship between the pharmacokinetic and safety profiles of RBP-7000, a new, long-acting, sustained-released formulation of risperidone. J Clin Pharmacol. 2013;53(10):1010-1019.
10. Perseris [package insert]. North Chesterfield, VA: Indivior Inc; 2018.
11. Malik K, Singh I, Nagpal M, et al. Atrigel: a potential parenteral controlled drug delivery system. Der Pharmacia Sinica. 2010;1(1):74-81.
12. Sartor O. Eligard: leuprolide acetate in a novel sustained-release delivery system. Urology. 2003;61(2 Suppl 1):25-31.
13. Risperdal [package insert]. Titusville, NJ: Janssen Pharmaceuticals, Inc; 2018.
14. de Leon J, Wynn G, Sandson NB. The pharmacokinetics of paliperidone versus risperidone. Psychosomatics. 2010;51(1):80-88.
15. Ivaturi V, Gopalakrishnan M, Gobburu JVS, et al. Exposure-response analysis after subcutaneous administration of RBP-7000, a once-a-month long-acting Atrigel formulation of risperidone. Br J Clin Pharmacol. 2017;83(7):1476-1498.
16. Laffont CM, Gomeni R, Zheng B, et al. Population pharmacokinetics and prediction of dopamine D2 receptor occupancy after multiple doses of RBP-7000, a new sustained-release formulation of risperidone, in schizophrenia patients on stable oral risperidone treatment. Clin Pharmacokinet. 2014;53(6):533-543.
17. Laffont CM, Gomeni R, Zheng B, et al. Population pharmacokinetic modeling and simulation to guide dose selection for RBP-7000, a new sustained-release formulation of risperidone. J Clin Pharmacol. 2015;55(1):93-103.