

**RISPERIDONE LONG-ACTING INJECTION
(RISPERDAL CONSTA™ (Janssen Pharmaceutica))**

CLASSIFICATION: Long-Acting Injectable Atypical Antipsychotic

INDICATIONS: This product has not received final FDA approval for the treatment of schizophrenia.

PHARMACOLOGY: Same as Risperdal tablets.

PHARMACOKINETICS: After a single gluteal injection of risperidone long-acting, there is a small initial release of the drug (<1% of the dose), followed by an absorption lag time of approximately 3 weeks. The main release of risperidone from the microspheres begins about 3 weeks after injection as the polymer in the microspheres breaks down naturally following continuous exposure to body water. The erosion of the microspheres releases risperidone into the body at a consistent rate. The main release of risperidone starts from week 3, is maintained for 4 to 6 weeks, and subsides by week 7 following administration. Antipsychotic supplementation should be given during the first three weeks of treatment with risperidone long-acting to maintain therapeutic levels until the main release of risperidone from the injection site has begun. Final by-products of the Medisorb® polymer breakdown are eliminated from the body as water and carbon dioxide, leaving no residual material.

Risperidone is totally absorbed from the microspheres. The combination of the release profile and the dosage regimen (administration every 2 weeks) of risperidone long-acting results in sustained therapeutic concentrations. Steady-state plasma concentrations are reached after 4 injections and are maintained for 4 to 6 weeks after the last injection. Plasma concentrations of risperidone, 9-hydroxyrisperidone, and risperidone plus 9-hydroxyrisperidone are linear over the dosing range of 25 mg to 50 mg. The half-life of risperidone plus 9-hydroxyrisperidone is 3 to 6 days, and is associated with a monoexponential decline in plasma concentrations. The elimination phase is complete approximately 7 to 8 weeks after the last injection. No accumulation of risperidone was observed during long-term use (up to 12 months) in patients treated every 2 weeks with 25 mg or 50 mg of risperidone long-acting.

Risperidone long-acting and RISPERDAL® tablets contain the same active ingredient, risperidone. Regardless of which formulation of risperidone is administered, metabolism and excretion of risperidone will follow similar processes. Risperidone is extensively metabolized in the liver. The main metabolic pathway is through hydroxylation of risperidone to 9-hydroxyrisperidone by the enzyme, cytochrome P₄₅₀IID₆ (CYP2D6). A minor metabolic pathway is through N-dealkylation. The main metabolite, 9-hydroxyrisperidone, has similar pharmacological activity as risperidone. Consequently, the clinical effect of the drug results from the combined concentrations of risperidone plus 9-hydroxyrisperidone.

DOSING: While specific dosing guidelines will be finalized in the product labeling, currently the dosing will be 25mg, 37.5mg, or 50mg via gluteal IM injection every 2 weeks. The total 2cc injection must be given at once. Microspheres do not distribute uniformly in solution, so dividing the dose may provide inconsistent drug concentrations.

EFFICACY: Three Phase III clinical trials have been completed:

- 12-week, double-blind, placebo-controlled trial to assess the efficacy and tolerability of risperidone long-acting administered every two weeks (Kane et al, 2003).
- 12-week, double-blind, double-dummy, non-inferiority efficacy trial to evaluate the hypothesis that treatment with risperidone long-acting is not inferior to risperidone tablets (Chue et al, 2002).
- 1-year, open-label trial to evaluate the long-term safety and tolerability of risperidone long-acting administered every two weeks (Eerdeken et al, 2002).

12-week, double-blind, placebo-controlled, phase III clinical trial

Kane et al (2003) published the results from a 12-week, double-blind, placebo-controlled multicenter, randomized trial to evaluate the efficacy and tolerability of risperidone long-acting. Inpatients and outpatients (18-55 years) with schizophrenia, in good general health, and a baseline Positive and Negative Syndrome Scale (PANSS) score between 60-120 were included in the trial. Prior to the 12-week double-blind period, patients were screened for one week followed by a run-in phase of one week when previous treatments were discontinued and oral risperidone was initiated at 2 mg/day and then titrated up to 4 mg/day for at least three days. Patients then entered the double-blind period and were randomized to receive six injections of placebo, risperidone long-acting 25 mg, risperidone long-acting 50 mg, or risperidone long-acting 75 mg every two weeks. Oral risperidone supplementation was given to patients randomized to risperidone long-acting during the first 3 weeks of the double-blind phase. Patients randomized to receive risperidone long-acting 25 mg, risperidone long-acting 50 mg, and risperidone long-acting 75 mg were given oral risperidone 2 mg, 4 mg, and 6 mg, respectively. Patients randomized to receive placebo injections were given oral placebo supplementation. No oral supplementation was permitted during weeks 4-12 of the double-blind phase. The PANSS was the primary measure of efficacy along with the Clinical Global Impression (CGI) scale. Safety and tolerability assessments included adverse events, vital signs, electrocardiograms, injection site pain assessments, and extrapyramidal symptoms by the Extrapyramidal Symptom Rating Scale (ESRS).

Four hundred patients with schizophrenia entered the double-blind period, and 370 were included in the intent-to-treat analysis (at least 1 injection and 1 post-baseline assessment). Reasons for discontinuation are listed in Appendix I. According to a Kaplan-Meier analysis, the dropout rate was similar in the four treatment groups during days 1-15, after which more placebo patients than patients receiving long-acting risperidone discontinued treatment. The average age of the patients was approximately 38 years (range 36-39) and median previous hospitalizations were approximately 4 (range 3.5-4). Equal proportions were hospital outpatients and inpatients.

There were significant improvements from baseline on the PANSS total score as well as the positive and negative subscale scores in the three risperidone long-acting groups compared to placebo ($p < 0.05$). Clinical improvement ($\geq 20\%$ reduction in PANSS total scores) occurred in significantly more patients in the risperidone long-acting groups versus those in the placebo group ($p < 0.001$). According to the CGI, the risperidone long-acting groups had significantly greater improvements in mean scores from baseline to endpoint versus placebo ($p < 0.001$).

**Efficacy Measures at Endpoint
(12-week, double-blind trial)**

	Risperidone long-acting			
	Placebo (n=92)	25 mg (n=93)	50 mg (n=98)	75 mg (n=87)
Average PANSS total at baseline	82.0	81.7	82.3	80.1
Change in PANSS total at endpoint	2.6	-6.2*	-8.5**	-7.4**
Average PANSS total at endpoint	84.6	75.5	73.8	72.7
Clinical Improvement (%)	17	47**	48**	39**
Mean CGI rating at baseline	3.1	3.1	3.1	3.1
Mean CGI rating at endpoint	0.3	-0.3**	-0.3**	-0.4**

* $p = 0.002$, ** $p < 0.001$ vs. placebo

12-week trial: use of risperidone long-acting in patients previously treated with oral olanzapine
Jones et al (2003) used data obtained in the 12-week, double-blind, randomized, placebo-controlled trial of risperidone long-acting described above (Kane et al, 2003) to conduct an analysis to examine the effect on symptom control and quality of life after switching patients with schizophrenia previously treated with oral olanzapine to risperidone long-acting given every two weeks. Safety and efficacy assessments made while patients were maintained on olanzapine (prior to receiving any oral or risperidone long-acting) were used as baseline measurements when available. Inclusion criteria, exclusion criteria, and assessments are described in the Kane et al, 2003 summary above.

Sixty-seven patients who had been receiving oral olanzapine were enrolled in the trial (16.8% of the total patient population). All patients previously taking oral olanzapine were gradually started on 4 mg/day of oral risperidone during the run-in phase. At the beginning of the study, in the double-blind phase, patients were randomized to receive 25 mg, 50 mg, or 75 mg of risperidone long-acting injection or placebo every 2 weeks. Oral risperidone or oral placebo was continued at the start of the double-blind phase for 3 weeks. The majority of patients were male (76-88%) and the average age of the patients was approximately 39 years old. The mean daily dose of olanzapine at screening was approximately 16 mg/day in patients who were randomized to placebo or the risperidone long-acting groups.

A total of 58 patients (16 randomized to placebo and 42 to risperidone long-acting) were screened for the trial and had at least one post-baseline visit. Of those, 26 patients (44.8%) completed the trial: 6 patients in the placebo arm and 20 patients in the risperidone long-acting groups. PANSS total scores at endpoint improved significantly from baseline in the risperidone long-acting treatment groups ($p=0.05$ vs. placebo, $p=0.03$ vs. baseline) and worsened in the placebo group. Improvements in the PANSS positive symptoms, negative symptoms, and anxiety/depression factor scores were significant at endpoint in patients who were switched from olanzapine to risperidone long-acting ($p<0.05$ vs. baseline). According to the CGI, 35% of the risperidone long-acting group and 25 % of the placebo group were determined as having very mild or mild illness (CGI scores of 2 or 3) at endpoint, whereas 23% of the risperidone long-acting group and 50 % of the placebo group were determined as having marked to extremely severe illness (CGI scores of 5-7).

According to the SF-36, patients who were switched from oral olanzapine to the risperidone long-acting groups showed statistically significant improvements in the mental health index and on the social functioning domain ($p<0.05$ vs. baseline).

12-week, double-blind, double-dummy, non-inferiority, phase III clinical trial comparing risperidone oral and long-acting

Chue et al (2002) describe the results of a short-term, double-blind study comparing risperidone long-acting with risperidone oral tablets in a non-inferiority analysis. Adult patients with a diagnosis of schizophrenia and a PANSS score ≥ 50 were included. Patients were given oral risperidone for up to 8 weeks during the run-in phase. Other antipsychotics were discontinued during the first 2-weeks of the run-in phase while oral risperidone was introduced. The oral risperidone dose was adjusted during the next 2 weeks. Patients were then continued on their optimal dose of oral risperidone 2 mg, 4 mg, or 6 mg/day during the last 4 weeks of the run-in period. Patients were then randomized to a 12-week, double-blind, double-dummy study if they were symptomatically stable at the end of the 8-week run-in phase. After run-in, patients who were on a stable dose of oral risperidone were randomized to receive risperidone long-acting 25 mg, 50 mg, or 75 mg every two weeks and placebo tablets daily or risperidone oral 2 mg, 4 mg, or 6 mg daily and placebo injections every two weeks. Patients in the risperidone long-acting group received oral risperidone supplementation during the first 3 weeks of the double-blind study. Stratification factors for randomization were site, PANSS and ESRS score at randomization, use of depot neuroleptics in the previous 6 months, and oral risperidone dose prior to the double-blind phase.

Assessments included the PANSS Structured Clinical Interview, the Clinical Global Impressions (CGI) scale, adverse events, vital signs, clinical laboratory tests, electrocardiogram, and the ESRS. A non-inferiority analysis of between-group differences in PANSS total change scores from baseline to endpoint was performed to determine whether the switch from one formulation to the other altered symptom control. A non-inferiority analysis is designed to show no significant differences between groups.

Out of 801 patients with schizophrenia screened, 321 patients were randomized to oral risperidone and 319 patients were randomized to risperidone long-acting (N=640). Baseline characteristics of the two groups were similar. The average patient age was approximately 40. Baseline PANSS total scores were approximately 69 in the oral risperidone group and 68 in the risperidone long-acting group. The majority of patients (82%) completed the double-blind phase.

The non-inferiority analysis included patients who received 4 or more injections: oral risperidone group, n=275; risperidone long-acting group, n=266. Similar improvements in PANSS total scores were seen for both groups with an average improvement of approximately 5-6 points. Risperidone long-acting was as efficacious as oral risperidone in improving PANSS total scores. Similar improvements in both groups were also seen on the 5 PANSS subscale scores and the CGI-severity scale.

**Efficacy Measures at Endpoint
(12-week, double-blind, noninferiority trial)**

	Oral risperidone (n=275)	Risperidone long-acting (n=266)
Average PANSS total at baseline	69.3	68.4
Change in PANSS total at endpoint	-6.3	-5.4
Average PANSS total at endpoint [†]	63.3	63.3

[†]least squares means

1-year, open-label, phase III clinical trial

Eerdekens et al (2002) presented the results of a 1-year, open-label, international, multicenter (Europe and Canada), prospective trial in stable adult patients with schizophrenia or schizoaffective disorder. All patients had been receiving a stable dose of an antipsychotic for at least 4 weeks at study entry. Other antipsychotics were discontinued and oral risperidone was given at a dose up to 6 mg/day during the 2-week run-in period. Risperidone long-acting (25, 50, or 75 mg) was given at day one and every 2 weeks thereafter for up to 50 weeks. The risperidone long-acting doses were determined by clinician judgment and the oral risperidone dose at the end of the run-in period. Doses of risperidone long-acting could be adjusted as needed during the trial. Oral risperidone treatment was continued for 2-3 weeks after the first risperidone long-acting injection. Tolerability and efficacy assessments included adverse events, injection site pain, ESRS, physical examinations, vital signs, clinical laboratory tests, electrocardiograms, and the PANSS.

Seven hundred and eighty-six patients (786) were screened and 725 patients received at least one injection [25 mg (n=147), 50 mg (n=270), 75 mg (n=308)]. The average age of the patients was approximately 42 years (average range 40-47) and most patients were diagnosed with schizophrenia (85%) versus schizoaffective disorder (15%). Sixty-five percent of patients (n=474) completed the trial. 74% of patients in the risperidone long-acting 25 mg group, 69% of patients in the risperidone long-acting 50 mg group, and 58% of patients in the risperidone long-acting 75 mg group received all 25 injections. Twenty-six percent of patients in the risperidone long-acting 25 mg group, 31% in the 50 mg group, and 42% in the 75 mg group discontinued the trial.

Significant reductions at endpoint were noted on the PANSS total scores in patients with mild-to-moderately ill symptoms at baseline treated with risperidone long-acting 25 mg, 50 mg, and 75 mg. Clinical improvement was defined as a 20% or greater reduction in PANSS total scores.

Significant improvements from baseline were seen for all 5 PANSS subscales (positive symptoms, negative symptoms, disorganized thoughts, uncontrolled hostility/excitement, and anxiety/depression) in the risperidone long-acting 25 mg group (p<0.01). In the risperidone long-acting 50 mg group, there were

significant improvements from baseline on 4 of the PANSS subscales ($p < 0.001$), excluding the uncontrolled hostility/excitement subscale. In the risperidone long-acting 75 mg group, there were significant improvements from baseline on 2 of the PANSS subscales (positive and negative symptoms, $p < 0.01$).

WARNINGS AND PRECAUTIONS/ADVERSE REACTIONS: Same as Risperdal tablets.

**12-week, double blind, placebo-controlled, phase III trial
(Kane et al, 2003)**

Reasons for discontinuation

Patients discontinued	Placebo (n=98) %	Risperidone long-acting		
		25 mg (n=99) %	50 mg (n=103) %	75 mg (n=100) %
Any reason	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
Ineligibility	0	3	3	2
Death	1	0	0	0
Other	5	6	4	4

*Spontaneously reported adverse events**

Adverse Event	Placebo (n=98) %	Risperidone long-acting		
		25 mg (n=99) %	50 mg (n=103) %	75 mg (n=100) %
Headache	12	15	22	21
Agitation	25	15	11	20
Psychosis	23	15	10	12
Insomnia	14	16	13	16
Anxiety	15	7	6	14
Rhinitis	8	14	4	7
Dizziness	6	8	11	8
Extrapyramidal disorder	3	4	8	10
Hyperkinesia	4	2	9	10
Somnolence	3	5	6	10
Hypertonia	5	4	5	10
Pain	4	10	3	4

*Events listed occurred in 10% or more of patients in any group

Spontaneously reported adverse events related to extrapyramidal symptoms

%	Risperidone long-acting			
	Placebo	25 mg	50 mg	75 mg
	%	%	%	%
Overall	13	10	24	29
During weeks 1-3 (oral supplementation and injectable)	9	8	17	18
During weeks 4-12 (only injectable received)	9	3	14	23

Extrapyramidal Symptom Rating Scale scores

	Risperidone long-acting			
	Placebo (n=93)	25 mg (n=97)	50 mg (n=98)	75 mg (n=90)
ESRS Total				
Mean baseline score	5.0	5.4	4.4	4.2
Mean change at endpoint	-0.1	-1.5	0.1	0.0
ESRS Parkinsonism				
Mean baseline score	3.8	4.1	3.4	3.0
Mean change at endpoint	-0.5	-1.1	0.0	0.3
ESRS Dystonia				
Mean baseline score	0.1	0.1	0.1	0.1
Mean change at endpoint	0.0	0.0	0.0	0.0
ESRS Dyskinesia				
Mean baseline score	1.1	1.2	0.9	1.1
Mean change at endpoint	0.4	-0.4	0.1	-0.3

Injection-site reactions – patient and investigator ratings

	Risperidone long-acting			
	Placebo (n=96)	25 mg (n=97)	50 mg (n=102)	75 mg (n=100)
Patient ratings^A				
Mean VAS score at 1 st injection	16.7	12.0	18.2	16.7
Mean VAS at 6 th injection	12.6	9.0	11.8	8.5
Investigator ratings^{AA}				
Pain after 6th injection (% rated as absent)	90	80	81	84
Swelling after 6th injection (% rated as absent)	100	100	100	100

INTERACTIONS: Same as Risperdal tablets.

COSTS: Product cost information is not yet available.

PRODUCT AVAILABILITY: Risperidone long-acting will be available in 2ml injections of 25, 37.5, and 50mg each. The product will be packaged as a kit including a vial of powdered drug and dosing syringe pre-filled with diluent (sterile water for injection).

SUMMARY: Risperidone long-acting is manufactured using a novel drug-delivery system in which the active medication, risperidone, is encapsulated in a Medisorb® polymer (poly-D, L-lactide-co-glycolide or PLG) to form microspheres. The polymer (PLG) is a medically accepted dissolving material used for other drug delivery systems and sutures. Each reconstituted injection of risperidone long-acting is composed of risperidone microspheres suspended in an aqueous-based diluent. Risperidone long-acting is administered by intramuscular injection into the gluteal area every 2 weeks.

RECOMMENDATION: Add to formulary.

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REFERENCES:

RISPERIDONE LONG-ACTING – CLINICAL REVIEW—JANSSEN PHARMACEUTICA

Canuso C, Bossie C, Lasser R et al. Reduced serum prolactin levels following treatment with long-acting risperidone [poster]. Presented at the American Psychiatric Association, San Francisco, CA, May 17-21, 2003.

Chouinard G, Lasser R, Bossie C et al. Does a long-acting atypical antipsychotic offer a low risk of tardive dyskinesia in patients with schizophrenia? [poster]. Presented at the 41st Annual Meeting of the American College of Neuropsychopharmacology, San Juan, Puerto Rico, December 8-12, 2002.

Chue P, Eerdeken M, Augustyns I et al. Efficacy and safety of long-acting risperidone microspheres and risperidone oral tablets [poster]. Presented at the 11th Biennial Winter Workshop on Schizophrenia, Davos, Switzerland, February 24-March 1, 2002.

Data on file, Janssen Pharmaceutica Products, L.P.

Eerdeken M, Fleischhacker WW, Xie Y et al. Long-term safety of long-acting risperidone microspheres [poster]. Presented at the Collegium International Neuro-Pharmacologicum XXIII Congress (CINP), Montreal, Canada, June 23-27, 2002.

Freyberger HJ, Eerdeken M, Mehnert A et al. Patient satisfaction with their medication during long-term treatment with long-acting risperidone injection [poster]. Presented at the 23rd Congress of the Collegium Internationale Neuropsychopharmacologicum (CINP), Montreal, Canada, June 23-27, 2002.

Gharabawi G, Lasser R, Bossie CA et al. Enhanced one-year outcomes with three doses of long-acting injectable risperidone in 336 chronically psychotic, stable patients switched from oral risperidone [poster]. Presented at the 41st Annual Meeting of the American College of Neuropsychopharmacology, San Juan, Puerto Rico, December 8-12, 2002.

Gharabawi G, Bossie C, Zhu Y et al. An assessment of dyskinesia in high-risk patients receiving long-acting risperidone [poster]. Presented at the American Association for Geriatric Psychiatry Annual Meeting, Waikiki, Hawaii, March 1-4, 2003.

Jones R, Lasser RA, Bossie CA et al. Clinical improvement with long-acting risperidone in patients previously receiving oral olanzapine [poster]. Presented at the American Psychiatric Association, San Francisco, CA, May 17-21, 2003.

Kane J, Eerdekens M, Lindenmayer JP. Long-acting injectable risperidone: efficacy and safety of the first long-acting atypical antipsychotic. *Am J Psychiatry* 2003;160(6):1125-1132.

Kane J, Gharabawi G, Bossie CA et al. Effect of a novel long-acting antipsychotic formulation in stable patients with schizoaffective disorder [poster]. Presented at the 41st Annual Meeting of the American College of Neuropsychopharmacology, San Juan, Puerto Rico, December 8-12, 2002.

Lasser R, Bossie CA, Zhu Y et al. Does constant therapy infer optimal efficacy in schizophrenia? Moving to an advanced pharmacotherapeutic option [poster]. Presented at the 41st Annual Meeting of the American College of Neuropsychopharmacology, San Juan, Puerto Rico, December 8-12, 2002.

Lasser R, Bossie C, Eerdekens M et al. Stable elderly patients with psychotic disorders improve with long-acting risperidone (Risperdal Consta) [poster]. Presented at the American Association for Geriatric Psychiatry Annual Meeting, Waikiki, Hawaii, March 1-4, 2003.

Lasser R, Rodriguez S, Bossie C, et al. Exploring remission in schizophrenia: a preliminary evaluation of core symptoms during treatment with long-acting risperidone (RISPERDAL CONSTA™) [poster]. Presented at the 156th American Psychiatric Association Annual Meeting, San Francisco, California, May 17-22, 2003.

Martin SD, Libretto SE, Pratt DJ et al. Clinical experience with the long-acting injectable formulation of the atypical antipsychotic, risperidone. *Current Medical Research and Opinion* 2003;19(4)298-305.

Nasrallah HA, Duchesne I, Mehnert A et al. Long-acting risperidone injection improves quality of life [poster]. 41st Annual Meeting of the American College of Neuropsychopharmacology, San Juan, Puerto Rico, December 8-12, 2002.

Pandina G, Gharabawi G, Eerdekens M et al. Long-acting risperidone (Risperdal Consta™) for the management of elderly patients with psychotic disorders: A favorable benefit/risk ration [poster]. American Psychiatric Association, Philadelphia, PA, May 18-23, 2002.