National PBM Drug Monograph
Risperidone Long-acting Injection (Risperdal® Consta™)
VHA Pharmacy Benefits Management Strategic Healthcare Group and Medical Advisory Panel

The following recommendations are based on current medical evidence and expert opinion from clinicians. The content of the document is dynamic and will be revised as new clinical data becomes available. The purpose of this document is to assist practitioners in clinical decision-making, to standardize and improve the quality of patient care, and to promote cost-effective drug prescribing. The clinician should utilize this guidance and interpret it in the clinical context of the individual patient situation.

Introduction

Haloperidol and fluphenazine decanoate long-acting injections have been available treatment options for patients with schizophrenia and other chronic psychiatric conditions since the 1960s. These formulations are usually reserved for patients who are noncompliant with oral medications.

Risperidone is the first atypical or second-generation antipsychotic to be available in a long-acting formulation. Like its decanoate predecessors, risperidone long-acting (RLA) is given via intra-muscular (IM) injection. Unlike haloperidol or fluphenazine decanoate, RLA is not an esterfied form of the oral drug suspended in sesame oil.

Pharmacology/Pharmacokinetics[1,2]

Risperidone long-acting is formulated by encapsulating risperidone in microspheres, which are suspended in diluent upon reconstitution. The microencapsulation is composed of polylactide-co-glycolide. The diluent consists of polysorbate 20, sodium carboxymethylcellulose, disodium hydrogen phosphate dihydrate, citric acid anhydrous, sodium chloride, sodium hydroxide and water for injection. Similar microencapsulation technology has been used with leuprolide (Lupron) depot injection.

Risperidone's exact mechanism of action is unknown. Like other atypical antipsychotics, risperidone's antagonism of dopamine type-2 and serotonin type-2 receptors is thought to account for its therapeutic effects in schizophrenia. Risperidone also has affinity for other dopamine and serotonin receptor sub-types as well as alpha-1and –2 adrenergic, and histamine-1 receptors.

Absorption

There is approximately a 3-week lag time following an intragluteal injection of long-acting risperidone and the primary release of medication from the encapsulation matrix; less than 1% is released immediately after injection. This lag is due to the time needed for hydrolysis of the encapsulation polymer to glycolic and lactic acids which are metabolized to carbon dioxide and water. The primary release of medication takes place weeks 3 to 6 and is nearly complete by week 7 following injection. Risperidone plasma concentrations increase rapidly during the primary release phase, peaking between weeks 4 and 5 after injection. Plasma concentrations return to pre-primary release values around 7 weeks following a single IM injection. Steady-state concentrations are reached within 6 to 8 weeks following repeated (every 2 weeks) IM injections.

Distribution

Once released from its encapsulation, risperidone is extensively distributed throughout the body having a volume of distribution of 1 – 2 L/kg. Risperidone is 90% bound to plasma albumin and alpha-1 acid glycoprotein, and its active metabolite, 9-hydroxyrisperidone, is 77% bound to plasma proteins. There is no competitive displacement between the parent compound and its metabolite.

A comparison of maximum (Cmax) and trough (Cmin) plasma concentrations of comparable doses of oral and RLA injection found a significant difference between mean Cmax, but not Cmin (See Table 1.). Median Cmax concentrations were also lower for the RLA injection compared to oral administration.

Mean plasma Cmin concentrations were not significantly different between the two formulations. Mean plasma concentration fluctuation was reduced by 36.8% on average with long-acting risperidone injection.

Table 1. Mean Peak and Trough Plasma Concentrations (±SD) Following Oral and Long-acting IM Risperidone[2]

Risperidone, oral	*C_{max}, ng/mL	C_{min}, ng/mL	Risperidone, IM	*C_{max}, ng/mL	C_{min}, ng/mL
2 mg	32.9 (9.2)	11.4 (3.6)	25 mg	22.7 (9.2)	11.3 (4.5)
4 mg	74.1 (31.5)	22.3 (12.1)	50 mg	57.3 (32.3)	24.3 (16.0)
6 mg	107.0 (49)	32.6 (15.7)	75 mg	80.6 (40.0)	32.6 (16.5)

* p<.001

Metabolism
Risperidone's major metabolic route is hydrolysis in the liver by the cytochrome P450 2D6 isozyme to an active moiety, 9-hydroxyrisperidone. Both risperidone and 9-hydroxyrisperidone account for the medications pharmacologic effects. N-alkylation is a minor metabolic pathway.

Elimination
Risperidone and metabolites primary route of elimination is in the urine, with lesser amounts eliminated in the feces. The elimination half-life for risperidone and 9-hydroxyrisperidone following administration of RLA is between 3 to 6 days. The prolonged half-life is due to the continuous release of encapsulated medication.

Risperidone and risperidone + 9-hydroxyrisperidone have been studied in extensive and poor CYP2D6 metabolizers. Extensive metabolizers cleared risperidone and risperidone + 9-hydroxyrisperidone at rates of 13.7 L/h and 5.0 L/h, respectively. The clearances by poor metabolizers were 3.3 L/h and 3.2 L/h, respectively.

FDA Approved Indication(s) and Off-label Uses[1]

Risperidone long-acting injection is FDA approved for the treatment of schizophrenia.

Current VA National Formulary Status

Risperidone long-acting injection is not on the VA National Formulary. The oral formulation of risperidone is on the National Formulary.

Dosage and Administration[1]

Patients who have never taken risperidone are to be given oral risperidone prior to receiving the long-acting form to establish tolerability.

The initial dose of RLA is 25 mg IM every 2-weeks regardless of prior antipsychotic and/or dose. Patients are to be maintained on their previous therapy until 3-weeks after their initial injection of RLA. Upward dosage adjustments should not be made more frequently than every 4-weeks.

Risperidone long-acting is to be administered using the diluent and safety needle that accompanies the dose pack. The use of other needles may disrupt the integrity of formulation and alter absorption and response. Risperidone long-acting is given via a deep IM injection into the gluteus. The injection site is to be alternated between the two buttocks at each dose. Risperidone long-acting is not to be given intravenously.

Patients with hepatic or renal impairment should be titrated to at least 2 mg per day of oral risperidone prior to receiving RLA 25 mg. Their oral dose should be continued for 3-weeks following their initial RLA injection.

Storage[1]

The dose pack should be refrigerated (36° – 46°F; 2° - 8°C) and protected from light. If refrigeration is not available, the dose pack can be stored (protected from light) in temperatures less than or equal to 77° F (25° C) for not more than 7 days prior to administration.

Adverse Effects (Safety Data)[1]

Risperidone in pregnancy is FDA Category C. Risperidone long-acting has not been studied in individuals < 18 years old.

Precautions/Contraindications[1]

Risperidone long-acting is contraindicated in patients who are hypersensitive to risperidone or any of the components of the diluent.

There is a risk for the following serious adverse events: neuroleptic malignant syndrome, tardive dyskinesia, cerbrovascular events, including stroke, in elderly patients with dementia, and hyperglycemia or diabetes mellitus.

Precautions include orthostatic hypotension, seizures, dysphagia, osteodystrophy and tumors in animals (the FDA has required post-marketing study of these events), hyperprolactinemia, potential for cognitive and motor impairment, priapism, thrombocytopenia purpura, disruption in regulation in body temperature, and an antiemetic effect.

Drug Interactions[1]

Risperidone long-acting injection has not been systematically studied with other drugs, rather drug interaction information is based on what is known about the oral formulation.Risperidone is a CYP2D6 substrate and as such its plasma concentration and that of its active metabolite are reduced by enzyme inducers such as carbamazepine and elevated by enzyme inhibitors such as fluoxetine. In addition, individuals who are genetically CYP2D6 deficient (poor metabolizers) will have elevated concentrations of risperidone and lower concentrations of its active metabolite.

1. Clozapine is known to reduce the clearance of risperidone.
2. The concurrent use of other drugs that lower blood pressure may increase a patient's risk for orthostatic hypotension.
3. The sedating effects of other drugs taken concurrently with risperidone may be increased.
4. Risperidone may antagonize the effects of levodopa and dopamine agonists.

Clinical Trials[3,4]

Kane, et al. conducted a 12-week double-blind, randomized, placebo-controlled, parallel group design study to evaluate the efficacy of RLA 25 mg, 50 mg, and 75 mg IM every 2-weeks in patients with schizophrenia.[3] Eligible patients could be either inpatients or outpatients between 18 and 55 years of age and have Positive and Negative Symptom Scale (PANSS) score between 60 and 120. Patients were excluded if they had a substance dependence, received a dose of depot antipsychotic within the past 120 days, had a history of neuroleptic malignant syndrome, tardive dyskinesia, a clinically significant ECG abnormality, pregnancy or likely to become pregnant, lactating, hypersensitivity or lack of response to risperidone.

Efficacy was assessed by the PANSS, repeated every 2-weeks, with the primary efficacy measure being changed from baseline at endpoint using the last observation carried forward. Clinical improvement was defined as a decrease of 20% or greater in the PANSS. The Clinical Global Impression scale, performed weekly, was another efficacy measure. Adverse effects and safety were assessed every 2-weeks using the Extrapyramidal Symptom Rating Scale (ESRS), patient reported complaints, pain of injection using a 100 mm visual analog scale (VAS), and physical inspection of the injection site. Statistical analysis included paired t-tests, analysis of covariance (ANOCVA), and Kaplan-Meyer analysis.

Following a 1-week screening period and a 1-week run in period (baseline) during which patients were titrated to 4 mg per day of oral risperidone, patients were randomized to placebo or one of the three RLA IM doses. Five hundred fifty-four individuals were screened, 461 entered the run-in phase, and 400 were randomized and initiated the double-blind phase (91 placebo, 99 RLA 25 mg, 103 RLA 50 mg, and 100 RLA 75 mg). Three hundred seventy patients had at least one post-injection evaluation.

Sixty-eight percent of the placebo group discontinued treatment prematurely compared to 51%-52% in RLA groups. Drop out rates were similar on Days 1 – 15 for all groups; after Day 15 more subjects in the

placebo group dropped out than in the RLA group. Lack of response was sighted as the most common reason for dropping out (See Table 2).

Table 2. Reasons (% of patients) For Trial Discontinuation

Reason	Placebo	RLA 25 mg	RLA 50 mg	RLA 75 mg
Any	68%	52%	51%	52%
Insufficient response	30%	22%	15%	12%
Adverse event	12%	11%	12%	14%
Withdrew consent	10%	7%	13%	11%
Lost to follow-up	6%	2%	3%	6%
Noncompliance	4%	0	3%	3%

After adjusting for covariates the mean change in total PANSS scores at endpoint for each RLA group was significant compared to placebo. Improvement was noted in the Positive and Negative Symptom subscales and the mean CGI severity scores for patients in the RLA group vs. placebo (Table 3).

Table 3. Baseline Total PANSS, Positive and Negative Symptoms, and CGI Scores and Mean Changes After 12-weeks (observed) and LOCF for Placebo and RLA Groups..

Measure	Placebo	RLA 25 mg	RLA 50 mg	RLA 75 mg
Baseline total PANSS score	82.0	81.7	82.3	80.1
Change at week 12 (observed)	-6.8	-22.1	-16.2	-14.9
Change at endpoint (LOCF)	2.6	-6.2	-8.5	-7.4
Baseline Positive symptoms	24.5	25.2	24.9	24.5
Change at week 12 (observed)	-3.8	-7.2	-5.9	-5.7
Change at endpoint (LOCF)	-0.2	-2.3	-3.5	-3.0
Baseline Negative symptoms	20.0	20.2	20.1	19.0
Change at week 12 (observed)	-0.1	-5.6	-2.1	-2.8
Change at endpoint (LOCF)	0.9	-2.4	-1.2	-1.2
Baseline CGI	3.1	3.1	3.1	3.1
Change at week 12 (observed)	-0.3	-0.9	-0.8	-0.5
Change at endpoint (LOCF)	0.3	-0.3	-.03	-0.4

Patients demonstrating clinical improvement (a ≥20% decrease in PANSS score) for each treatment group were the following: 17% placebo, 47% RLA 25 mg, 48% RLA 50 mg, and 39% RLA 75 mg ($p<.001$).

Concomitant medications were taken by 82% in the placebo group and 86% in the RLA groups. Their distribution by group (% of patients) is shown below.

Table 4.

RLA Dose	Antiparkinson's	Sedatives	Beta-blocker
Placebo	13%	51%	3%
25 mg	12%	43%	5%
50 mg	23%	45%	57%
75 mg	23%	57%	10%

Eighty percent of patients taking placebo and 83% taking RLA reported at least one adverse effect. Serious adverse effects were experienced by 23.5% of patients in the placebo group compared to 13% in the RLA 25 mg, 14% RLA 50 mg, and 15% RLA 75 mg groups. The severity of ESRS scores did not change from baseline in any of the groups over the 12 weeks. The percentage of patients experiencing EPS during weeks 4 – 12 were 9% placebo, 3% RLA 25 mg, 14% RLA 50 mg, and 23% RLA 75 mg. Rates were higher in the RLA 25 mg and 50 mg groups during weeks 1 – 3 when subjects were receiving both oral and IM risperidone.

Table 5. Spontaneously reported adverse events occurring in ≥ 5% of subjects by percent of group reporting[3].

Adverse Event	Placebo	RLA 25 mg	RLA 50 mg	RLA 75 mg
Any AE	83	80	83	82
Headache	12	15	55	51
Agitation	25	15	11	20
Psychosis	23	15	10	12
Insomnia	14	16	13	16
Anxiety	15	7	6	14
Dizziness	6	8	11	8
EPS disorder	3	4	8	10
Dyspepsia	2	7	7	9
Hyperkinesia	4	2	9	10
Somnolence	3	5	6	10
Hypertonia	5	4	5	10
Hallucination	5	7	6	5
Rhinitis	8	14	4	7
Pain	4	10	3	4
Nausea	5	3	4	9
Constipation	1	5	7	7
Vomiting	6	4	3	4
Coughing	4	5	2	5
Weight increase	2	5	4	4
Fatigue	0	3	7	3
Tachycardia	6	1	4	1
Nervousness	5	2	2	2
Injury	6	0	2	5
Diarrhea	3	5	1	2
Dry mouth	1	0	7	2
Increased salivation	1	6	2	1

Mean changes in body weight after 12 weeks were -1.4 kg placebo, 0.5 kg RLA 25 mg, 1.2 kg RLA 50 mg, and 1.9 kg RLA 75 mg ($p<.001$). There were no differences in QTc interval or other markers of cardiovascular safety between placebo and active treatment.

Pain on injection diminished over the course of six injections in all 4 groups. Mean measures of pain on the VAS following the first injection ranged from 15.8 to 18.2 mm at baseline and 8.5 to 12.6 mm after the sixth injection. Investigators rated between 80% to 90% of injection sites as normal after the first injection and 100% as normal following the sixth injection.

The authors concluded that RLA in doses of 25 mg, 50 mg, and 75 mg every two weeks was significantly more effective than placebo in treating the positive and negative symptoms of schizophrenia, that adverse events were dose-related occurring at greater frequencies in the 50 mg and 75 mg groups, and that the RLA IM injection was well tolerated.

A second safety, tolerability, and efficacy study used an open-label design, was 12 months in duration and involved centers in Europe and Canada.[4] To be eligible for inclusion, subjects had to be 18-years of age or older, meet DSM-IV criteria for schizophrenia, and be symptomatically stable. Patients were excluded if they were diagnosed substance dependent, had tardive dyskinesia or a history of neuroleptic malignant syndrome, clinically significant ECG abnormality, pregnancy or likely to become pregnant, lactating, hypersensitivity or lack of response to risperidone. Patients were also excluded if they had used another depot antipsychotic with 1 treatment cycle of screening or had been treated with clozapine in the 2 months prior to screening. Patients were allowed to continue medications to treat EPS, sleep and mood disorders.

Prior to receiving RLA, there was a 2-week run-in period to allow the discontinuation of previous antipsychotic therapy (except oral risperidone) and the initiation of flexible dosing oral risperidone to risperidone-naive patients (1 – 6 mg per day). Patients initial RLA dose was based on their oral risperidone dose: ≤ 2 mg/day, RLA 25 mg IM every 2 weeks; >2 mg - ≤4 mg/day, RLA 50 mg IM every 2 weeks; and >4mg - ≤6 mg/day, 75 mg RLA IM every 2 weeks. Investigators could adjust this dose up or down at their discretion at any time throughout the trial.

Efficacy was assessed with the PANSS scale at baseline and every 3 months and with the CGI-Severity of Illness scale monthly. Clinical improvement was defined as a decrease in the total PANNS score of ≥20%. Patients were assessed every 2 weeks for adverse events, for EPS by the ESRS scale monthly for the first 3 months, then every 3 months. Pain and the injection site were assessed using a 100 mm VAS and investigator inspection, respectively. Body weight and an ECG were measured at baseline, 6 months and study end.

Data analysis for efficacy included all patients who received at least one dose of RLA and at least one post-baseline assessment. Data analysis for safety included all patients who received at least one dose of RLA. Last observation carried forward and observed case data were reported.

Six hundred sixty-three persons were screened and 615 (93%) received at least one dose of RLA. Seventy-eight percent of patients who received one dose of RLA were previously on an oral antipsychotic; 60% risperidone. Thirty-eight percent had received a conventional depot antipsychotic in the past.

Sixty-five percent of patients completed the trial, with reasons for dropping out equal across three treatment groups except 15% of those taking 75mg RLA discontinued due insufficient response, compared to 2% and 3% in the 25 mg and 50 mg RLA groups, respectively. Five percent of patients dropped out of the study due to adverse events. Six patients died, 4 by suicide. Eighteen percent required hospitalization during the study period. The percent of patients by number of injections received is shown in Table 6.

Table 6.

Number of Injections Received	Percent Receiving
<12	19
12 – 24	23
25	58

Eighty-five percent of patients reported one or more adverse drug events (Table 7). The percentage of patients reporting adverse events decreased over time with 68% reporting an event in the first 3 months of treatment versus 43% in the last 3 months. Overall, 25% of patients experienced EPS, ranging from 21% of RLA 25 mg recipients to 27% in the 50 mg group. The incidence of hyperkinesias, EPS disorder, tremor, and hypertonia all were higher in the first 3 months than in any of the 3 following quartiles, all being less than 3% in months 10 – 12. ESRS total and factor scores also decreased over time. Four patients developed tardive dyskinesia during the trial. There were no clinically significant changes in laboratory measures or on ECG over the 12 months. The average weight gain by dose group was as follows: 25 mg 1.7 kg, 50 mg 2.6 kg, and 75 mg 1.9 kg. Measures of pain on injection and site reactions for the 1st and 25th injections are shown in Table 8.

Table 7. Spontaneously Reported Adverse Events Occurring in ≥ 5%

of Patients (% of patients).

Adverse Event	RLA 25 mg	RLA 50 mg	RLA 75 mg	Total
Any AE	81.7	84.2	86.5	84.7
Anxiety	13.3	24.6	28.8	24.2
Insomnia	13.3	21.5	24.3	21.2
Psychosis	10.0	9.6	27.3	17.4
Depression	13.3	12.3	16.9	14.5
Headache	8.3	13.6	12.4	12.0
Hyperkinesia	12.5	11.8	10.5	11.4
Rhinitis	10.8	12.7	907	11.1
Fatigue	6.7	9.2	8.6	8.5
Dizziness	4.2	8.3	7.1	7.0
EPS disorder	5.8	7.5	7.1	7.0
Injury	4.2	6.1	7.1	6.2
Back pain	7.5	5.3	5.2	5.7
Hallucination	1.7	2.2	9.4	5.2
Somnolence	3.3	6.1	4.9	5.0
Agitation	3.3	4.4	6.0	4.9
Constipation Nausea	4.2	3.5	6.4	4.9
Bronchitis	7.5	3.9	4.5	4.9
Suicide attempt	3.3	3.1	6.7	4.7
Tremor	5.0	4.4	4.9	4.7
Flu-like symptoms	5.8	4.4	4.5	4.7
Vomiting	3.3	3.5	5.2	4.2
Dyspepsia	1.7	3.9	5.2	4.1
Pharyngitis	5.0	2.6	3.4	3.4
Arthralgia	5.0	2.2	1.9	2.6

Table 8. Pain on injection and injection site reactions (% of patients)

Measure	1st Injection	25th Injection
Median VA score, mm	10	5
No Pain	68%	80%
No Redness	95%	100%
No Swelling	98%	100%
No Induration	100%	93%

Concomitant medications were used by 88% of patients.

Table 9. Percent of Patients Taking Concomitant Medications by RLA Dose.

RLA Dose	Antiparkinson's	Benzodiazepines
25 mg	23%	45%
50 mg	34%	54%
75 mg	37%	72%

Overall, 49% of patients demonstrated clinical improvement based on their PANSS score by the end of the study. In the 25 mg RLA group, 55% of patients improved clinically, with 56% and 40% improving in the 50 mg and 75 mg groups respectively. The total mean PANSS as well as the positive and negative symptom subscales decreased from baseline to study endpoint (LOCF) .

Table 10. Baseline and Change in PANSS by Treatment Group

Score	RLA 25mg	RLA 50 mg	RLA 75 mg	Total
Baseline PANSS Total	61.9	67.3	69.4	67.1
Change at endpoint	-8.0	-8.3	-3.3	-6.1
Baseline Positive Symptoms	16.4	18.3	19.9	18.6
Change at endpoint	-1.9	-2.3	-1.1	-1.7
Baseline Negative Symptoms	17.7	19.2	18.8	18.8
Change at endpoint	-2.8	-2.9	-1.4	-2.2

Based on observed-case data of mean total PANSS scores, improvement was noted in all three groups by week 12 with the majority of improvement attained by week 24which was sustained with some additional improvement until week 50. The CGI-S results also showed that patients had improved over the course of the study (Table 11).

Table 11. Percent rated as "not ill", "very mildly ill", or "mildly ill" by CGI-S

Time point	RLA 25 mg	RLA 50 mg	RLA 75 mg
Baseline	58	40	33
End point	78	65	44

The authors concluded that stable schizophrenics can be safely switched from oral or conventional depot antipsychotics to risperidone long-acting injection and that additional improvement as measured in the severity of their symptoms were obtained over the 12-month period.

Acquisition Costs and Available Strengths

Dose	FSS cost q 2-weeks ($)	FSS cost/month ($)	FSS cost/day ($)
25 mg	159.45	318.90	11.39
37.5 mg	239.18	478.36	17.08
50 mg	318.91	637.82	22.77

Summary and Points of Consideration

Risperidone long-acting injection is an alternative to haloperidol and fluphenazine decanoate for patients requiring a depot antipsychotic; presumably offering these patients the benefits of an atypical antipsychotic. However, there are no published trials comparing the efficacy and safety of RLA to conventional depot antipsychotics.

Risperidone was not accepted by all patients as noted by dropout rates of >50% and 35% in the two clinical trials with lack of efficacy being a common reason for dropouts. Patient selection in both trials was not limited to only those patients whose compliance may have been improved with a depot antipsychotic. The difference in drop out and efficacy rates between the two trials may be because 60% of patients in the second trial were stable on oral risperidone prior to being switched to RLA and that patients in the first trial were more symptomatic as evidenced by the baseline PANSS scores in the two trials.

Dose creep has been observed with the conventional depot antipsychotics and while the second clinical trial allowed investigators to adjust the dose as needed, data on the frequency and direction of dose adjustments were not provided. The authors do comment that as this was an open-label trial there was a tendency for higher doses to be used. The use of higher doses would increase drug costs, and presumably result in more concentration related side effects.

Recommendations

Because risperidone long-acting injection is the first atypical available as a depot injection it presumably offers the same advantages over haloperidol and fluphenazine decanoate as oral risperidone compared to conventional antipsychotics. Risperidone long-acting injection should be available for use in the VA system with criteria for use whether or not it is added to the VA National Formulary.

References

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