

Sustained-Release Risperidone via Subcutaneous Injection: A Systematic Review of RBP-7000 (PERSERIS™) for the Treatment of Schizophrenia

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Abstract

RBP-7000 (PERSERIS™) is a once-monthly subcutaneously administered formulation of risperidone that does not require oral supplementation when initiated. As with risperidone microspheres, RBP-7000 is required to be stored in a refrigerator. The injection kit, consisting of two syringes (one containing liquid polymer, the other containing risperidone powder), will need to come to room temperature prior to mixing their contents. RBP-7000 is administered in the abdomen using an 18 G 5/8-inch length needle. In an 8-week Phase 3 study in patients with acute schizophrenia, monthly RBP-7000 at doses of 90 mg (equivalent to oral risperidone 3 mg/day) and 120 mg (equivalent to oral risperidone 4 mg/day) were superior to placebo on changes in the PANSS total score. Overall tolerability was consistent with what is already known about risperidone/paliperidone, and the most common adverse reactions ($\geq 5\%$ and greater than twice placebo) were increased weight, sedation/somnolence, and musculoskeletal pain. Mean subject-reported injection site pain Visual Analog Scale scores (0=no pain to 100=unbearably painful) were similar for all treatment groups following both injections; with pain scores decreasing from a mean of 27 at 1 minute after the first dose to a range of 3 to 7 at 30 to 60 minutes postdose. RBP-7000 represents the first second-generation antipsychotic to be available as a subcutaneously administered long-acting injectable; having different choices of formulations can make the difference in finding the right intervention for the right patient.

Key Words: Schizophrenia, Risperidone, Long-Acting Injectable, Subcutaneous, Evidence-Based Treatment

Introduction

RBP-7000 (brand name PERSERIS™) is a sustained release formulation of risperidone administered by subcutaneous injection every 4 weeks, and received approval by the U.S. Food and Drug Administration (FDA) in July 2018 for the treatment of schizophrenia in adults (1, 2). Risperidone itself received initial FDA approval in 1993 and generic oral formulations are widely available (3). A long-acting intramuscular formulation of risperidone (risperidone microspheres), administered every 2 weeks, was commercial-

ized in 2003 (4, 5). Paliperidone, the active metabolite of risperidone, was subsequently made available in oral and long-acting injectable formulations, with dosing intervals as long as 3 months for the latter (6-10). RBP-7000 represents a new formulation for the risperidone/paliperidone group of antipsychotics and is the first second-generation antipsychotic to become available as a subcutaneous extended-release injection. Although this route of administration is not new to antipsychotics, as fluphenazine decanoate was able to be injected either subcutaneously or intramuscularly (11), it is a relatively novel antipsychotic injection technique for most clinicians and their patients. Apart from the risperidone/paliperidone group of antipsychotics, the only other currently available long-acting injectable second-generation antipsychotics are olanzapine (12, 13), and two different preparations of aripiprazole (14-18).

This paper reviews the pharmacology of RBP-7000 and the evidence supporting its use in persons with schizophre-

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What are number needed to treat (NNT) and number needed to harm (NNH)?*

“P-values,” even as low as $p < 0.00001$, do not necessarily mean that a result is clinically relevant. In order to determine possible clinical relevance (i.e., clinical significance), effect size needs to be evaluated. Number needed to treat (NNT) and number needed to harm (NNH) are measures of effect size that are clinically intuitive. NNT answers the question: “How many patients would you need to treat with Intervention A instead of Intervention B before you would expect to encounter one additional positive outcome of interest?” NNH answers the question: “How many patients would you need to treat with Intervention A instead of Intervention B before you would expect to encounter one additional outcome of interest that you would like to avoid?”

NNT (used for desired outcomes) and NNH (used for undesired outcomes) are simple to calculate:

A=frequency of outcome for Intervention A

B=frequency of outcome for Intervention B

$NNT \text{ or } NNH = 1/(A-B)$

For example, if giving a test medication results in response 50% of the time and giving placebo results in response 25% of the time, NNT for response for the test medication vs. placebo is $1/(50\%-25\%)=1/(0.50-0.25)=1/(0.25)=4$. Thus, for every 4 persons given the test medication instead of placebo, you would expect to encounter one additional responder.

Most psychotropic medications for most indications have NNT values between 3 and 9 for clinically relevant definitions of response. The *lower* the NNT the more often desired outcomes are encountered. On the other hand, *higher* NNH values are optimal, so that adverse outcomes are seldom encountered.

NNH values 10 or greater generally denote tolerability outcomes that are not excessively problematic; however, there are always exceptions if the adverse effect is serious and/or persistent—in that case desirable NNH values could be much higher. On the other hand, a single-digit NNH (i.e., < 10) may be acceptable if the adverse event is mild or moderate, does not lead to discontinuation, is temporary or causes little distress, and does not pose a serious health risk, or if a treatment has good (single-digit NNT) efficacy and there is a compelling need for efficacy that mitigates the low NNH tolerability limitation.

An additional tutorial for the use of NNT and NNH that is free to access can be found at www.ncbi.nlm.nih.gov/pmc/articles/PMC4140623/

*Reprinted from McEvoy JP, Citrome L: Brexpiprazole for the treatment of schizophrenia: a review of this novel serotonin-dopamine activity modulator. *Clinical Schizophrenia & Related Psychoses* 2016;9(4):177-186.

nia. A literature search was conducted 29 July 2018 using the U.S. National Library of Medicine’s PubMed.gov resource (<https://www.ncbi.nlm.nih.gov/pubmed/>), the Web of Science bibliographic resource (<https://clarivate.com/products/web-of-science/>), the EMBASE literature database (<https://www.embase.com>), as well as querying ClinicalTrials.gov (<https://clinicaltrials.gov/>), using the search term ‘RBP-7000’. Other sources of information included the product label (1). Effect sizes are described using the evidence-based medicine metrics of number needed to treat (NNT) and number needed to harm (NNH) whenever these could be calculated (see Box).

Literature Search Results

A total of 8 entries were found on PubMed.gov, 18 on Web of Science, and 20 using EMBASE, and after eliminating duplicates, there were 6 reports specifically on RBP-

7000 (21-26), one paper on dose equivalents for long-acting injectable antipsychotics (including RBP-7000) (27), and a paper focusing on therapeutic drug monitoring studies for long-acting risperidone (28). There was only one extant placebo-controlled efficacy trial conducted and this was reported in a primary publication (22). An additional 3 conference abstracts were found (29-31) that covered topics that appeared to be different from that of the published papers. The search of ClinicalTrials.gov provided 6 records (see Table 1).

Pharmacodynamics

The product label describes risperidone as having high affinity for the serotonin type 2 (5-HT₂), dopamine type 2 (D₂), α 1 and α 2 adrenergic, and H₁ histaminergic receptors, low to moderate affinity for the serotonin 5-HT_{1C}, 5-HT_{1D}, and 5-HT_{1A} receptors, weak affinity for the dopamine D₁

Table 1 Completed Clinical Trials of RBP-7000 for Schizophrenia, as Registered at ClinicalTrials.gov; All Were Conducted in the U.S.

ClinicalTrials.gov identifier, other identifier(s)	Title	Length (weeks)	Phase	N	Dose (monthly)	Comments
NCT02765555, RB-US-09-0007	An Open-Label, Single-Center, Single-Dose, Phase 1, First in Man Study of the Safety, Tolerability and Pharmacokinetic Profile of RBP-7000	12	1	12	60 mg	Started March 2010 and completed September 2010.
NCT02768649, RB-US-09-0008	A Phase I, Open-Label, Single-Center, Single Ascending Dose Study of the Safety, Tolerability, and Pharmacokinetic Profile of RBP-7000 at Low, Medium, and High Doses	12	1	45	60, 90, 120 mg	Started April 2011 and completed February 2012. See also (23, 25).
NCT01677377, RB-US-09-0009	Phase 2A Study as an Open-Label, Multiple Ascending Dose With Randomized Subjects to Receive a Single Dose of One of Three Dose Levels	15	2	45	60, 90, 120 mg	Started August 2012 and completed April 2013. See also (23, 24).
NCT02109562, RB-US-09-0010	A Phase 3, Randomized, Double-Blind, Placebo-Controlled, Multicenter Study to Evaluate the Efficacy, Safety and Tolerability of RBP-7000 as a Treatment in Subjects With Acute Schizophrenia Over 8 Weeks (2 Subcutaneous Doses)	8	3	354*	90, 120 mg	Started April 2014 and completed December 2014. See also (21, 22, 26).
NCT02687984, RB-US-15-0001	A Multicenter, Randomized, Open-Label, Single-Dose Study to Evaluate the Pharmacokinetics, Safety, and Tolerability of RBP-7000 Using Poly (DL-lactide-co-glycolide) Polymer of Two Different Molecular Weights (Low and High Molecular Weights as Test Treatments) Compared to Intermediate Molecular Weight (Reference Treatment) Polymer in Subjects With Schizophrenia	4	1	44	120 mg with differing polymers	Started February 2016 and completed May 2016.
NCT02203838, RB-US-13-0005	An Open-Label, Long-Term Safety and Tolerability Study of RBP-7000 in the Treatment of Subjects With Schizophrenia	58	3	500	120 mg	Option to down-titrate to 90 mg. Started June 2014 and completed September 2016. See also (29).

*Randomized

receptor and the haloperidol-sensitive sigma site, and no affinity for cholinergic muscarinic or β_1 and β_2 adrenergic receptors (1). More precise examination of affinity and function informs us that the receptor for which risperidone has the strongest affinity is the 5-HT_{2A} receptor, with a K_i of 0.49 nM and with risperidone functioning as an antagonist/inverse agonist at that receptor (3). This is followed by somewhat lower affinity at α_2c (K_i 2.4 nM, antagonist), D₂ (K_i 3.2 nM, antagonist), 5-HT₇ (K_i 3.5 nM, irreversible antagonist), α_2b (K_i 4.6 nM, antagonist), α_1a (K_i 8 nM, antagonist), and α_2a (K_i 9.5 nM, antagonist) receptors, with the remainder of other receptors associated with K_i values >10 nM (3). The main active metabolite of risperidone, 9-OH risperidone (paliperidone), has generally similar binding affinities, but with a notably higher affinity (lower K_i) for D₃ receptors (K_i 7.5 nM, antagonist), which may have some clinical relevance (19, 20).

Pharmacokinetics and Dosing

RBP-7000 is supplied as a sterile two-syringe mixing system. One syringe is prefilled with the liquid delivery system consisting of a biodegradable DL-lactide-co-glycolide polymer (80:20 molar ratio of lactide to glycolide) dissolved in N-methyl-2-pyrrolidone, a water-miscible, biocompatible solvent (1); this delivery system is also referred to as the ATRIGEL delivery system (25). The second syringe is prefilled with risperidone powder (1). Once RBP-7000 is prepared by mixing the contents of the 2 syringes, it is injected subcutaneously in the abdomen. The risperidone in RBP-7000 is both dissolved and suspended in that polymeric solution (23). After injection, the delivery system solidifies upon contact with body fluids and the resulting biodegradable implant delivers risperidone in a controlled fashion over an extended period of time. RBP-7000 dosages of 60, 90 and 120 mg monthly were tested; however, only the 90 and 120 mg doses are commercially available.

The pharmacokinetics of risperidone and total active moiety (risperidone + paliperidone) following subcutaneous injection were evaluated in persons with clinically stable schizophrenia after single doses (60 mg, 90 mg, and 120 mg) (N=101 across 3 studies [NCT02765555, NCT02768649, NCT02687984]) and repeated monthly doses (60 mg, 90 mg, and 120 mg) (N=45 in 1 study [NCT01677377]). In the latter study (24), the open-label design included patients clinically stabilized on oral risperidone (2, 3 or 4 mg/day) who were switched to receive monthly 60-, 90- or 120-mg injections of RBP-7000, respectively. Patients were thereafter switched back to oral risperidone. A report combined data from this study with an earlier one (25) (NCT02768649) in order to estimate clinically effective doses of RBP-7000, and showed similar active moiety plasma exposure at steady-state for 90 mg of RBP-7000 monthly and 25 mg of risperidone microspheres every 2 weeks (23). RBP-7000 at the doses of 60 and 90 mg provided similar active moiety plasma concentrations at steady-state compared to 50 and 100 mg equivalent of paliperidone monthly (i.e., 78 mg and 156 mg paliperidone palmitate monthly), respectively (23).

Risperidone plasma concentrations were observed with a time to maximum concentration of 4 to 6 hours and approached steady-state levels after the first subcutaneous injection, with a similar pattern observed for paliperidone and total active moiety. Steady-state plasma concentrations were reached by the end of the second injection for risperidone, paliperidone, and total active moiety and were maintained for 4 weeks after the last injection with mean accumulation ratios for risperidone ranging from 1.2 to 1.7 based on total exposure measured by the area under the concentration time curve, and from 0.9 to 1.3 based on overall maximum concentration, indicating no or modest accumulation; similar values were observed for paliperidone and total active moiety. Of importance, total active moiety concentrations reached clinically relevant levels after the first injection without use of a loading dose or any supplemental oral risperidone. With multiple dosing, plasma levels were dose-proportional over the range of 60 to 120 mg administered monthly. Based on average plasma concentrations of risperidone and total active moiety, the 90-mg dose of RBP-7000 monthly corresponds to 3 mg/day of oral risperidone and RBP-7000 120 mg monthly corresponds to 4 mg/day of oral risperidone.

After single subcutaneous injection, RBP-7000 demonstrated two absorption peaks for risperidone in plasma, both with similar magnitude. The first occurs 4 to 6 hours as noted earlier and is due to an initial release of the drug during the depot formation process. The second peak of plasma risperidone is observed at 10 to 14 days postdose and is associated with the slow release of risperidone from the subcutaneous depot. Similar effects were seen for paliperidone and total

active moiety. Following a single subcutaneous injection of RBP-7000, the apparent terminal half-life of risperidone ranges between 9 and 11 days on average. Specific analyses to evaluate dose dumping were also done where the differences in active moiety concentrations due to possible dose dumping effects were small and not deemed to be clinically relevant (31). The apparent volume of distribution is large. Risperidone is bound to albumin and α 1-acid glycoprotein; plasma protein binding of risperidone is about 90%, and that of paliperidone, 77%.

Risperidone is extensively metabolized in the liver via cytochrome CYP2D6 with a minor contribution by CYP3A4. A minor metabolic pathway is through N-dealkylation. There is no need for dose adjustment based on genotype of CYP2D6. Risperidone and its metabolites are eliminated via the urine and, to a much lesser extent, via the feces. Based on population pharmacokinetic analyses, age, sex and race do not have a clinically meaningful effect on the pharmacokinetics of RBP-7000. The product label notes that no specific drug interaction studies have been performed with RBP-7000, nor has RBP-7000 been studied in persons with renal or hepatic impairment, and thus the guidance provided regarding drug-drug and drug-disease interactions is based on studies with oral risperidone. It is noted that carbamazepine and other strong CYP3A4 inducers decrease plasma concentrations of risperidone and that fluoxetine, paroxetine, and other strong CYP2D6 inhibitors increase risperidone plasma concentration (1). Prior to initiating treatment with RBP-7000 in persons with renal or hepatic impairment, the product label advises that patients be carefully titrated up to at least 3 mg daily of oral risperidone and that if patients can tolerate 3 mg of oral risperidone and are psychiatrically stable, a dose of RBP-7000 90 mg may be considered (1).

Efficacy in Patients with Schizophrenia

Table 1 outlines the clinical trials of RBP-7000, as registered on ClinicalTrials.gov. Efficacy data are available from the pivotal trial (NCT02109562) as published in primary (22) and secondary reports (21, 26), and summarized in the product label (1), with supplemental information reported in a conference abstract (30). The ClinicalTrials.gov record provides additional information about study design.

The pivotal trial consisted of randomizing acutely ill inpatients with schizophrenia, age 18 to 55 years, to receive 8 weeks of double-blind monthly treatment with 90 or 120 mg of RBP-7000 or placebo (i.e., the delivery system only), administered subcutaneously in the lower quadrant of the abdomen rotating right and left on Day 1 and 29. Patients who completed this study had the option of entering into a long-term safety study in which they would receive RBP-7000 (NCT02203838) (29).

Individuals who met the initial screening criteria at the first visit were placed into an inpatient setting if they were not already in such a setting and remained as inpatients during the course of the study. Inclusion criteria included a Positive and Negative Syndrome Scale (PANSS) total score between 80 and 120 at the first visit and a score of >4 on ≥ 2 of the following 4 PANSS items: hallucinatory behavior, delusions, conceptual disorganization, or suspiciousness/persecution. The diagnosis of acute exacerbation of schizophrenia and the PANSS total score between 80 and 120 were confirmed through an independent video-conferenced interview. Excluded were patients with an improvement in their PANSS total score of $\geq 20\%$ between the initial screening visit and first injection (Day 1), or if they had been treated at any time with clozapine for treatment-resistant schizophrenia, or if they had met the criteria for substance dependence (other than for nicotine or caffeine) before screening. Patients taking daily oral risperidone at a dose ≥ 6 mg/day were also excluded, as were patients who received a depot antipsychotic within 120 days of screening. Patients were tapered off their current oral antipsychotics (if applicable) during the screening period (week prior to Day 1). During the initial screening visit, subjects received a 0.25-mg tablet of oral risperidone on 2 consecutive days to assess the tolerability of risperidone. Concomitant administration of lorazepam was permitted for agitation and/or anxiety through the end of Week 2. Zolpidem for insomnia was permitted throughout the study. Newly emergent extrapyramidal symptoms (EPS) could be treated with propranolol and concomitant use of benztropine. However, no concomitant medications were allowed 12 hours before administration of the efficacy or EPS rating scales. Clinical assessments for efficacy included the PANSS and the Clinical Global Impression-Severity (CGI-S) rating scales. Injection-specific adverse outcomes were evaluated by ascertainment of injection site reactions and assessing subject-reported injection site pain using a Visual Analog Scale (VAS).

The quality of the pivotal efficacy study (i.e., the risk of bias) appears reasonable in that randomization was by an interactive Web response system and that blinded study personnel were not allowed to be present during study drug preparation or when the injection was administered. After the injection and the removal of study-related injection materials from the treatment area, the injection site was assessed to document any injection site reactions. Injection volume was identical for placebo vs. RBP-7000. Study completion rates were 70.6%, 77.6%, and 71.4% of persons in the placebo, 90-mg, and 120-mg groups, respectively.

Among the 354 patients randomized, 116 were assigned to RBP-7000 90 mg, 119 assigned to RBP-7000 120 mg, and 119 assigned to placebo. Mean baseline PANSS total scores ranged from 94 to 96 across the groups. Most patients were

male (74% to 83% per group), and the mean ages were 40 to 43 years in each group. Most patients in this study were African American (71% to 75% per group). The most common reason for early discontinuation was withdrawal of consent, with rates of 17.6%, 17.2%, and 21.0% in the placebo, 90-mg, and 120-mg groups, respectively.

Patients randomized to RBP-7000 evidenced superiority to placebo on the primary outcome of change from baseline on the PANSS total score, with placebo-subtracted differences of -6.1 and -7.2 PANSS points for the 90- and 120-mg groups, respectively (the product label reports placebo-subtracted differences of -6.5 and -10.2 PANSS points, respectively; the FDA required a slightly different analysis to be done than what was originally executed [Indivior, personal communication, 7 August 2018]). Significant improvement in the mean change from baseline in the PANSS total scores for both the 90- and 120-mg groups vs. placebo were observed at each time point (Days 15, 29, and 43 and at the end of the study). Both RBP-7000 treatment groups were superior to placebo on the CGI-S (the key secondary outcome measure), with placebo-subtracted differences of -0.35 and -0.40 CGI-S points for the 90- and 120-mg groups, respectively. As with the PANSS total score, significant improvement in the mean change from baseline in the CGI-S scores for both the 90- and 120-mg groups vs. placebo were also observed at each time point. Additional analyses demonstrated statistically significant advantages of RBP-7000 vs. placebo for the PANSS positive and general psychopathology subscales, but not for the PANSS negative subscale. Subgroup analyses by gender, age, and race did not suggest any clear evidence of differential responsiveness to RBP-7000 (1); however, preliminary analyses suggest that polymorphisms in the HTR2C, HTR2A, and MC4R receptors may affect individual responses to RBP-7000 (30). Exposure-response analysis was established between total active moiety plasma exposure (risperidone + paliperidone) and PANSS and CGI-S scores (21). Measures of health-related quality of life were also assessed (26); significantly greater improvements in these outcomes as well as overall well-being were demonstrated in patients randomized to RBP-7000 compared to placebo, with a greater effect observed for the 120-mg dose.

Categorical outcomes using the PANSS and/or CGI-S were not reported (such as percentage of subjects who improved by $\geq 30\%$ from baseline on the PANSS total score) and, hence, estimates of NNT vs. placebo could not be calculated. However, from the data made available in the published report (22), the standardized mean difference (Cohen's *d*) for the primary outcome of change from baseline on the PANSS total score was calculated to be 0.48 (95% CI 0.21–0.74) for the 90-mg group vs. placebo, and 0.56 (95% CI 0.29–0.83) for the 120-mg group vs. placebo, represent-

Table 2 Potentially Relevant Adverse Events Associated with the Use of RBP-7000 ($\geq 2\%$ in Any RBP-7000 Treated Group and Greater than Placebo) as Observed in the Pivotal Trial for Schizophrenia, Percentage of Subjects, and Number Needed to Harm vs. Placebo and 95% Confidence Intervals*

Adverse Event	Placebo (N=118) n (%)	RBP-7000					
		90 mg (N=115)		120 mg (N=117)		Pooled Doses (N=232)	
		n (%)	NNH (95% CI)	n (%)	NNH (95% CI)	n (%)	NNH (95% CI)
Abdominal discomfort	2 (1.7)	3 (2.6)	110 (ns)	3 (2.6)	116 (ns)	6 (2.6)	113 (ns)
Akathisia	5 (4.2)	3 (2.6)	NA	8 (6.8)	39 (ns)	11 (4.7)	199 (ns)
Anxiety	6 (5.1)	3 (2.6)	NA	8 (6.8)	57 (ns)	11 (4.7)	NA
Back pain	5 (4.2)	4 (3.5)	NA	8 (6.8)	39 (ns)	12 (5.2)	107 (ns)
Constipation	6 (5.1)	8 (7.0)	54 (ns)	9 (7.7)	39 (ns)	17 (7.3)	45 (ns)
Dry mouth	2 (1.7)	2 (1.7)	2262 (ns)	3 (2.6)	116 (ns)	5 (2.2)	218 (ns)
Extrapyramidal disorder	1 (0.8)	5 (4.3)	29 (ns)	2 (1.7)	116 (ns)	7 (3.0)	47 (ns)
Increased appetite	2 (1.7)	2 (1.7)	2262 (ns)	4 (3.4)	58 (ns)	6 (2.6)	113 (ns)
Injection site erythema	6 (5.1)	7 (6.1)	100 (ns)	5 (4.3)	NA	12 (5.2)	1141 (ns)
Injection site pain	23 (19.5)	18 (15.7)	NA	26 (22.2)	37 (ns)	44 (19.0)	NA
Muscle spasms	0	0	NA	3 (2.6)	39 (ns)	3 (1.3)	78 (ns)
Musculoskeletal pain	3 (2.5)	6 (5.2)	38 (ns)	6 (5.1)	39 (ns)	12 (5.2)	38 (ns)
Musculoskeletal stiffness	2 (1.7)	3 (2.6)	110 (ns)	1 (0.9)	NA	4 (1.7)	3422 (ns)
Pain in extremity	6 (5.1)	1 (0.9)	NA	9 (7.7)	39 (ns)	10 (4.3)	NA
Sedation and somnolence combined terms	0	8 (7.0)	15 (9–44)	9 (7.7)	13 (8–35)	17 (7.3)	14 (10–26)
Somnolence	0	6 (5.2)	20 (11–87)	5 (4.3)	24 (13–165)	11 (4.7)	22 (14–50)
Toothache	7 (5.9)	9 (7.8)	53 (ns)	8 (6.8)	111 (ns)	17 (7.3)	72 (ns)
Weight gain	4 (3.4)	15 (13.0)	11 (6–38)	15 (12.8)	11 (7–40)	30 (12.9)	11 (7–25)

*From the published report for those events where the rate was $\geq 5\%$ for any RBP-7000 group (22) and from the product label where the 5% threshold was not reached (n's for these events were calculated by multiplying percentage reported in the product label by the total N for that group) (1).

CI=confidence interval; NA=no difference or rate was higher for placebo; NNH=number needed to harm; ns=not significant at the $p < 0.05$ threshold and thus the 95% CI is not shown.

ing a moderate effect size and consistent with what has generally been observed with other first-line second-generation antipsychotic medications. The corresponding standardized mean differences as calculated from the data in the product label differ slightly, 0.39 (95% CI 0.13–0.66) and 0.61 (95% CI 0.34–0.87), respectively, but are more suggestive of a dose-response.

Side Effects, Safety and Tolerability in Patients with Schizophrenia

Safety and tolerability data collected during the 8-week pivotal trial are reported in the published paper (22). There are also data from a long-term safety and tolerability study that has been presented at a conference (29). As per the product label, the safety of RBP-7000 was evaluated in a total of 814 adult subjects with schizophrenia who received at least 1 dose during the clinical development program (1). A total of 322 persons were exposed to RBP-7000 for at least 6 months, of which 234 subjects were exposed for at least 12

months; 281 and 176 of these, respectively, received the 120-mg dose.

In the pivotal study, discontinuation rates because of adverse events were low: 2.5%, 0%, and 1.7% of persons in the placebo, 90-mg, and 120-mg groups, respectively. The most common adverse drug reactions ($\geq 5\%$ in any RBP-7000 treated group and greater than placebo) were weight increase, constipation, sedation/somnolence, pain in extremity, back pain, akathisia, anxiety, and musculoskeletal pain. Table 2 lists in alphabetical order all adverse events that were reported in $\geq 2\%$ in any RBP-7000 treated group and greater than placebo, their rates, and their respective calculated NNH estimates. Statistically significant NNH values vs. placebo were observed for sedation/somnolence (for both RBP-7000 doses pooled, NNH 14, 95% CI 10–26), somnolence (NNH 22, 95% CI 14–50), and weight gain (NNH 11, 95% CI 7–25). Overall, the systemic safety profile for RBP-7000 was consistent with the known safety profile of oral risperidone.

In the pivotal study, the frequency of reported injection

Table 3 Rates and Number Needed to Harm vs. Placebo for Weight Gain, Somnolence, and Akathisia, for Approved Long-Acting Injectable Second-Generation Antipsychotics in Adults as Observed in Acute Short-Term Studies for Schizophrenia (Doses Pooled)*

Antipsychotic, length of study(ies)	Weight gain ≥7% from baseline			Sedation adverse events			Akathisia adverse events		
	Rate (%)		NNH (95% CI)	Rate (%)		NNH (95% CI)	Rate (%)		NNH (95% CI)
	Placebo	Drug		Placebo	Drug		Placebo	Drug	
RBP-7000, 8 weeks	18.0	37.6	6 (4–10)	0 [†]	7.3 [†]	14 (10–26)	4.2	4.7	199 (ns)
Risperidone microspheres, 12 weeks	6	9	33 (ns)	3 [†]	5.4 [†]	42 (ns)	6 [‡]	7.6 [‡]	69 (ns)
Paliperidone palmitate, 9 and 13 weeks	3.3	8.7	19 (13–33)	3 [†]	8.7 [†]	59 (ns)	3	3.1	1839 (ns)
Aripiprazole monohydrate, 12 weeks	8.5	21.5	8 (5–21)	1.2	5.4	24 (13–225)	3.5	11.4	13 (8–43)
Aripiprazole lauroxil, 12 weeks	5.8	9.2	30 (ns)	1.4	2.2	139 (ns)	4.3	11.6	14 (9–33)
Olanzapine pamoate, 8 weeks	12.4	28.6	7 (5–13)	7 [†]	11.3 [†]	24 (ns)	NR	NR	NA

*Data relate to the long-acting injectable clinical trials in persons with acute schizophrenia (1, 4, 6, 8, 11-17, 22); however, the product label may also contain data from other clinical trials and in other populations, as well as provide information on dose-response. [†]Pooled term of somnolence/sedation as reported in the product label. [‡]Pooled term of akathisia/restlessness as reported in the product label.

CI=confidence interval; NA=not applicable; NR=not reported (did not meet threshold for reporting); NNH=number needed to harm; ns=not significant at the p<0.05 threshold and thus the 95% CI is not shown.

site reactions was similar across treatment groups, and the most common (≥5%) were injection site pain and erythema. Pain at the abdominal injection site was reported in 19.5%, 15.7%, and 22.2% of persons in the placebo, 90-mg, and 120-mg groups, respectively, suggesting no or little contribution to pain from the active medication, with pain mostly attributable to the injection itself. Mean subject-reported injection site pain VAS scores (0=no pain to 100=unbearably painful) were similar for all treatment groups following both injections; with pain scores decreasing from a mean of 27 at 1 minute after the first dose to a range of 3 to 7 at 30 to 60 minutes postdose (1). Similarly, in the 12-month, long-term safety study, the 1-minute postdose injection site pain VAS scores were highest on Day 1 with a mean score of 25 and decreased over time with subsequent injections with scores 14 to 16 following the last injection. Throughout the RBP-7000 clinical development program, the maximum reported intensity at any time point for each injection site assessment (pain, tenderness, inflammation/swelling and erythema) was none or mild for most subjects. Most subjects (≥79%) reported no tenderness, ≥75% reported no pain, ≥92% reported no erythema, and ≥88% reported no inflammation/swelling.

In the pivotal study, the overall incidence of EPS-related adverse events was low and similar across treatment groups compared with placebo, and consistent with what is known about exposure to oral risperidone at doses no higher than 4 mg/day. Moreover, there was minimal to no mean difference from baseline to the end of the study for rating scales used to assess antipsychotic-related movement disorders. The percentage of subjects in each treatment group who received

benztropine was 8.5%, 11.3%, and 9.4% in the placebo, 90-mg, and 120-mg groups, respectively. The percentage of subjects in each treatment group who received propranolol was 2.7%, 3.5%, and 4.3% in the placebo, 90-mg, and 120-mg groups, respectively.

In the pivotal study, compared with baseline, subjects had a mean weight gain at the end of the study of 2.8 kg, 5.1 kg, and 4.7 kg in the placebo, 90-mg, and 120-mg groups, respectively. The incidence of subjects with ≥7% increase in weight from baseline was 18.0%, 32.7%, and 42.1% in the placebo, 90-mg, and 120-mg groups, respectively; this resulted in NNH values vs. placebo of 7 (95% CI 4–31) and 5 (95% CI 3–8) for the 90-mg and 120-mg dose groups, respectively. Using a threshold of weight gain of ≥10%, the rates observed were 5.4%, 19.6%, and 19.3% in the placebo, 90-mg, and 120-mg groups, respectively; this resulted in NNH values vs. placebo of 7 (95% CI 5–18) and 8 (95% CI 5–19) for the 90-mg and 120-mg dose groups, respectively. These observations regarding weight gain are greater in magnitude than one would expect; the authors of the study (22) proffered the explanation that the patient demographics may be the reason for this because approximately 80% of patients in the study were African American, a group with an increased risk for obesity and weight gain, perhaps because of the increased prevalence of a risk allele associated with antipsychotic drug-induced weight gain. This explanation was also provided to help explain the weight gain observed in the acute trial of aripiprazole monohydrate (15), where the NNH vs. placebo was 8 (95% CI 5–21) for ≥7% increase in weight from baseline (see Table 3). Although mean glucose levels slightly increased from baseline to the end of the

study in the RBP-7000 groups compared with the placebo group where similar levels were observed from baseline to the end of the study, the levels themselves were still within the normal reference limits. Overall, there were no clinically relevant differences in mean values for mean fasting glucose and cholesterol parameters from baseline to the end of the study assessments for all groups. As anticipated for a risperidone-containing product, increases in mean prolactin levels were observed in both RBP-7000 groups, whereas prolactin levels for the placebo group remained stable. Larger increases in prolactin levels were observed with RBP-7000 120 mg than with 90 mg. Because most patients in the study were male, reproductive and other side effects in women (amenorrhea, galactorrhea, etc.) may have been underestimated.

A one-year, open-label, long-term, safety and tolerability study was completed (29). The study included completers from the pivotal 8-week study (rollover subjects) and new patients (de novo subjects). The new patients were required to have a diagnosis of schizophrenia and have a PANSS total score no higher than 70. Rollover subjects, who received 2 injections of placebo or RBP-7000 in the prior study, received 11 additional injections of open-label RBP-7000 (120 mg) in the current study. New subjects received 13 injections of open-label RBP-7000 (120 mg) after being titrated or converted to oral risperidone (3 or 4 mg/day). A single down-titration to 90 mg and a single up-titration back to 120 mg was permitted based on tolerability. The safety population included 500 subjects (92 rollover patients and 408 new patients) and 234 (46.8%) completed the study. Overall, demographics were similar to that of the pivotal study. Mean baseline PANSS total scores were 58 for the de novo subjects and 71 to 76 for the rollover patients. Overall, 11.6% of participants had an adverse event that led to study discontinuation, and 8.6% had an adverse event leading to dose modification. Adverse events that were reported in >5% of all subjects were injection site pain (13.0%), weight increase (12.8%), schizophrenia (7.8%), insomnia (7.0%), injection site nodule (6.8%), akathisia (6.0%), injection site induration (5.8%), and upper respiratory tract infection (5.2%). Most subjects (>80%) did not experience injection site reactions (pain, tenderness, erythema/redness or induration/swelling), either immediately after dosing or at 3 hours postdose. Only 2 subjects discontinued the study due to an injection site reaction. There were no clinically meaningful changes, patterns or trends observed in laboratory parameters or vital signs. Mean scores on antipsychotic-related movement disorder scales remained relatively stable across study visits. Although there is no placebo control to help interpret changes in the PANSS total score, rollover patients demonstrated continued improvement, and the de novo patients remained stable.

There were no clinically relevant differences in ECG intervals in subjects at rest in any treatment group compared with placebo in the pivotal trial (1, 22); similarly, in the 12-month, long-term safety study, there were no clinically relevant changes in mean ECG interval values from baseline to postdose assessments (1).

Instructions for Use

As with risperidone microspheres (4), RBP-7000 is required to be stored in a refrigerator at 2° to 8°C (36° to 46°F) (1). The injection kit will need to come to room temperature, 20°C to 25°C (68°F to 77°F), for at least 15 minutes prior to mixing. RBP-7000 can be stored in its unopened original packaging at room temperature for up to 7 days prior to administration, but after removal from the refrigerator the product needs to be used within 7 days or discarded.

For patients who have never taken risperidone, the product label recommends that tolerability with oral risperidone be established prior to starting RBP-7000 (1). Neither a loading dose nor any supplemental oral risperidone is recommended. Regarding missed doses, the instructions are for the patient to receive the next dose as soon as possible.

RBP-7000 is approved for abdominal subcutaneous injection by a healthcare professional (1). RBP-7000 is not intended for self-administration. The needle gauge is 18 (relatively larger than other long-acting injectable products where the range is 19–23 G) but the needle length is short (5/8-inch, compared with the 1- to 2-inch needle lengths required for intramuscular injection) (8). The total volume injected is 0.6 mL for the 90-mg dose and 0.8 mL for the 120-mg dose and these volumes are smaller than almost all the intramuscular formulation options (8). Preparation involves checking the kit, making sure two syringes are present: one syringe containing a liquid (used to inject) and one syringe containing the risperidone powder (to mix with the liquid). The next step is tapping the powder syringe upright to dislodge any packed powder, then removing the syringe caps and connecting the 2 syringes. The contents of the two joined syringes are mixed together by transferring the contents of the liquid syringe into the powder syringe and continuing with a back and forth motion, until there is a cloudy suspension that is uniform in color (the product label advises a total of 60 cycles of back and forth). Once fully mixed, the entire contents are transferred to the syringe that originally only contained the liquid, and the syringes are separated. The needle is then placed on the liquid syringe. The injection site on the abdomen needs to have adequate subcutaneous tissue that is free of skin conditions (e.g., nodules, lesions, excessive pigment). It is recommended that the patient is in the supine position. Injections are to be avoided where the skin is irritated, reddened, bruised, infected or scarred in any way.

Table 4 Summary of Characteristics of Risperidone- or Paliperidone-Containing Long-Acting Injectable Antipsychotics Commercially Available in the U.S.

	RBP-7000 (1)	Risperidone Microspheres (4)	Paliperidone Palmitate Once Monthly (9)	Paliperidone Palmitate Every Three Months (10)
Brand name (US)	Perseris	Risperdal Consta	Invega Sustenna	Invega Trinza
Year commercialized	2018	2003	2009	2015
Active moiety	Risperidone and paliperidone	Risperidone and paliperidone	Paliperidone	Paliperidone
Approved indications (all adult)	Schizophrenia	Schizophrenia; bipolar I disorder maintenance treatment (monotherapy or adjunctive to lithium or valproate)	Schizophrenia; schizoaffective disorder (monotherapy or adjunctive to stabilizers or antidepressants)	Schizophrenia
Contraindications	Known hypersensitivity to risperidone, paliperidone, or other components in the product	Known hypersensitivity to risperidone, paliperidone, or to any excipients in the product	Known hypersensitivity to paliperidone, risperidone, or to any excipients in the product	Known hypersensitivity to paliperidone, risperidone, or to any excipients in the product
Dosage forms/ strengths	Syringe kits: 90 mg, 120 mg	Vial kits: 12.5 mg, 25 mg, 37.5 mg, 50 mg	Injectable suspension: 39 mg, 78 mg, 117 mg, 156 mg, 234 mg	Injectable suspension: 273 mg, 410 mg, 546 mg, 819 mg
Requires adding diluent/liquid	Yes	Yes	No	No
Injection type	Subcutaneous	Intramuscular	Intramuscular	Intramuscular
Approved injection sites	Abdomen	Deltoid or gluteal muscle	Deltoid or gluteal muscle	Deltoid or gluteal muscle
Needle gauge and length	18 G and 5/8-inch	20 G and 2-inch, 21 G and 1-inch	22 G and 1.5-inch, 23 G and 1-inch	22 G and 1- or 1.5-inch
Injection volume	0.6 mL (90 mg), 0.8 mL (120 mg)	Approximately 2 mL	156 mg/mL; range 0.25 mL (39 mg) to 1.5 mL (234 mg)	312 mg/mL; range 0.9 mL (273 mg) to 2.6 mL (819 mg)
Injection interval (weeks)	4	2	4	12
Starting dose	90 or 120 mg	25 mg	234 mg day 1 and 156 mg day 8 (deltoid)	After treatment with 1-month paliperidone palmitate for at least 4 months: 273 mg, 410 mg, 546 mg, 819 mg (3.5 times the last dose of the once monthly formulation)
Maintenance dose	90 or 120 mg	25 mg, maximum 50 mg/2 weeks	117 mg, range 39–234 mg/4 weeks	Same as above
Half-life	9–11 days	3–6 days	25–49 days	84–95 days (deltoid), 118–139 days (gluteal)
Oral supplementation?	No	21 days after the initial injection and after any change in dose	No	No
Early dosing permitted?	No data	No data	21 days after last injection	2.5 months after last injection
Stored refrigerated?	Yes	Yes	No	No
Acquisition cost range (US)*	90 mg: \$1710 120 mg: \$2280	12.5 mg: \$213; 25 mg: \$426 37.5 mg: \$639; 50 mg: \$851	39 mg: \$391, 78 mg: \$783; 117 mg: \$1174 156 mg: \$1566; 234 mg: \$2349	273 mg: \$2349; 410 mg: \$3523; 546 mg: \$4697 819 mg: \$7046

IM=intramuscular; SC=subcutaneous; * Wholesale Acquisition Cost (WAC) on September 10, 2018 (rounded to nearest dollar); amounts for risperidone microspheres and paliperidone palmitate courtesy of SUNY Upstate University Hospital and amounts for RBP-7000 courtesy of Indivior. Prices are for the individual kits. Monthly costs can be calculated for risperidone microspheres by multiplying the stated cost by 2, and for paliperidone palmitate every three months by dividing the stated cost by 3.

Skin irritation can be minimized by rotating injection sites. The injection technique recommended consists of pinching the skin around the injection area enough to accommodate the size of the needle and, hence, lifting the adipose tissue from the underlying muscle to prevent accidental intramuscular injection. The acute angle of injection will depend on the amount of subcutaneous tissue. The needle is inserted fully into the subcutaneous tissue and the injection should be slow and steady. After injection, the needle is withdrawn at the same angle used for insertion and the pinched skin is then released. It is advised not to rub the injection area after the injection. If there is bleeding, a gauze pad or bandage can be applied but with minimal pressure. The patient should be advised that they may have a lump for several weeks that will decrease in size over time, and that it is important that the patient not rub or massage the injection site and to be aware of the placement of any belts or clothing waistbands.

RBP-7000 in Perspective

RBP-7000 will be competing directly with risperidone microspheres and to some extent with paliperidone palmitate. Table 4 outlines the “amenities of care” regarding risperidone- and paliperidone-containing long-acting injectable products. RBP-7000 will be an option where subcutaneous injection may be preferred, although cost and access issues may determine actual availability. Table 3 outlines the tolerability profiles for the available long-acting injectable antipsychotics with respect to weight gain, sedation/somnolence, and akathisia in persons with acute schizophrenia. Differences among the same molecular entities may be partly explained by the different populations being studied (differing demographics) and whether the study was conducted exclusively in an inpatient setting, as well as differences in doses tested and overall drug exposure. Overall, when comparing groups of patients, the data for the long-acting injectables are generally consistent with what we know about their orally administered counterparts (i.e., oral risperidone, paliperidone, aripiprazole, and olanzapine) (32). However, individual variation in tolerability, including the consideration of possible dose-response for both efficacy and tolerability, will dictate the optimal choice for the person being treated (33, 34). Although oral risperidone, risperidone microspheres and paliperidone palmitate have been approved for multiple indications, RBP-7000 at this time has received FDA approval only for the treatment of schizophrenia in adults (1).

An additional search was made using PubMed.gov for other mentions of new risperidone long-acting injectable formulations and this resulted in many reports summarizing both the techniques being developed and clinical trials

that have been completed (35-43). As per ClinicalTrials.gov, in Phase 3 of development are risperidone in situ microparticles (ISM) intended to be injected intramuscularly once-monthly (NCT03160521), a 6-month removable implant (BB-0817) for subcutaneous insertion (NCT02773576), and an injectable suspension (TV-46000) intended for subcutaneous use (NCT02773576). Two published reports of risperidone ISM were found (35, 36); oral supplementation is not required but reconstitution is needed prior to injection. Limited information has been published regarding BB-0817 (37); this polyurethane implant is designed to be placed in the upper arm and the active drug is released at a constant rate for 6 months, with a rapid onset of therapeutic drug levels. No published reports of TV-46000 were found. The ongoing development of these other long-acting injectable preparations of risperidone will add to the treatment armamentarium, but ease of use will spur adoption or lack thereof. Key considerations will be storage requirements, time and effort needed to prepare the injection, needle gauge and recommended injection sites, and dosing flexibility in terms of amount administered and time interval between injections.

Summary

RBP-7000 is the first of what promises to be a selection of long-acting formulations of risperidone administered by subcutaneous injection. RBP-7000 offers a once monthly option of a well-known second-generation antipsychotic without the need for oral supplementation. Its adoption will be predicated on the actual ease of storage (the refrigeration required is similar to that for risperidone microspheres) and the labor involved in reconstitution (also required for some of the other injectables, including risperidone microspheres, aripiprazole monohydrate, and olanzapine pamoate). It is unknown if subcutaneous injection into the abdomen will be preferred over deep intramuscular deltoid or gluteal injection, and the subjective perception of pain and discomfort may vary between individuals as well. A limiting factor may be the maximum dose of RBP-7000—120 mg monthly—equivalent to oral risperidone 4 mg/d; the product label advises that patients who are on stable oral risperidone doses lower than 3 mg/day or higher than 4 mg/day may not be candidates for RBP-7000. In the end, product acquisition cost to the hospital or health plan will determine extent of use given the availability of similar interventions. A limitation to our understanding of RBP-7000 is that the only extant controlled efficacy data come from a single short-term study. Controlled long-term data for RBP-7000 regarding maintenance of response and avoidance of relapse would be desirable to further characterize this new intervention.

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