**INTRODUCTION AND OVERVIEW OF OLDER AND NEWER AGENTS**

Schizophrenia is a complex psychiatric disorder that presents with symptoms such as hallucinations, delusions, disorganization, and cognitive dysfunction, and can vary greatly in severity between individuals. Patients can be classified under different stages of treatment known as acute, stabilization, or maintenance.

Antipsychotic medications are the mainstay of treatment in all phases. Although these drugs are efficacious, they are associated with a spectrum of adverse effects ranging from anticholinergic effects and weight gain to extrapyramidal symptoms (EPS), agranulocytosis, and seizures. Adverse drug reactions, and factors such as poor patient insight into their illness, substance abuse, and inadequate discharge planning, can contribute to non-adherence rates, which are as high as 41.2%. 

For many patients, non-adherence to pharmacotherapy leads to decompensation and relapse. Non-adherence results in generally negative outcomes for patients and increases the economic burden of treatment. Relapse and hospitalizations are major factors in the cost of treating schizophrenia. One study found that the average annual cost of relapse was $33,187 per patient, with hospitalizations making up most of that cost. Patients who had previously relapsed also had costs that were three times higher than those who had no prior relapse. Another study reported similar findings among patients taking atypical oral antipsychotics, showing that patients with at least two relapses had higher costs than those who had fewer than two relapses. These findings indicate that more relapses result in higher healthcare costs and that interventions to prevent relapse could reduce those costs.

One method that is believed to increase patient adherence is the utilization of long-acting injectable (LAI) antipsychotics. The following are available as LAI formulations: haloperidol, fluphenazine, olanzapine, risperidone, paliperidone, and aripiprazole. These formulations differ by their mechanism of drug release, dosing interval, and possible need for oral supplementation or loading dose regimens. Dosing intervals include biweekly, monthly, every six weeks, bimonthly, and quarterly administration depending on the agent and dose. It is well known that LAIs can reduce relapse rates, hospitalizations, and hospital length of stay, and studies suggest that atypical LAIs are cost-effective.

In addition, several studies show that some atypical LAIs, such as risperidone LAI (Risperdal Consta), improve patient quality of life. In several studies, risperidone LAI dose was found to be significantly higher continuation rates in comparison to other LAIs.

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Disclosure: Dr. Burdge and Dr. Karas report no financial or commercial interest in regard to this article. Professor Rey is a speaker for Alkermes PLC, Janssen.

**CHEMICAL AND PHYSICAL PROPERTIES**

Risperidone subcutaneous monthly injection (RSQM) uses Atrigel®, a drug delivery system utilized by several FDA-approved formulations of buprenorphine, leuprolide, octreotide, and doxycycline (for treatment of periodontitis), to allow a controlled release of medication over time. The injection solution employs a copolymer—poly D, L-lactide-co-glycolide (PLG)—which is dissolved in an N-methyl-2-pyrrolidone (NMP) solvent. Risperidone, a benzoisoxazole-derived atypical antipsychotic, is suspended in this solution. Post-injection and upon contact with bodily fluids, the NMP dissipates, leaving the PLG to solidify into a biodegradable implant that degrades over time to deliver a continuous release of

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**Perseris™: A New and Long-Acting, Atypical Antipsychotic Drug-Delivery System**

Andrew Karas, PharmD; Gary Burdge, PharmD; and Jose A. Rey, MS, PharmD, BCPP
Risperidone from the polymer matrix.\textsuperscript{27} This is in contrast to the microspherical risperidone LAI system, which uses a static flow method to integrate risperidone into a D, L-lactide-co-glycolide copolymer matrix for degradation over a 14-day period (via twice-monthly injection).\textsuperscript{28,29}

**PHARMACOLOGY AND MECHANISM OF ACTION**

Glycoprotein for both risperidone and paliperidone, which could limit the importance of this information.\textsuperscript{37} All other available LAIs—with the exception of fluphenazine decanoate, which can also be administered SQ—must be administered via IM injections in the deltoid or gluteal muscles, depending on the agent.\textsuperscript{35,36} Tolerance for oral treatment of risperidone should be established prior to starting RSQM. The labeling does not recommend a specific duration for establishing tolerability, but clinical studies used two 0.25-mg doses of risperidone on sequential days to establish tolerance.\textsuperscript{28,30}

The monthly injection is available in 90-mg and 120-mg doses, which are approximately equivalent to oral risperidone 3 mg/day and 4 mg/day, respectively. Unlike other atypical LAIs, no loading dose or oral overlap is required upon initiation. Although there is no recommendation on how to switch between formulations of other LAIs and RSQM, trial data and subsequent reviews compare this new information to the available literature to help establish approximate dose equivalencies. Based on a population pharmacokinetic model examining active moiety concentration and D\textsubscript{2} receptor occupancy, RSQM 90 mg and 120 mg are approximately equivalent to paliperidone palmitate 78 mg and 156 mg monthly LAI (50-mg and 100-mg paliperidone base), respectively, and RSQM 90 mg is approximately equivalent to 25 mg of the biweekly risperidone LAI.\textsuperscript{32} Rothe et al. compared phase 3 trial data for RSQM with published data for other atypical LAIs and extrapolated approximate dose equivalencies. Risperidone subcutaneous monthly injection may be approximately equivalent to 441 mg of aripiprazole lauroxil (Aristada\textsuperscript{®}), but there was no equivalent dose of RSQM for olanzapine (Zyprexa\textsuperscript{®} and Relpreviv\textsuperscript{TM}); however, the mechanism and use of aripiprazole and olanzapine are different from that of risperidone and paliperidone, which could limit the importance of this information.\textsuperscript{27}

Risperidone subcutaneous monthly injection is supplied as a powder syringe and a liquid drug delivery syringe. The syringes must be stored in a refrigerated environment and can be mixed by connecting them via their locking tips. The liquid contents are transferred to the powder-filled syringe for five cycles to complete the premixing of the medication, then transferred back and forth between the syringes for an additional 55

**PHARMACOKINETICS**

**Absorption**

After injection of RSQM, an SQ depot forms upon contact with body fluids. There are two absorption peaks, the first of which occurs four to six hours post-injection as a result of an initial release of risperidone while the depot is solidifying. A second peak occurs 10 to 14 days post-injection due to slow release from the SQ depot. Both peaks have a similar magnitude. An integrated population pharmacokinetic model revealed that patients with a smaller body mass index (BMI) had a higher initial peak, but BMI did not influence the second peak.\textsuperscript{31} Risperidone’s active metabolite 9HR also has two absorption peaks: the first occurs four to 48 hours post-injection and the second occurs seven to 11 days post-injection.\textsuperscript{30}

**Distribution**

Post-injection, the volume of risperidone distribution is large, with high protein binding to albumin and α1-acid glycoprotein for both risperidone and 9HR (90% and 77%, respectively).\textsuperscript{30}

**Metabolism and Elimination**

Risperidone is predominately metabolized through hydroxylation by CYP2D6, with minor metabolism by CYP3A4 to 9HR. The CYP2D6 enzyme is known for having genetic polymorphisms expressed as poor, intermediate, extensive, or ultra-rapid metabolizers. In a clinical pharmacokinetic study of RSQM, a range of patients with different CYP2D6 phenotypes were included. An active moiety concentration was created based on calculations derived from observed risperidone and 9HR serum concentrations, which showed that although risperidone and 9HR ratios vary among patients with different CYP2D6 phenotypes, their active moiety concentrations remain similar.\textsuperscript{32,33} Thus, there is no current data supporting the need to dose-adjust based on genotype of CYP2D6.\textsuperscript{30} In addition, the prescribing information for oral risperidone does not give any recommendations to adjust dosages based on phenotypic variations in CYP2D6 enzyme metabolizers.\textsuperscript{30}

Both risperidone and 9HR are excreted primarily in the urine (70%). The terminal half-life of RSQM following one injection is between nine and 11 days, and of 9HR it is between eight and nine days.\textsuperscript{30}

**ADVERSE EFFECTS**

Clinical trial data indicate that the safety profile of RSQM is similar to that of risperidone LAI. During the eight-week phase 3 trial, the most common adverse effects (incidence, ≥ 5%) included: headache, injection-site pain, weight gain, constipation, back pain, extremity pain, musculoskeletal pain, sedation, somnolence, akathisia, and anxiety.\textsuperscript{28,30} In the 12-month open label extension, adverse effects (incidence, ≥ 5%) included: injection-site pain, weight increase, schizophrenia, insomnia, injection-site nodule, akathisia, injection-site induration, and upper respiratory tract infection.\textsuperscript{24} During the eight-week clinical trial, two patients in the 120-mg RSQM group withdrew from the study because of adverse effects. In the open label extension, two patients discontinued RSQM because of injection-site reactions. The drug was not thought to cause any serious treatment-emergent adverse effects in the eight-week trial or the open label extension.

**INDICATIONS AND USES**

Risperidone subcutaneous monthly injection is indicated for the treatment of schizophrenia in adults.\textsuperscript{30}

**DOSE AND ADMINISTRATION**

**General Recommendations**

Risperidone subcutaneous monthly injection is the first atypical LAI to be administered via SQ injection.\textsuperscript{30} The monthly injection is available in 90-mg and 120-mg doses, which are approximately equivalent to oral risperidone 3 mg/day and 4 mg/day, respectively. Unlike other atypical LAIs, no loading dose or oral overlap is required upon initiation. Although there is no recommendation on how to switch between formulations of other LAIs and RSQM, trial data and subsequent reviews compare this new information to the available literature to help establish approximate dose equivalencies. Based on a population pharmacokinetic model examining active moiety concentration and D\textsubscript{2} receptor occupancy, RSQM 90 mg and 120 mg are approximately equivalent to paliperidone palmitate 78 mg and 156 mg monthly LAI (50-mg and 100-mg paliperidone base), respectively, and RSQM 90 mg is approximately equivalent to 25 mg of the biweekly risperidone LAI.\textsuperscript{32} Rothe et al. compared phase 3 trial data for RSQM with published data for other atypical LAIs and extrapolated approximate dose equivalencies. Risperidone subcutaneous monthly injection may be approximately equivalent to 441 mg of aripiprazole lauroxil (Aristada\textsuperscript{®}); however, there was no equivalent dose of RSQM for olanzapine (Zyprexa\textsuperscript{®} and Relpreviv\textsuperscript{TM}); however, the mechanism and use of aripiprazole and olanzapine are different from that of risperidone and paliperidone, which could limit the importance of this information.\textsuperscript{27}

Risperidone subcutaneous monthly injection is supplied as a powder syringe and a liquid drug delivery syringe. The syringes must be stored in a refrigerated environment and can be mixed by connecting them via their locking tips. The liquid contents are transferred to the powder-filled syringe for five cycles to complete the premixing of the medication, then transferred back and forth between the syringes for an additional 55
cycles prior to injection to ensure that a uniform, cloudy suspension is created. (It is not clear how long this process takes, but prescribing instructions stress that failure to fully mix the product could result in an incorrect dosage.) Next, the mixture can be administered via SQ injection to the transpyloric or transtubercular planes to an area that is free of irritation, skin conditions, scarring, or other recent injections. As it is not designed for IM administration, RSQM’s subcutaneous administration makes it unique among other LAIs, with the exception of fluphenazine decanoate, which can also be administered SQ. The formation of an SQ depot implant may cause a lump to form; the patient should not rub or massage this lump, which can remain for several weeks. When choosing an injection site, the clinician should attempt to avoid areas where belts or waistbands could compress the depot.30

SPECIAL POPULATIONS

Recommendations for dosing RSQM in patients with hepatic or renal impairment are limited, as these populations were not included in clinical studies. However, as risperidone undergoes extensive hepatic metabolism and is excreted renally, caution is advised for patients with renal or hepatic impairment.

Pregnant patients were not included in RSQM’s clinical trials. Available pregnancy information is extrapolated from fluphenazine decanoate, which has been shown to cause birth defects in animal studies at doses of 0.1 to 3 times the maximum recommended human dose of 16 mg/day of risperidone. Published human data on risperidone exposure during the first trimester show an increased risk of major birth defects and cardiac malformations. The administration of the Atrigel system to pregnant rabbits and rats at high doses caused fetal developmental toxicity; however, these effects were not seen at doses of 17 times the dose in the 120-mg formulation. With the lack of data on Atrigel in pregnant women, switching from RSQM to oral risperidone during pregnancy could be preferable if antipsychotic treatment is warranted. Published literature shows that risperidone and 9HR pass into breast milk and can cause sedation, failure to thrive, jitteriness, and EPS in breastfed infants. There is no information regarding components of Atrigel being excreted into breast milk, and the risk of fetal exposure is unknown.30

The efficacy and safety of RSQM is unknown in geriatric and pediatric populations as they were excluded from clinical trials. The package labeling regarding risk of death reflects similar warnings on the labeling of other antipsychotics, when used to treat dementia-related psychosis in older patients.30

DRUG INTERACTIONS, CONTRAINDICATIONS, AND PRECAUTIONS

Drug interaction studies have not been performed with RSQM, and interaction information is based on oral risperidone data. The concomitant use of RSQM with known strong CYP2D6 inhibitors may increase systemic exposure to risperidone, as well as lower 9HR exposure. If RSQM is initiated with a strong CYP2D6 inhibitor (e.g., fluoxetine or paroxetine), recommendations include not exceeding 90 mg and possibly delaying initiation of the inhibitor for two to four weeks after RSQM initiation. There is no recommendation to adjust the dose or increase monitoring for strong CYP3A4 inhibitors. Strong enzyme inducers, particularly of CYP3A4 (e.g., rifampin, carbamazepine, or phenytoin), may decrease the overall exposure to risperidone and 9HR. Patients should be closely monitored during the first four to eight weeks of starting an enzyme inducer; the RSQM dose may need to be increased from 90 mg to 120 mg. Patients who receive 120 mg RSQM may require additional oral risperidone therapy.

Risperidone has pharmacodynamic drug interactions when used concomitantly with centrally acting drugs (i.e., benzodiazepines) and alcohol, which cause additive central nervous system (CNS) depression; with antihypertensive agents, which potentiate hypotensive events; and with dopamine agonists, which cause impaired response via agonist–antagonist effects.30

The use of RSQM is contraindicated in patients with a known hypersensitivity to risperidone, paliperidone, or the Atrigel system or any of its components. Risperidone subcutaneous monthly injection carries similar warnings and precautions to oral risperidone for the following: increased mortality in elderly patients with dementia-related psychosis; cerebrovascular adverse reactions in patients with dementia-related psychosis; neuroleptic malignant syndrome; tardive dyskinesia; hyperglycemia and diabetes mellitus; dyslipidemia; weight gain; hyperprolactinemia; orthostatic hypotension; falls; leukopenia; neutropenia; agranulocytosis; seizures; potential for cognitive and motor impairment; dysphagia; priapism; and disruptions in body temperature regulation.30

CLINICAL EFFICACY

Nasser et al.

An eight-week randomized, double-blind, placebo-controlled, multicenter, multiple-dose phase 3 study in adults with acute schizophrenia was conducted across 35 sites to determine the safety and efficacy of RSQM. Patients were randomized 1:1:1 to receive RSQM 90 mg, RSQM 120 mg, or placebo (PBO), and were seen and screened through 10 visits during the study period (Days −8, −1, 1, 2, 15, 29, 30, 43, 56, and 64). They received either RSQM or PBO during Visits 3 and 6 (Days 1 and 29) and upon completion, and those who completed the study were eligible to enroll in a long-term safety study of RSQM.

Eligible patients were either tapered off their current oral antipsychotic regimen during the seven-day screening period or received an oral dose of 0.25 mg on two consecutive days during the screening period to assess for tolerance. If patients required additional antipsychotics or if their safety was compromised, they were discharged from the study. Patients were included in the study if they met the following criteria:

- Male or female aged 18–55 years.
- Met Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, Text Revision (DSM-IV-TR) criteria for schizophrenia, and had acute exacerbation occurring ≤ 8 weeks prior to Visit 1 and would have benefitted from psychiatric/continued hospitalization.
- Had a Positive and Negative Syndrome Scale (PANS) score of 80–120 at Visit 1, with a score of ≥ 4 on two of the following: hallucinations, delusions, conceptual disorganization, or suspiciousness/persecution.
Patients were excluded if:

- Their PANSS total score improved by ≥ 20% between Visit 1 (initial screening) and Visit 3 (initial injection).
- They had received clozapine at any time for treatment-resistant schizophrenia.
- They met DSM-IV-TR criteria for substance dependence other than caffeine and nicotine.

Study endpoints for efficacy were the change in PANSS and Clinical Global Impression-Schizophrenia (CGI-S) scores from Visits 3 to 9. Subscale PANSS scores and Columbia-Suicide Severity Rating Scale (C-SSRS) scores were also collected and analyzed during these same visits. Extrapyramidal symptoms were assessed on Visits 1 to 9 via the following: the Simpson-Angus Scale (SAS), Abnormal Involuntary Movement Scale (AIMS), and Barnes Akathisia Rating Scale (BARS). Other possible treatment-emergent adverse events (AEs) were collected throughout the study period. In addition, safety and tolerability parameters were collected through injection-site tolerability, subject-reported Visual Analog Scale, concomitant medications, 12-lead electrocardiograms, physical examinations, body weight and height, BMI, and abdominal fat measurements.

A total of 538 subjects were screened, and 188 were determined to be ineligible. The remaining 354 patients were randomized into PBO, RSQM 90-mg, and RSQM 120-mg groups, with 70.6%, 77.6%, and 71.4% completing the study, respectively. The intent-to-treat (ITT) population included 337 patients. Demographic and baseline characteristics were similar across the groups and reflected a predominantly African American male population with a PANSS total score of 95 and a CGI-S of 4.8. The rating scores for EPS were also similar among the groups at baseline and reflected a low-to-no incidence of symptoms.

Significant changes were observed in the reduction of PANSS total score across the three groups of the ITT population, with both RSQM doses showing statistical superiority over PBO (PBO: –9.219 [standard error (SE), 1.2162]; RSQM 90 mg: –15.367 [SE, 1.2324]; P = 0.0004; RSQM 120 mg: –16.456 [SE, 1.2073], P < 0.0001). There were also significant improvements in PANSS total score for the RSQM 90-mg and 120-mg patients compared with the PBO patients at each study time point (Days 15, 29, 43, and end of study).

Improvements in CGI-S scores were also observed in the RSQM 90-mg and 120-mg groups compared with the PBO group (PBO: –0.518 [SE, 0.0659]; RSQM 90 mg: –0.868 [SE, 0.0662], P = 0.0002; RSQM 120 mg: –0.914 [SE, 0.0654], P < 0.0001). Significant improvements in CGI-S score were also observed for patients receiving RSQM 90 mg and 120 mg compared to patients receiving PBO at each study time point (Days 15, 29, 43, and end of study).

When PANSS score subgroups were analyzed, statistical superiority of RSQM over PBO was observed for positive symptoms scores (PBO: –2.805 [SE, 0.3831]; RSQM 90 mg: –4.788 [SE, 0.3851], P = 0.0003; RSQM 120 mg: –5.105 [SE, 0.3805], P < 0.0001) and general psychopathology scores (PBO: –4.213 [SE, 0.6344]; RSQM 90 mg: –7.768 [SE, 0.6367], P < 0.0001; RSQM 120 mg: –8.245 [SE, 0.6307], P = 0.0001), but not for negative symptoms scores (PBO: –2.226 [SE, 0.3308]; RSQM 90 mg: –2.799 [SE, 0.3336]; RSQM 120 mg: –3.174 [SE, 0.3288]).

The most common AEs reported were headache, injection-site pain, and weight gain. Patients were weighed at baseline and at end of study, and all patients had gained weight regardless of group. The incidence of clinically significant weight gain (≥7% increase from baseline) was higher in both the RSQM 90-mg and 120-mg groups than in the PBO group (32.7%, 42.1%, and 18.0%, respectively), as was the incidence of a >10% increase in weight from baseline (19.6%, 19.3%, and 5.4%, respectively). The incidence of treatment-emergent AEs was also higher in the RSQM groups than in the PBO group (70.4%, 77.89%, and 68.6%, respectively). Two serious treatment-emergent AEs (dyspepsia and chest pain) were reported but were determined not to be treatment-related. A total of five patients withdrew from the study because of AEs (two RSQM 120-mg patients with groin pain and paraesthesia, and three PBO patients with hematuria and worsening of psychotic disorder).

The incidence of EPS and the use of medications to treat them were low and similar across the groups. Although weight gain was observed in both treatment groups, there were no important differences in the metabolic parameters (fasting blood glucose, cholesterol panel, and HbA1c). Dose-dependent changes in mean prolactin levels for males were observed in the treatment groups that were not seen in the PBO group. There were no clinically relevant differences in QT intervals corrected by Bazett’s (QTcB) formula or by Fridericia’s (QTcF) formula between the treatment and placebo groups; however, the proportion of patients with an increase from baseline of ≥30 ms in QTcB was higher for both RSQM 90-mg and 120-mg doses than for placebo (RSQM 90 mg, 7–12%; RSQM 120 mg, 6–14%; and PBO, 3–6%). No participant had a QTc interval >500 ms, and there was no difference in the proportion of patients with prolonged QTcB or QTcF intervals.

The study investigators concluded that many of the endpoints, such as PANSS, CGI-S, AEs, and EPS, were similar to those found in studies of patients who had been treated with risperidone LAI. The investigators hypothesized that the increased incidence of weight gain in the treatment population was related to their being predominantly African American, and it is thought to arise from an increased incidence of a risk allele associated with antipsychotic-induced weight gain, which is prevalent in this population.36 The investigators stated that longer studies are needed to assess for the incidence of metabolic syndrome, as that would likely not appear within eight weeks. Based on its efficacy at reducing PANSS and CGI-S scores, with no significant treatment-emergent AEs, RSQM is a viable long-acting treatment for the acute exacerbation of schizophrenia and can be given less frequently than the risperidone LAI formulation.28
biweekly LAI and paliperidone palmitate (Invega Sustenna®). The objective of the PK model was to estimate which doses of RSQM would have similar active moiety plasma concentrations to these medications. Active moiety could then be used to calculate dopamine D₂ receptor occupancy.39

The data used to create the PK model were from 90 patients with clinically stable schizophrenia, predominantly Black or African-American males, most of whom were documented as phenotypically extensive metabolizers of the CYP2D6 enzyme (70.0% extensive, 23.3% intermediate, 3.3% poor, and 3.3% ultrarapid, overall). From those patients, 3,724 risperidone and 3,844 9HR concentrations from single- and multiple-dose exposures of RSQM were included.

The final PK model included a two-compartment model with first-order absorption and a transit-compartment absorption model to represent the delayed release of risperidone from the solidified implant. A one-compartment, first-order elimination model was used to represent the kinetics of 9HR. Variations were seen for BMI and race in the PK model, and first-order absorption constants were higher for individuals with a higher BMI. Black or African-American patients, when compared to the rest of the patients sampled (who were predominantly white), had a twofold higher absorption constant for the transit compartment model.

Simulations of the active moiety plasma concentrations and D₂ receptors occupancy for RSQM at doses of 60 mg, 90 mg, and 120 mg were compared with risperidone biweekly LAI 25 mg every two weeks and with paliperidone palmitate 50 mg (base) every four weeks. Although risperidone biweekly LAI took four to six weeks to reach steady state concentrations, RSQM attained close to steady state concentrations within four to six hours post-SQ injection. Based on active moiety concentrations and subsequent D₂ occupancy calculations, RSQM 90 mg was similar to risperidone biweekly LAI 25 mg; however, RSQM 120 mg did not achieve similar active moiety concentrations to risperidone biweekly LAI 50 mg. The study investigators assumed, based on the linearity of risperidone biweekly LAI dose escalation, that a 180-mg dose of RSQM would be needed to match the active moiety concentrations of risperidone biweekly LAI 50 mg (confirmed by unpublished simulation data). When they were compared with paliperidone palmitate, RSQM doses of 60 mg and 90 mg achieved similar active moiety concentrations and D₂ receptor occupancy to paliperidone doses of 78 mg and 156 mg (50 mg and 100 mg paliperidone base), respectively. Further, RSQM achieved near steady state concentrations after the first dose, whereas paliperidone required a loading dose regimen with IM injections on Days 1 and 8 to achieve similar steady state concentrations.

The rapid plasma peaks of risperidone that were observed are thought to be caused by a fraction of the active drug not being trapped in the biodegradable implant during its solidification process. The investigators concluded that use of BMI as a covariate on the first peak absorption was a result of adipose tissue at the injections site and the lipophilicity of risperidone itself, which is similar to paliperidone palmitate IM injection as it is also a lipophilic drug (BMI was also found to be a significant covariate).40 Race was also observed to be a significant covariate, although it had a limited effect on active moiety concentrations. Further PK studies would be needed to validate both covariates. Although this PK model does not consider RSQM’s efficacy and safety, the authors reasoned that because of the similar active moiety concentrations and D₂ receptor occupancy to risperidone LAI and paliperidone palmitate at comparable doses, the optimal antipsychotic effect and risk of ADRs like EPS should be similar for RSQM, as the optimal D₂ occupancy range of 65% to 80% was seen in these simulations.32

**COST**

A significant impediment to using the newer atypical antipsychotic LAIs is their cost: for RSQM, the 90-mg and 120-mg strengths cost $2,052.00 and $2,736.00, respectively. These high prices are comparable to currently available LAI antipsychotics such as Invega Sustenna®, Invega Trinza®, Aristada®, Abilify Maintena®, and Zyprexa® Relprev™, but more expensive per month than Risperdal® Consta®, haloperidol decanoate, and fluphenazine decanoate (Table 1).41 Patient costs can be limited through insurance copays and manufacturer discount programs such as the INSUPPORT program offered by the manufacturer, Indivior.42 When they are compartmentalized, drug costs can seem astronomical; but if those drugs can improve adherence and prevent relapses, as discussed earlier, overall healthcare costs may go down by the reduction in hospitalizations.43-45 The average cost of care for inpatient psychiatric hospitalization for schizophrenia can range from $5,707 to $8,509 for an average length of stay of 7.4 to 11.1 days.46 In addition, higher care costs for relapse probably do not stop upon patient discharge, given the

**Table 1 Average Wholesale Price (AWP)* of Currently Available Long-Acting Injectable Antipsychotics**

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<thead>
<tr>
<th>Antipsychotics</th>
<th>AWP*</th>
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<tr>
<td>Perseris®</td>
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<td>90 mg – $2,052.00</td>
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<tr>
<td>120 mg – $2,736.00</td>
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<tr>
<td>Risperdal® Consta®</td>
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<td>12.5 mg – $272.10</td>
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<td>25 mg – $544.15</td>
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<td>37.5 mg – $816.26</td>
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<td>50 mg – $1,088.38</td>
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<td>Risperda Sustenna®</td>
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<td>39 mg – $500.30</td>
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<td>Fluphenazine decanoate</td>
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<td>25 mg/mL (5 mL) – $93.60</td>
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* Red Book (as of July 2019)41
elevated frequency of outpatient psychiatric clinic visits in the weeks or months following discharge. Much of this is conjecture, however, and is extrapolated from research on other LAI antipsychotics. In clinical studies, RSQM has not been proven to prevent relapses.

**CONCLUSION**

Risperidone subcutaneous monthly injection is the second formulation of a risperidone LAI and one of nine LAIs that are now available. With its projected similar efficacy and safety to risperidone biweekly LAI, RSQM offers the advantage of once-monthly dosing and no oral supplementation requirements. The rapid achievement of plasma concentrations near that of steady state concentrations within four to six hours suggests that RSQM may be useful in an acute setting. Other LAIs cannot achieve this target concentration as rapidly or without the addition of loading doses or oral supplementation. Also, patients might choose SQ over IM administration because of convenience, which has been seen in preference-of-medication scores in health-related quality of life studies; interestingly, RSQM had higher pain VAS scores than risperidone biweekly LAI (27 vs. 12–18.2).\(^\text{23}\)\(^\text{30}\)\(^\text{34}\)

Results from the pivotal phase 3 trial support the use of RSQM in acute patients, and not only in well-controlled patients who wish to transition to an LAI. There appears to be a role for RSQM in the inpatient psychiatric setting as well as the outpatient setting. However, there is a lack of robust, long-term data on efficacy, as patients in the phase 3 trial received only two doses of treatment. A 12-month open-label extension of the trial demonstrated RSQM’s long-term safety, and although the extension was not powered for efficacy, a sustained reduction in PANSS scores suggests that, over time, RSQM improves schizophrenic symptoms.\(^\text{34}\)

Pharmacokinetic studies show that RSQM 120 mg, the highest strength available, is approximately equivalent to oral risperidone 4 mg. But converting patients who require doses of oral risperidone exceeding 4 mg could pose a clinical challenge, as RSQM 120 mg may not supply enough medication exposure and D\(_2\) occupancy in those patients. Nasser et al. often mention RSQM as being clinically comparable to risperidone; but when one considers current drug costs, the latter is superior.\(^\text{41}\)

It is not known if the decreased injection frequency from every two weeks to every four weeks will further improve patient adherence and have a clinical and healthcare cost-savings effect on relapses. Certain questions remain to be answered: Are clinical endpoints maintained? Do patients require further dose escalation and, if so, how is this done? Is the depot able to be removed if serious adverse drug events are observed or if the patient requires abdominal surgery? Will patients initiate self-injurious behavior to attempt to remove or damage the implant lump? The answers may change future clinical opinion regarding RSQM; but at present, it appears to be an efficacious alternative treatment option for patients with schizophrenia.

**REFERENCES**


18. Montemagni C, Frieri T, Roccia P, Sec-


