PRODUCT NAME
RISPERDAL® CONSTA® 25 mg Prolonged Release Suspension for Intramuscular Injection
RISPERDAL® CONSTA® 37.5 mg Prolonged Release Suspension for Intramuscular Injection
(risperidone)

DOSAGE FORMS AND STRENGTHS
RISPERDAL® CONSTA® contains 25 mg or 37.5 mg risperidone.

RISPERDAL® CONSTA® is an extended release microspheres formulation of risperidone, composed of risperidone drug substance micro-encapsulated in polylactide-co-glycolide, at a concentration of 381 mg risperidone per gram of microspheres.

Prolonged-release powder and diluent for suspension for injection.

Vial with powder
White to off-white free flowing powder.

Pre-filled syringe of diluent for reconstitution
Clear, colorless aqueous solution.

For excipients, see *List of Excipients*.

CLINICAL INFORMATION
Indications
RISPERDAL® CONSTA® is indicated for the treatment of acute and chronic schizophrenic psychoses, hallucinations and delusions.

RISPERDAL® CONSTA® also alleviates affective symptoms (such as depression, guilt feelings, anxiety) associated with schizophrenia

Dosage and Administration
For risperidone naive patients, it is recommended to establish tolerability with oral risperidone prior to initiating treatment with RISPERDAL® CONSTA®.

Adults (older than 18 years of age)
The recommended dose is 25 mg intramuscular every two weeks. Some patients may benefit from the higher doses of 37.5 mg or 50 mg. Doses higher than 50 mg every 2 weeks are not recommended.

Where patients are not stabilized on oral risperidone the recommended dose is 25 mg RISPERDAL® CONSTA® every two weeks. Should a dosage adjustment be required, see two paragraphs down for guidance on dose increments. Patients who have no previous history of risperidone use should be pretreated with oral RISPERDAL® for several days as clinically feasible, to assess tolerability before the first injection.

For those patients stabilized on a fixed dose of oral risperidone for two weeks or more, the following conversion schemes should be considered. Patients treated with a dosage of 4mg or less oral risperidone should receive 25mg RISPERDAL® CONSTA®, patients treated with higher oral doses should be considered for the higher RISPERDAL® CONSTA® dose of 37.5 mg.

Dose increments from 25mg to 37.5mg or from 37.5mg to 50mg should be considered after a minimum of four weeks after the previous dose of adjustment. The effect of this dosage adjustment on the patient's clinical status should not be anticipated earlier than 3 weeks after the first injection with the higher dose.

Supplementation with oral risperidone, where appropriate, with the previously used dose, should be provided during the first three weeks after the first injection of RISPERDAL® CONSTA® to ensure coverage until main release of risperidone from the injection site has begun.

After the first three weeks of RISPERDAL® CONSTA® treatment, oral risperidone should be discontinued. However, if clinically appropriate, oral risperidone up to 4mg/day can be temporarily added to the treatment with RISPERDAL® CONSTA® while establishing an individual patient's optimal dose. The clinical value of adding oral risperidone should be routinely reassessed and, if there is continuing need for oral supplementation, consideration should be given to increasing dose of RISPERDAL® CONSTA®.

Special populations

Elderly (65 years of age and older)

The recommended dose is 25 mg intramuscular every two weeks. Sufficient antipsychotic coverage should be ensured during the three-week lag period following the first RISPERDAL® CONSTA® injection (see *Pharmacokinetic Properties*).

Hepatic and renal impairment

RISPERDAL® CONSTA® has not been studied in hepatically and renally impaired patients.

If hepatically or renally impaired patients require treatment with RISPERDAL® CONSTA®, a starting dose of 0.5 mg twice daily oral risperidone is recommended during the first week. The second week 1 mg twice daily or 2 mg once daily can be given. If an oral total daily dose of at least 2 mg is well tolerated, an injection of 25 mg RISPERDAL® CONSTA® can be administered every 2 weeks.

Children (18 years of age and younger)

RISPERDAL® CONSTA® has not been studied in children younger than 18 years.

Administration

RISPERDAL® CONSTA® should be administered every two weeks by deep intramuscular deltoid or gluteal injection using the appropriate safety needle. For deltoid administration, use the 1-inch needle alternating injections between the two arms. For gluteal administration, use the 2-inch needle alternating injections between the two buttocks. Do not administer intravenously (see *Warnings and Precautions – Administration* and *Instructions for use and Handling*).

Contraindications

RISPERDAL® CONSTA® is contraindicated in patients with a known hypersensitivity to the product or any of the components.

Warnings and Precautions

For risperidone naive patients, it is recommended to establish tolerability with oral risperidone prior to initiating treatment with RISPERDAL® CONSTA®.

Elderly patients with dementia

Overall mortality

Elderly patients with dementia treated with atypical antipsychotic drugs have an increased mortality compared to placebo in a meta-analysis of 17 controlled trials of atypical antipsychotic drugs, including RISPERDAL®. In placebo-controlled trials with oral RISPERDAL® in this population, the incidence of mortality was 4.0% for RISPERDAL®-treated patients compared to 3.1% for placebo-treated patients. The mean age (range) of patients who died was 86 years (range 67-100).

Concomitant use with furosemide

In the oral RISPERDAL® placebo-controlled trials in elderly patients with dementia, a higher incidence of mortality was observed in patients treated with furosemide plus risperidone (7.3%; mean age 89 years, range 75-97) when compared to patients treated with risperidone alone (3.1%; mean age 84 years, range 70-96) or furosemide alone (4.1%; mean age 80 years, range 67-90). The increase in mortality in patients treated with furosemide plus risperidone was observed in two of the four clinical trials.

No pathophysiological mechanism has been identified to explain this finding, and no consistent pattern for cause of death observed. Nevertheless, caution should be exercised and the risks and benefits of this combination should be considered prior to the decision to use. There was no increased incidence of mortality among patients taking other diuretics as concomitant medication with risperidone. Irrespective of treatment, dehydration was an overall risk factor for mortality and should therefore be carefully avoided in elderly patients with dementia.

Cerebrovascular Adverse Events (CAE)

For specific posology recommendations for elderly patients, patients with renal and liver disease and patients with dementia, see *Dosage and Administration*. Cerebrovascular adverse events (e.g. stroke, transient ischemic attack), including fatalities, were reported in patients (mean age 85 years; range 73-97) in trials of risperidone in elderly patients with dementia-related psychosis.
In placebo-controlled trials, there was a significant higher incidence of cerebrovascular adverse events in patients treated with risperidone compared to patients receiving placebo. RISPERDAL® is not approved for the treatment of patients with dementia-related psychosis.

Orthostatic hypotension

Due to the alpha-blocking activity of risperidone, (orthostatic) hypotension can occur, especially during initiation of treatment. Clinically significant hypotension has been observed postmarketing with concomitant use of risperidone and antihypertensive treatment. Risperidone should be used with caution in patients with known cardiovascular disease (e.g. heart failure,

myocardial infarction, conduction abnormalities, dehydration, hypovolemia, or cerebrovascular disease). In these patients the dosage should be gradually increased. The risk/benefit of further treatment with RISPERDAL® CONSTA® should be assessed if clinically relevant orthostatic hypotension persists.

Leukopenia, neutropenia, and agranulocytosis

Events of leukopenia, neutropenia and agranulocytosis have been reported with antipsychotic agents, including RISPERDAL® CONSTA®. Agranulocytosis has been reported very rarely (< 1/10,000 patients) during post-marketing surveillance.

Patients with a history of a clinically significant low white blood cell count (WBC) or a drug-induced leukopenia/neutropenia should be monitored during the first few months of therapy and discontinuation of RISPERDAL® CONSTA® should be considered at the first sign of a clinically significant decline in WBC in the absence of other causative factors.

Patients with clinically significant neutropenia should be carefully monitored for fever or other symptoms or signs of infection and treated promptly if such symptoms or signs occur. Patients with severe neutropenia (absolute neutrophil count < 1 X 10^9/L) should discontinue RISPERDAL® CONSTA® and have their WBC followed until recovery.

Venous thromboembolism

Cases of venous thromboembolism (VTE) have been reported with antipsychotic drugs. Since patients treated with antipsychotics often present with acquired risk factors for VTE, all possible risk factors for VTE should be identified before and during treatment with RISPERDAL® CONSTA® and preventive measures undertaken.

Tardive Dyskinesia/Extrapyramidal Symptoms (TD/EPS)

Drugs with dopamine receptor antagonistic properties have been associated with the induction of tardive dyskinesia characterized by rhythmic involuntary movements, predominantly of the tongue and/or face. It has been reported that the occurrence of extrapyramidal symptoms is a risk factor for the development of tardive dyskinesia. Because risperidone has a lower potential to induce extrapyramidal symptoms than classical neuroleptics, it should have a reduced risk of inducing tardive dyskinesia as compared to classical neuroleptics. If signs and symptoms of tardive dyskinesia appear, the discontinuation of all antipsychotic drugs should be considered.

Extrapyramidal symptoms and psychostimulants - Caution is warranted in patients receiving both psychostimulants (e.g. methylphenidate) and risperidone concomitantly, as extrapyramidal symptoms could emerge when adjusting one or both medications. Gradual withdrawal of one or both treatments should be considered (see *Interactions*).

Neuroleptic Malignant Syndrome (NMS)

Neuroleptic Malignant Syndrome, characterized by hyperthermia, muscle rigidity, autonomic instability, altered consciousness and elevated serum creatine phosphokinase levels, has been reported to occur in association with antipsychotics. Additional signs may include myoglobinuria (rhabdomyolysis) and acute renal failure. In this event, all antipsychotic drugs, including risperidone, should be discontinued. After the last administration of RISPERDAL® CONSTA®, plasma levels of risperidone are present for up to (a minimum) of 6 weeks.

Parkinson's Disease and Dementia with Lewy Bodies

Physicians should weigh the risks versus the benefits when prescribing antipsychotics, including RISPERDAL® CONSTA®, to patients with Parkinson's Disease or Dementia with Lewy Bodies (DLB) since both groups may be at increased risk of Neuroleptic Malignant Syndrome as well as having an increased sensitivity to antipsychotic medications. Manifestation of this increased sensitivity can include confusion, obtundation, postural instability with frequent falls, in addition to extrapyramidal symptoms.

Hypersensitivity reactions

Although tolerability with oral risperidone should be established prior to initiating treatment with RISPERDAL® CONSTA®, very rare cases of anaphylactic reaction have been reported during postmarketing experience in patients who have previously tolerated oral risperidone (see *Dosage and Administration* and *Adverse Reactions*).

If hypersensitivity reactions occur, discontinue use of RISPERDAL® CONSTA®; initiate general supportive measures are clinically appropriate and monitor the patient until signs and symptoms resolve (see *Contraindications* and *Adverse Reactions*).

Hyperglycemia and diabetes mellitus

Hyperglycemia, diabetes mellitus and exacerbation of pre-existing diabetes have been reported in patients treated with atypical antipsychotics including RISPERDAL®. Assessment of the relationship between atypical antipsychotic use and glucose abnormalities is complicated by the possibility of an increased background risk of diabetes mellitus in patients with schizophrenia and the increasing incidence of diabetes mellitus in the general population. Given these confounders, the relationship between atypical antipsychotic use and hyperglycemia-related adverse events is not completely understood. Any patient treated with atypical antipsychotics, including RISPERDAL® CONSTA® should be monitored for symptoms of hyperglycemia and diabetes mellitus. However, epidemiology studies suggest an increased risk of diabetes and hyperglycemia with atypical antipsychotics.

Patients with an established diagnosis of diabetes mellitus, risk factors for diabetes (e.g. obesity, family history of diabetes), or those who develop symptoms of hyperglycemia during treatment with atypical antipsychotics should be monitored regularly for worsening of glucose control. Patients should be monitored for symptoms of hyperglycemia including polydipsia, polyuria, polyphagia and weakness.

Weight gain

Significant weight gain has been reported. Monitoring weight gain is advisable when RISPERDAL® CONSTA® is being used.

QT Interval

As with other antipsychotics, caution should be exercised when RISPERDAL® CONSTA® is prescribed in patients with a history of cardiac arrhythmias, in patients with congenital long QT syndrome, and in concomitant use with drugs known to prolong the QT interval.

Priapism

Drugs with alpha-adrenergic blocking effects have been reported to induce priapism. Priapism has been reported with RISPERDAL® during postmarketing surveillance (see *Adverse Reactions*).

Body temperature regulation
Disruption of the body's ability to reduce core body temperature has been attributed to antipsychotic agents. Appropriate care is advised when prescribing RISPERDAL® CONSTA® to patients who will be experiencing conditions which may contribute to an elevation in core body temperature, e.g., exercising strenuously, exposure to extreme heat, receiving concomitant medication with anticholinergic activity, or being subject to dehydration.

Antiemetic effect
An antiemetic effect was observed in preclinical studies with risperidone. This effect, if it occurs in humans, may mask the signs and symptoms of overdosage with certain drugs or of conditions such as intestinal obstruction, Reye's syndrome, and brain tumor.

Seizures
As with other antipsychotic drugs, RISPERDAL® CONSTA® should be used cautiously in patients with a history of seizures or other conditions that potentially lower the seizure threshold.

Intraoperative Floppy Iris Syndrome
Intraoperative Floppy Iris Syndrome (IFIS) has been observed during cataract surgery in patients treated with medicines with alpha1a-adrenergic antagonist effect, including RISPERDAL® CONSTA® (see *Adverse Reactions*).

IFIS may increase the risk of eye complications during and after the operation. Current or past use of medicines with alpha1a-adrenergic antagonist effect should be made known to the ophthalmic surgeon in advance of surgery. The potential benefit of stopping alpha1 blocking therapy prior to cataract surgery has not been established and must be weighed against the risk of stopping the antipsychotic therapy.

Administration
Care must be taken to avoid inadvertent injection of RISPERDAL® CONSTA® into a blood vessel (see *Adverse Reactions - retinal artery occlusion*).

Interactions
The interactions of RISPERDAL® CONSTA® with co-administration of other drugs have not been systematically evaluated. The drug interaction data provided in this section are based on studies with oral RISPERDAL®.

Pharmacodynamic-related interactions
Centrally- acting drugs and alcohol
Given the primary CNS effects of risperidone it should be used with caution in combination with other centrally acting drugs or alcohol.

Levodopa and dopamine agonists
Risperidone may antagonize the effect of levodopa and other dopamine agonists.

Psychostimulants
The combined use of psychostimulants (e.g. methylphenidate) with risperidone can lead to the emergence of extrapyramidal symptoms upon change of either or both treatments (see *Warnings and Precautions*).

Drugs with hypotensive effects
Clinically significant hypotension has been observed postmarketing with concomitant use of risperidone and antihypertensive treatment.

Drugs known to prolong the QT interval
Caution is advised when prescribing RISPERDAL® CONSTA® with drugs known to prolong the QT interval.

Pharmacokinetic-related interactions
Risperidone is mainly metabolized through CYP2D6, and to a lesser extent through CYP3A4. Both risperidone and its active metabolite 9-hydroxy-risperidone are substrates of P-glycoprotein (P-gp). Substances that modify CYP2D6 activity, or substances strongly inhibiting or inducing CYP3A4 and/or P-gp activity, may influence the pharmacokinetics of the risperidone active antipsychotic fraction.

Strong CYP2D6 inhibitors
Co-administration of RISPERDAL® CONSTA® with a strong CYP2D6 inhibitor may increase the plasma concentrations of risperidone, but less so of the active antipsychotic fraction. Higher doses of a strong CYP2D6 inhibitor may elevate concentrations of the risperidone active antipsychotic fraction (e.g., paroxetine, see below). When concomitant paroxetine or another strong CYP2D6 inhibitor, especially at higher doses, is initiated or discontinued, the physician should re-evaluate the dosing of RISPERDAL® CONSTA®.

CYP3A4 and/or P-gp inhibitors
Coadministration of RISPERDAL® CONSTA® with a strong CYP3A4 and/or P-gp inhibitor may substantially elevate plasma concentrations of the risperidone active antipsychotic fraction. When concomitant itraconazole or another strong CYP3A4 and/or P-gp inhibitor is initiated or discontinued, the physician should re-evaluate the dosing of RISPERDAL® CONSTA®.

CYP3A4 and/or P-gp inducers
Co-administration of RISPERDAL® CONSTA® with a strong CYP3A4 and/or P-gp inducer may decrease the plasma concentrations of the risperidone active antipsychotic fraction. When concomitant carbamazepine or another strong CYP3A4 and/or P-gp inducer is initiated or discontinued, the physician should re-evaluate the dosing of RISPERDAL® CONSTA®.

Highly protein -bound drugs
When risperidone is taken together with other highly protein-bound drugs, there is no clinically relevant displacement of either drug from the plasma proteins.

When using concomitant medication, the corresponding label should be consulted for information on the route of metabolism and the possible need to adjust dosages.

Examples

Examples of drugs that may potentially interact or that were shown not to interact with risperidone are listed below:

Antibacterials:

- Erythromycin, a moderate CYP 3A4 inhibitor, does not change the pharmacokinetics of risperidone and the active antipsychotic fraction.
- Rifampicin, a strong CYP3A4 inducer and a P-gp inducer, decreased the plasma concentrations of the active antipsychotic fraction.

Anticholinesterases:

- Donepezil and galantamine, both CYP2D6 and CYP3A4 substrates, do not show a clinically relevant effect on the pharmacokinetics of risperidone and the active antipsychotic fraction.

Antiepileptics:

- Carbamazepine, a strong CYP3A4 inducer and a P-gp inducer, has been shown to decrease the plasma concentrations of the active antipsychotic fraction of risperidone
- Topiramate modestly reduced the bioavailability of risperidone, but not that of the active antipsychotic fraction.
- Risperidone does not show a clinically relevant effect on the pharmacokinetics of valproate or topiramate.

Antifungals:

- Itraconazole, a strong CYP3A4 inhibitor and a P-gp inhibitor, at a dosage of 200mg/day increased the plasma concentrations of the active antipsychotic fraction by about 70%, at risperidone doses of 2 to 8mg/day.
- Ketoconazole, a strong CYP3A4 inhibitor and a P-gp inhibitor, at a dosage of 200mg/day increased the plasma concentrations of risperidone and decreased the plasma concentrations of 9-hydroxyrisperidone.

Antipsychotics:

- Phenothiazines may increase the plasma concentrations of risperidone but not those of the active antipsychotic fraction.
- Aripiprazole, a CYP2D6 and CYP3A4 substrate: Risperidone tablets or injections did not affect the pharmacokinetics of the sum of aripiprazole and its active metabolite, dehydroaripiprazole.

Antivirals:

- Protease inhibitors: No formal study data are available; however, since ritonavir is a strong CYP3A4 inhibitor and a weak CYP2D6 inhibitor, ritonavir and ritonavir-boosted protease inhibitors potentially raise concentrations of the risperidone active antipsychotic fraction.

Beta Blockers:

- Some beta-blockers may increase the plasma concentrations of risperidone but not those of the active antipsychotic fraction.

Calcium Channel Blockers:

- Verapamil, a moderate inhibitor of CYP3A4 and an inhibitor of P-gp, increases the plasma concentration of risperidone and the active antipsychotic fraction.

Digitalis Glycosides:

- Risperidone does not show a clinically relevant effect on the pharmacokinetics of digoxin.

Diuretics:

- Furosemide: See section "*Warnings and Precautions*" regarding increased mortality in elderly patients with dementia concomitantly receiving furosemide and oral RISPERDAL®.

Gastrointestinal Drugs:

- H2-receptor antagonists: Cimetidine and ranitidine, both weak inhibitors of CYP2D6 and CYP3A4, increased the bioavailability of risperidone, but only marginally that of the active antipsychotic fraction.

Lithium:

- Risperidone does not show a clinically relevant effect on the pharmacokinetics of lithium.

SSRIs and Tricyclic Antidepressants:

- Fluoxetine, a strong CYP2D6 inhibitor, increases the plasma concentration of risperidone but less so of the active antipsychotic fraction.
- Paroxetine, a strong CYP2D6 inhibitor, increases the plasma concentrations of risperidone, but, at dosages up to 20mg/day, less so of the active antipsychotic fraction. However, higher doses of paroxetine may elevate concentrations of the risperidone active antipsychotic fraction.
- Tricyclic antidepressants may increase the plasma concentrations of risperidone but not those of the active antipsychotic fraction. Amitriptyline does not affect the pharmacokinetics of risperidone or the active antipsychotic fraction.
- Sertraline, a weak inhibitor of CYP2D6, and fluvoxamine, a weak inhibitor of CYP3A4, at dosages up to 100mg/day are not associated with clinically significant changes in concentrations of the risperidone active antipsychotic fraction. However, doses higher than 100mg/day of sertraline or fluvoxamine may elevate concentrations of the risperidone active antipsychotic fraction.

Pregnancy and Breast-feeding

Pregnancy

The safety of risperidone for use during human pregnancy has not been established.

A retrospective observational cohort study based on a US claims database compared the risk of congenital malformations for live births among women with and without antipsychotic use during the first trimester of pregnancy. The risk of congenital malformations with risperidone, after adjusting for confounder variables available in the database, was elevated compared to no antipsychotic exposure (relative risk=1.26, 95% CI: 1.02-1.56). No biological mechanism has been identified to explain these findings and teratogenic effects have not been observed in

non-clinical studies. Based on the findings of this single observational study, a causal relationship between *in utero* exposure to risperidone and congenital malformations has not been established.

Although, in experimental animals, risperidone did not show direct reproductive toxicity, some indirect, prolactin- and CNS-mediated effects were observed.
Neonates exposed to antipsychotic drugs (including RISPERDAL®) during the third trimester of pregnancy are at risk for extrapyramidal and/or withdrawal symptoms that may vary in severity following delivery. These symptoms in the neonates may include agitation, hypertonia, hypotonia, tremor, somnolence, respiratory distress, or feeding disorder.

RISPERDAL® CONSTA® should only be used during pregnancy if the benefits outweigh the risks.

Breast-feeding
In animal studies, risperidone and 9-hydroxy-risperidone are excreted in the milk. It has been demonstrated that risperidone and 9-hydroxy-risperidone are also excreted in human breast milk. Therefore, women receiving RISPERDAL® CONSTA® should not breast-feed.

Effects on Ability to Drive and Use Machines
Risperidone may interfere with activities requiring mental alertness. Therefore, patients should be advised not to drive or operate machinery until their individual susceptibility is known.

Adverse Reactions
Clinical trial data
The safety of RISPERDAL® CONSTA® was evaluated from a clinical trial database consisting of 2392 patients exposed to one or more doses of RISPERDAL® CONSTA® for the treatment of schizophrenia. Of these 2392 patients, 332 were patients who received RISPERDAL® CONSTA® while participating in a 12-week double-blind, placebo-controlled trial. A total of 202 of the 332 were schizophrenic patients who received 25 mg or 50 mg RISPERDAL® CONSTA®. The conditions and duration of treatment with RISPERDAL® CONSTA® varied greatly and included (in overlapping categories) double-blind, fixed- and flexible-dose, placebo- or active-controlled studies and open-label phases of studies, inpatients and outpatients, and short-term (up to 12 weeks) and longer-term (up to 4 years) exposures.

The majority of all adverse reactions were mild to moderate in severity.

Double-Blind, Placebo-Controlled Data – Schizophrenia
Adverse reactions reported by ≥ 2% of RISPERDAL® CONSTA®-treated patients with schizophrenia in one 12-week double-blind, placebo-controlled trial are shown in Table 1.

Table 1. Adverse Drug Reactions Reported by ≥ 2% of RISPERDAL® CONSTA®-Treated Patients with Schizophrenia in a 12-Week Double-Blind, Placebo-Controlled Trial

System/Organ Class Adverse Reaction	**RISPERDAL® CONSTA® 25 mg (n=99)**	**RISPERDAL® CONSTA® 50 mg (n=103)**	**Placebo (n=98) %**

	%	%	
Infections and Infestations			
Upper respiratory tract infection	2	0	1
Nervous System Disorders			
Headache	15	21	12
Parkinsonism*	8	15	9
Dizziness	7	11	6
Akathisia*	4	11	6
Somnolence	4	4	0
Tremor	0	3	0
Sedation	2	2	3
Syncope	2	1	0
Hypoaesthesia	2	0	0
Eye Disorders			
Vision blurred	2	3	0
Respiratory, Thoracic and Mediastinal Disorders			
Cough	4	2	3
Sinus congestion	2	0	0
Gastrointestinal Disorders			
Constipation	5	7	1
Dry mouth	0	7	1
Dyspepsia	6	6	0
Nausea	3	4	5
Toothache	1	3	0
Salivary hypersecretion	4	1	0
Skin and Subcutaneous Tissue Disorders			
Acne	2	2	0
Dry skin	2	0	0
Musculoskeletal and Connective Tissue Disorders			
Pain in extremity	6	2	1
General Disorders and Administration Site Conditions			
Fatigue	3	6	0
Asthenia	0	3	0
Edema peripheral	2	3	1
Pain	4	1	0
Pyrexia	2	1	0
Investigations			
Weight increased	5	4	2
Weight decreased	4	1	1

* Parkinsonism includes extrapyramidal disorder, musculoskeletal stiffness, muscle rigidity, and bradykinesia. Akathisia includes akathisia and restlessness.

Other clinical trial data

Paliperidone is the active metabolite of risperidone, therefore the adverse reaction profiles of these compounds (including both the oral and injectable formulations) are relevant to one another. Hence, a comprehensive listing of adverse reactions across paliperidone and risperidone products provides relevant safety information for these related products. Adverse reactions detected for one formulation of risperidone or paliperidone were considered as relevant safety information for the other formulation of the same compound unless the adverse reaction was unique to either the formulation or the route of administration. Adverse drug reactions for one compound that were not listed for the other compound were also added to the label for the other compound unless no meaningful new safety information could be derived from the additional adverse reactions (i.e. the term was vague or the medical concept was already found in the current label). All ADRs and their frequencies of occurrence in patients on RISPERDAL® CONSTA® are reflected in the adverse reaction tables below.

Table 2. Additional Adverse Reactions Reported with Risperidone and/or Paliperidone by ≥ 2% of RISPERDAL® CONSTA®-treated Subjects with Schizophrenia[1] (The Terms within each System Organ Class are Sorted Alphabetically)

System/Organ Class Adverse Reaction
Psychiatric disorders Agitation, Anxiety, Depression, Insomnia*
Nervous system disorders Akathisia*, Parkinsonism*
Cardiac disorders Tachycardia
Respiratory, thoracic and mediastinal disorders Nasal congestion
Gastrointestinal disorders Abdominal discomfort, Diarrhoea, Vomiting
Skin and subcutaneous tissue disorders Rash
Musculoskeletal and Connective Tissue Disorders Back pain, Muscle spasms, Musculoskeletal pain
General disorders and administration site conditions Oedema*

* **Insomnia includes:** initial insomnia, middle insomnia; **Akathisia includes:** hyperkinesia, restless legs syndrome, restlessness; **Parkinsonism includes:** akinesia, bradykinesia, cogwheel rigidity, drooling, extrapyramidal symptoms, glabellar reflex abnormal, muscle rigidity, muscle tightness, musculoskeletal stiffness; **Oedema includes:** generalised oedema, oedema peripheral, pitting oedema.

[1] Frequencies calculated based on a 12-week double-blind, placebo-controlled trial in adults with schizophrenia.

Adverse reactions reported with risperidone and/or paliperidone by < 2% of RISPERDAL® CONSTA®-treated subjects with schizophrenia are shown in Table 3.

Table 3. Additional ADRs Reported with Risperidone and/or Paliperidone by < 2% of RISPERDAL® CONSTA®-treated Subjects with Schizophrenia[1] (The Terms within each System Organ Class are Sorted Alphabetically)

System/Organ Class Adverse Reaction
Infections and infestations Ear infection, Infection, Influenza, Sinusitis
Immune system disorders Hypersensitivity
Metabolism and nutrition disorders Decreased appetite, increased appetite
Psychiatric disorders Confusional state, libido decreased, nightmare
Nervous system disorders Dizziness postural, Dysarthria, Dyskinesia*, Paraesthesia
Eye disorders Photophobia
Ear and labyrinth disorders Ear pain
Cardiac disorders Bradycardia, Conduction disorder, Electrocardiogram abnormal, Electrocardiogram QT prolonged, Palpitations
Respiratory, thoracic and mediastinal disorders Dyspnoea, Pharyngolaryngeal pain, Wheezing
Hepatobiliary disorders Gamma-glutamyltransferase increased, Hepatic enzyme increased
Skin and subcutaneous tissue disorders Pruritus, Seborrhoeic dermatitis, Skin disorder
Musculoskeletal and connective tissue disorders Joint stiffness, Muscular weakness
Renal and urinary disorders Urinary incontinence
Reproductive system and breast disorders Breast discomfort, Ejaculation disorder, Erectile dysfunction, Galactorrhoea
General disorders and administration site conditions Chest discomfort, Feeling abnormal, Injection site reaction

* **Dyskinesia includes:** athetosis, chorea, choreoathetosis, movement disorder, muscle twitching, myoclonus[1]

[1]Frequencies calculated based on a 12-week double-blind, placebo-controlled trial in adults with schizophrenia.

Adverse Reactions reported with risperidone and/or paliperidone in other clinical trials but not reported by RISPERDAL® CONSTA® (25 mg or 50 mg)-treated subjects with schizophrenia are shown in Table 4.

Table 4. Additional ADRs Reported with Risperidone and/or Paliperidone in Other Clinical Trials but Not Reported by RISPERDAL® CONSTA® (25 mg or 50 mg)-treated subjects with Schizophrenia in the Trial Listed in Tables 2 and 3.[1] (The Terms within each System Organ Class are Sorted Alphabetically)

System/Organ Class Adverse Reaction
Infections and Infestations
Acarodermatitis, Bronchitis, Cellulitis, Cystitis, Eye infection, Localised infection, Onychomycosis, Pneumonia, Respiratory tract infection, Subcutaneous abscess, Tonsillitis, Urinary tract infection, Viral infection
Blood and Lymphatic System Disorders
Anaemia, Eosinophil count increased, Haematocrit decreased, Neutropenia, White blood cell count decreased
Immune System Disorders
Anaphylactic reaction
Endocrine Disorders
Glucose urine present, Hyperprolactinaemia
Metabolism and Nutrition Disorders
Anorexia, Blood cholesterol increased, Blood triglycerides increased, Hyperglycaemia, Hyperinsulinaemia, Polydipsia
Psychiatric Disorders
Anorgasmia, Blunted affect, Sleep disorder
Nervous System Disorders
Balance disorder, Cerebrovascular accident, Cerebrovascular disorder, Convulsion*, Coordination abnormal, Depressed level of consciousness, Diabetic coma, Dystonia*, Head titubation, Loss of consciousness, Neuroleptic malignant syndrome, Psychomotor hyperactivity, Tardive dyskinesia, Unresponsive to stimuli
Eye Disorders
Conjunctivitis, Dry eye, Eye movement disorder, Eye rolling, Eyelid margin crusting, Glaucoma, Lacrimation increased, Ocular hyperaemia
Ear and Labyrinth Disorders
Tinnitus, Vertigo

Cardiac Disorders Atrioventricular block, Postural orthostatic tachycardia syndrome, Sinus arrhythmia
Vascular Disorders Flushing, Hypotension, Orthostatic hypotension
Respiratory, Thoracic and Mediastinal Disorders Dysphonia, Epistaxis, Hyperventilation, Pneumonia aspiration, Pulmonary congestion, Rales, Respiratory disorder, Respiratory tract congestion
Gastrointestinal Disorders Cheilitis, Dysphagia, Faecal incontinence, Faecaloma, Flatulence, Gastroenteritis, Intestinal obstruction, Swollen tongue
Hepatobiliary Disorders Transaminases increased
Skin and Subcutaneous Disorders Drug eruption, Eczema, Erythema, Hyperkeratosis, Skin discolouration, Skin lesion, Urticaria
Musculoskeletal, Connective Tissue, and Bone Disorders Blood creatine phosphokinase increased, Joint swelling, Neck pain, Posture abnormal, Rhabdomyolysis
Renal and Urinary Disorders Dysuria, Pollakiuria
Reproductive System and Breast Disorders Breast discharge, Breast engorgement, Breast enlargement, Gynaecomastia, Menstrual disorder*, Menstruation delayed, Sexual dysfunction, Vaginal discharge
General Disorders and Administration Site Conditions Body temperature decreased, Body temperature increased, Chills, Discomfort, Drug withdrawal syndrome, Face oedema, Induration, Malaise, Peripheral coldness, Thirst
Injury, Poisoning and Procedural Complications Fall, Procedural pain

* **Convulsion includes:** Grand mal convulsion; **Dystonia includes:** blepharospasm, cervical spasm, emprosthotonus, facial spasm, hypertonia, laryngospasm, muscle contractions involuntary, myotonia, oculogyration, opisthotonus, oropharyngeal spasm, pleurothotonus, risus sardonicus, tetany, tongue paralysis, tongue spasm, torticollis, trismus; **Menstrual disorder includes:** Menstruation irregular, Oligomenorrhoea

Frequencies of ADRs listed in Tables 2 and 3 were calculated from a 12-week double-blind, placebo-controlled trial in adults with schizophrenia. The adverse reactions listed in the table above were not observed in that study, but were observed in other, nonpivotal clinical studies with RISPERDAL® CONSTA®-or in clinical studies with another risperidone- or paliperidone-containing product.

Postmarketing Data

Adverse events first identified as adverse reactions during postmarketing experience with risperidone and/or paliperidone are included in Table 5. In each table, the frequencies are provided according to the following convention:

Very common	≥1/10
Common	≥1/100 to <1/10
Uncommon	≥1/1,000 to <1/100
Rare	≥1/10,000 to <1/1,000
Very rare	<1/10,000, including isolated reports
Unknown	Cannot be estimated from the available data

In Table 5, adverse reactions are presented by frequency category based on incidence in clinical trials, when known.

Table 5. Adverse Reactions Identified During Postmarketing Experience with Risperidone and/or Paliperidone (The Frequency is Based on Reporting Rates in Clinical Trials with Risperidone)

Blood and Lymphatic Disorders	
Uncommon	Thrombocytopenia
Unknown	Agranulocytosis
Endocrine Disorders	
Rare	Inappropriate antidiuretic hormone secretion
Metabolism and Nutrition Disorders	
Uncommon	Diabetes mellitus[a]
Rare	Hypoglycaemia
Very rare	Diabetic ketoacidosis,
Unknown	Water intoxication
Psychiatric Disorders	
Uncommon	Mania
Rare	Catatonia, Somnambulism
Unknown	Sleep-related eating disorder
Nervous System Disorders	
Uncommon	Dysgeusia
Eye Disorders	
Unknown	Retinal artery occlusion[b], Floppy iris syndrome (intraoperative)
Cardiac Disorders	
Uncommon	Atrial fibrillation
Vascular Disorders	
Rare	Deep vein thrombosis, Pulmonary embolism
Respiratory, Thoracic, and Mediastinal Disorders	
Rare	Sleep apnoea syndrome
Gastrointestinal Disorders	
Rare	Pancreatitis, Ileus
Hepatobiliary Disorders	
Rare	Jaundice
Skin and Subcutaneous Tissue Disorders	
Uncommon	Alopecia
Very rare	Angioedema
Unknown	Stevens-Johnson syndrome/Toxic epidermal necrolysis

Renal and Urinary Disorders	
Uncommon	Urinary retention
Pregnancy, Puerperium and Perinatal Conditions	
Unknown	Drug withdrawal syndrome neonatal
Reproductive System and Breast Disorders	
Unknown	Priapism
General Disorders and Administration Site Conditions	
Rare	Hypothermia
Unknown	Injection site abscess, cellulitis, Injection site cyst, Injection site haematoma, Injection site necrosis, Injection site ulcer [e]

[a] In placebo-controlled trials diabetes mellitus was reported in 0.18% in risperidone-treated subjects compared to a rate of 0.11% in placebo group. Overall incidence from all clinical trials was 0.43% in all risperidone-treated subjects

[b] RISPERDAL® CONSTA® formulation only, reported in the presence of an intracardiac defect predisposing to a right-to-left shunt (e.g., a patent foramen ovale)

Very rarely, cases of anaphylactic reaction after injection with RISPERDAL® CONSTA® have been reported during postmarketing experience in patients who have previously tolerated oral risperidone.

Overdose

While overdosage is less likely to occur with parenteral than with oral medication, information pertaining to oral risperidone is presented.

Symptoms and signs

In general, reported signs and symptoms have been those resulting from an exaggeration of the drug's known pharmacological effects. These include drowsiness and sedation, tachycardia and hypotension, and extrapyramidal symptoms. In overdose, QT-prolongation and convulsion have been reported. Torsade de pointes has been reported in association with combined overdose of oral RISPERDAL® and paroxetine.

In case of acute overdosage, the possibility of multiple drug involvement should be considered.

Treatment

Establish and maintain a clear airway and ensure adequate oxygenation and ventilation. Cardiovascular monitoring should commence immediately and should include continuous electrocardiographic monitoring to detect possible arrhythmias.

There is no specific antidote to risperidone. Therefore, appropriate supportive measures should be instituted. Hypotension and circulatory collapse should be treated with appropriate measures such as intravenous fluids and/or sympathomimetic agents. In case of severe extrapyramidal symptoms, anticholinergic medication should be administered. Close medical supervision and monitoring should continue until the patient recovers.

PHARMACOLOGICAL PROPERTIES

Pharmacodynamic Properties

Pharmacotherapeutic group: antipsychotic drugs: ATC code: N05AX08

Risperidone is a selective monoaminergic antagonist with unique properties. It has a high affinity for serotoninergic 5-HT2 and dopaminergic D2 receptors. Risperidone binds also to alpha1-adrenergic receptors, and, with lower affinity, to H1-histaminergic and alpha2-adrenergic receptors. Risperidone has no affinity for cholinergic receptors. Although risperidone is a potent D2 antagonist, that is considered to improve the positive symptoms of schizophrenia, it causes less depression of motor activity and induction of catalepsy than classical neuroleptics. Balanced central serotonin and dopamine antagonism may reduce extrapyramidal side effect liability and extend the therapeutic activity to the negative and affective symptoms of schizophrenia.

Further information on clinical trials

Schizophrenia

The effectiveness of RISPERDAL® CONSTA® (25 mg and 50 mg) in the management of the manifestations of psychotic disorders (schizophrenia/ schizoaffective disorder) was established in one 12-week, placebo-controlled trial in adult psychotic inpatients and outpatients who met the DSM-IV criteria for schizophrenia.

In a 12-week comparative trial in stable patients with schizophrenia, RISPERDAL® CONSTA® was shown to be as effective as the oral tablet formulation. The long-term (50 weeks) safety and efficacy of RISPERDAL® CONSTA® was also evaluated in an open-label trial of stable psychotic inpatients and outpatients who met the DSM-IV criteria for schizophrenia or schizoaffective disorder. Over time efficacy was maintained with RISPERDAL® CONSTA®.The safety information is available in the safety section.

Figure 1. Mean in total PANSS score over time (LOCF) in patients with schizophrenia.

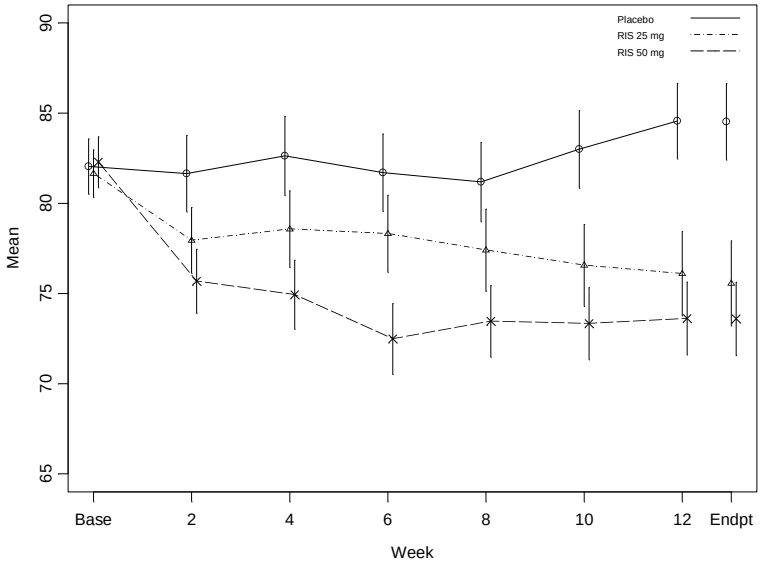
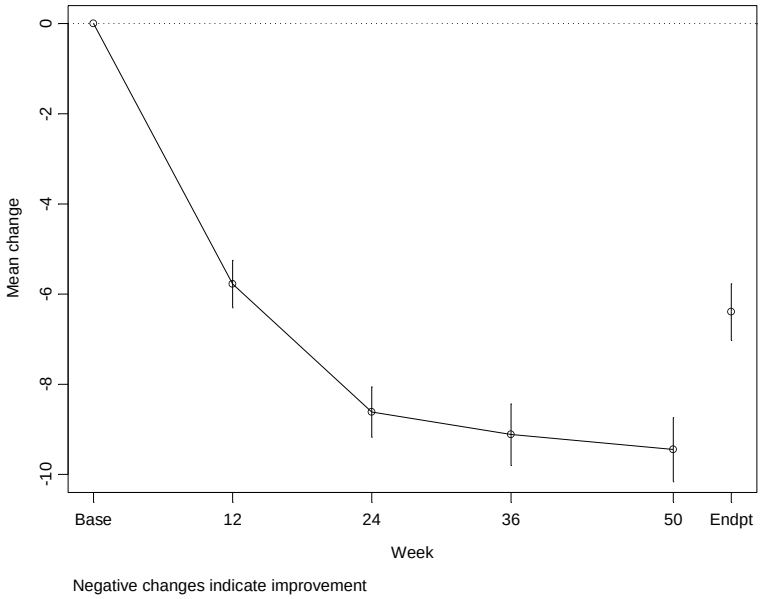


Figure 2. Mean change in total PANSS score from baseline for all doses tested in the 50-week, open-label trial.



Pharmacokinetic Properties

General characteristics of risperidone after administration of RISPERDAL® CONSTA® in patients

After a single intramuscular injection with RISPERDAL® CONSTA®, the release profile consists of a small initial release of drug (<1% of the dose), followed by a lag time of 3 weeks. The main release of drug starts from week 3 onwards, is maintained from 4 to 6 weeks, and subsides by week 7. Oral antipsychotic supplementation should therefore be given during the first 3 weeks of RISPERDAL® CONSTA® treatment (see *Dosage and Administration*).

[The pharmacokinetics of risperidone following single doses of RISPERDAL® CONSTA® are linear in the dose range of 12.5-50 mg.]

After repeated intramuscular injections with 25 or 50 mg RISPERDAL® CONSTA® every two weeks, median trough and peak plasma concentrations of the active antipsychotic fraction fluctuated between 9.9-19.2 ng/ml and 17.9-45.5 ng/ml respectively.

The pharmacokinetics of risperidone are linear in the dose range of 25–50 mg injected every 2 weeks. No accumulation of risperidone was observed during long-term use (12 months) in patients who were injected with 25–50 mg every two weeks.

The above studies were conducted with gluteal intramuscular injection. Deltoid and gluteal intramuscular injections at the same doses are bioequivalent and, therefore, interchangeable.

A single-dose study with oral risperidone showed higher active plasma concentrations and a reduced clearance of the active antipsychotic fraction by 30% in the elderly and 60% in patients with renal insufficiency. Risperidone plasma concentrations were normal in patients with liver insufficiency, but the mean free fraction of risperidone in plasma was increased by about 35%.

Pharmacokinetic/pharmacodynamic relationship
There was no relationship between the plasma concentrations of the active antipsychotic fraction and the change in total PANSS (Positive and Negative Syndrome Scale) and total ESRS (Extrapyramidal Symptom Rating Scale) scores across the assessment visits in any of the phase-III trials where efficacy and safety was examined.

Absorption
The absorption of risperidone from RISPERDAL® CONSTA® is complete.

Distribution
Risperidone is rapidly distributed. The volume of distribution is 1-2 L/kg. In plasma, risperidone is bound to albumin and alpha-1-acid glycoprotein. The plasma protein binding of risperidone is 90%, the active metabolite 9-hydroxy-risperidone is 77%.

Metabolism
Risperidone is metabolized by CYP2D6 to 9-hydroxy-risperidone, which has a similar pharmacological activity as risperidone. Risperidone plus 9-hydroxy risperidone form the active antipsychotic fraction. Another metabolic pathway of risperidone is N-dealkylation.

Elimination
The active antipsychotic fraction and risperidone clearances were 5.0 and 13.7 L/h in extensive metabolizers, respectively, and 3.2 and 3.3 L/h in poor metabolizers of CYP2D6, respectively.

The combination of the release profile and the dosage regimen (intramuscular injection every two weeks) result in sustained therapeutic plasma concentrations. Therapeutic plasma concentrations remain until 4 to 6 weeks after the last RISPERDAL® CONSTA® injection. The elimination phase is complete approximately 7 to 8 weeks after the last injection.

NON-CLINICAL INFORMATION
Animal Toxicology
Apart from the local irritation at high volumes, the RISPERDAL® CONSTA® formulation has a similar toxicological profile when compared to the oral formulation. In the (sub)chronic toxicity studies with oral risperidone in rats and dogs, the major effects of treatment with RISPERDAL® CONSTA® (up to 12 months of intramuscular administration) were prolactin-mediated mammary gland stimulation, male and female genital tract changes, and central nervous system (CNS) effects, related to the pharmacodynamic activity of risperidone. In an oral toxicity study with juvenile rats, increased pup mortality and a delay in physical development was observed. In a 40-week study with juvenile dogs treated with oral risperidone, sexual maturation was delayed. Long bone growth was not affected at a dose similar to the maximum human oral dose in adolescents (6 mg/day); effects were observed at a dose 4-fold (on an AUC basis) or 7-fold (on a mg/m2 basis) the maximum human oral dose in adolescents.

RISPERDAL® CONSTA® administration to male and female rats for 12 and 24 months produced osteodystrophy at a dose of 40 mg/kg/2 weeks. The effect dose for osteodystrophy in rats was on a mg/m2 basis 8 times the maximum recommended human dose and is associated with a plasma exposure 2 times the maximum anticipated exposure in humans at the maximum recommended

dose. No osteodystrophy was observed in dogs treated for 12 months with RISPERDAL® CONSTA® up to 20 mg/kg/2 weeks. This dose yielded plasma exposures up to 14 times the maximum recommended human dose.

Carcinogenicity and Mutagenicity

There was no evidence of mutagenic potential.

As expected for a potent dopamine D2-antagonist, in an intramuscular carcinogenicity study in Wistar (Hannover) rats (doses of 5 and 40 mg/kg/2 weeks), prolactin-mediated increased incidences of endocrine pancreas, pituitary gland, and adrenal medullary tumors were observed at 40 mg/kg, while mammary gland tumors were present at 5 and 40 mg/kg. Hypercalcemia, postulated to contribute to an increased incidence of adrenal medullary tumors, was observed in both dose groups. There is no evidence to suggest that hypercalcemia might cause phaeochromocytomas in humans.

Renal tubular adenomas occurred in male rats at 40 mg/kg/2 weeks. No renal tumors occurred in the low dose, the NaCl 0.9%, or the microspheres vehicle control group. The mechanism underlying the renal tumors in RISPERDAL® CONSTA® treated male Wistar (Hannover) rats is unknown. A treatment-related increase in renal tumor incidence did not occur in the oral carcinogenicity studies with Wistar (Wiga) rats or in Swiss mice administered oral risperidone. Studies conducted to explore the substrain differences in the tumor organ profile suggest that the Wistar (Hannover) substrain employed in the carcinogenicity study differs substantially from the Wistar (Wiga) substrain employed in the oral carcinogenicity study with respect to spontaneous age-related non-neoplastic renal changes, serum prolactin increases, and renal changes in response to risperidone. There are no data suggesting kidney-related changes in dogs treated chronically with RISPERDAL® CONSTA®.

The relevance of the osteodystropy, the prolactin-mediated tumors and of the presumed rat substrain-specific renal tumors in terms of human risk is unknown.

Local irritation at the injection site in dogs and rats was observed after administration of high doses of RISPERDAL® CONSTA®. In a 24-month IM carcinogenicity study in rats, no increased incidence of injection site tumors was seen in either the vehicle or active drug groups.

PHARMACEUTICAL INFORMATION

List of Excipients

RISPERDAL® CONSTA® Extended Release Microspheres
7525 DL JN1 [poly-(d,l-lactide-co-glycolide)] polymer

Diluent

carmellose sodium 40mPa.s
citric acid anhydrous
disodium hydrogen phosphate dihydrate
polysorbate 20
sodium chloride
sodium hydroxide
water for injection

Incompatibilities
RISPERDAL® CONSTA® cannot be mixed or diluted with drugs or fluids other than the supplied diluent for administration.

Shelf Life
36 months at 2-8°C.

After reconstitution: Chemical and physical in-use stability has been demonstrated for 24 hours at 25°C. From a microbiological point of view, the product should be used immediately. If not used immediately, in-use storage times and conditions prior to use are the responsibility of the user and would normally not be longer than 6 hours at 25°C, unless reconstitution has taken place in controlled and validated aseptic conditions.

Storage Conditions
The entire dose pack should be stored in the refrigerator (2-8°C) and protected from light. It should not be exposed to temperatures above 25°C.

If refrigeration is unavailable, RISPERDAL® CONSTA® can be stored at temperatures not exceeding 25°C for no more than 7 days prior to administration. Do not expose unrefrigerated product to temperatures above 25°C.

Keep out of the sight and reach of children.

Nature and Contents of Container
Needle-Free Vial Access Device
- One vial containing RISPERDAL® CONSTA® extended release microspheres
- One prefilled syringe containing the diluent for RISPERDAL® CONSTA®
- One Vial Adapter for reconstitution
- Two Terumo SurGuard®-3 Needles for intramuscular injection (a 21G UTW 1-inch safety needle with needle protection device for deltoid administration and a 20G TW 2-inch safety needle with needle protection device for gluteal administration) ("Rx - only" = device to be sold with Prescription Drugs only)

Instructions for Use and Handling and Disposal
Important information

RISPERDAL® CONSTA® requires close attention to these step-by-step Instructions for Use to help ensure successful administration.

Wait 30 minutes
Remove dose pack from the refrigerator and allow to sit at room temperature for at least 30 minutes before reconstituting.

Do not warm any other way.

Use components provided
The components in this dose pack are specifically designed for use with RISPERDAL® CONSTA®. RISPERDAL® CONSTA® must be reconstituted only in the diluent supplied in the dose pack.

Do not substitute ANY components of the dose pack.

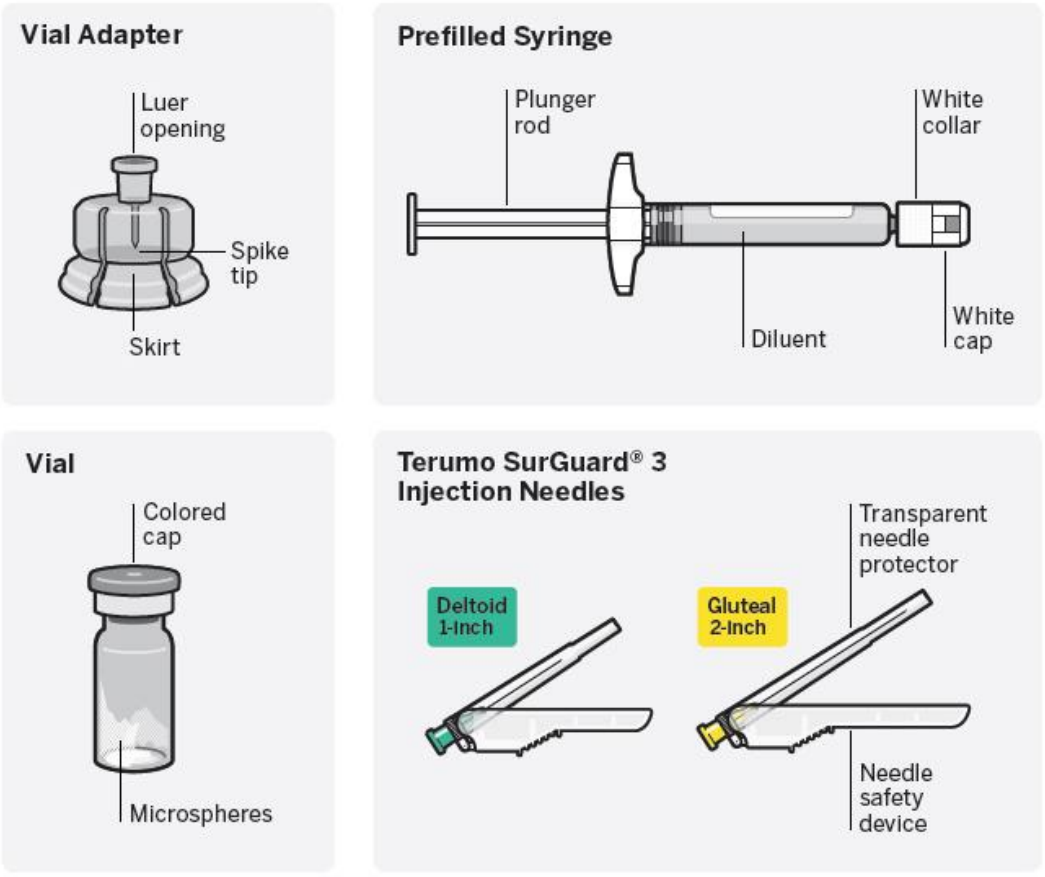
Do not store suspension after reconstitution
Administer dose as soon as possible after reconstitution to avoid settling.

Proper dosing
The entire contents of the vial must be administered to ensure intended dose of RISPERDAL® CONSTA® is delivered.

SINGLE-USE DEVICE

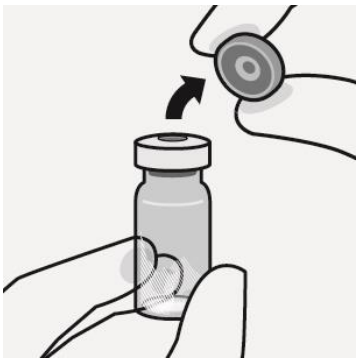
Do not reuse. Medical devices require specific material characteristics to perform as intended. These characteristics have been verified for single use only. Any attempt to re-process the device for subsequent re-use may adversely affect the integrity of the device or lead to deterioration in performance.

Dose pack contents



Step 1 Assemble components

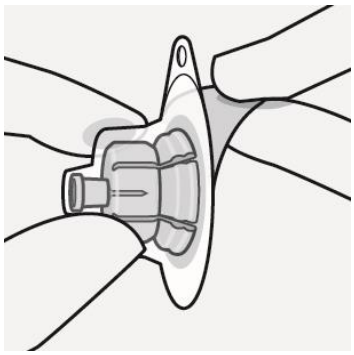
Connect vial adapter to vial



Remove cap from vial
Flip off colored cap from vial.

Wipe top of the grey stopper with an alcohol swab.
Allow to air dry.

Do not remove grey rubber stopper.

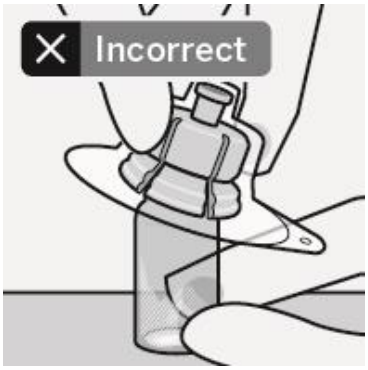


Prepare vial adapter
Hold sterile blister as shown.
Peel back and remove paper backing.

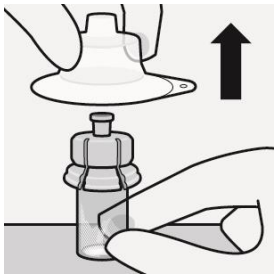
Do not remove vial adapter from blister.

Do not touch spike tip at any time. This will result in contamination.

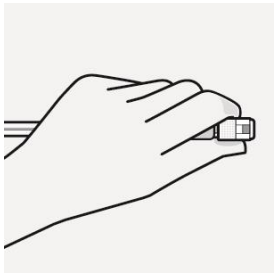
Connect vial adapter to vial
Place vial on a hard surface and hold by the base. Center vial adapter over the grey rubber stopper. Push vial adapter straight down onto vial top until it snaps securely into place.
Do not place vial adapter on at an angle or diluent may leak
upon transfer to the vial.



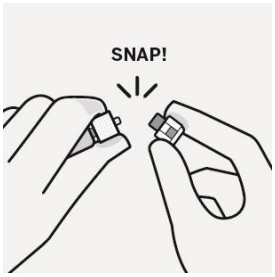
Connect prefilled syringe to vial adapter



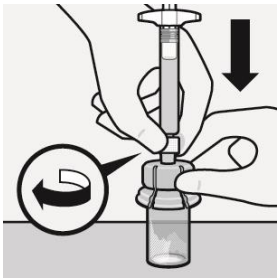
Remove sterile blister



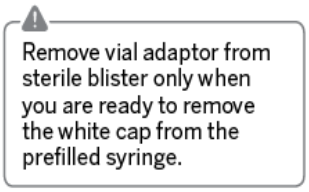
Use proper grip



Remove cap



Connect syringe to



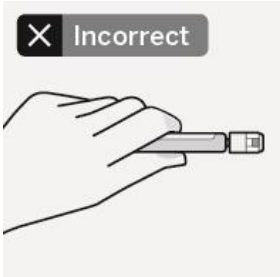
Keep vial vertical to prevent leakage. Hold base of vial and pull up on the sterile blister to remove.

Do not shake.

Do not touch exposed luer opening on vial adapter. This will result in contamination.

Hold by white collar at the tip of the syringe.

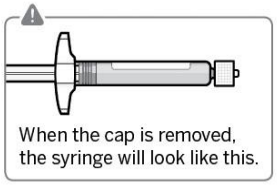
Do not hold syringe by the glass barrel during assembly.



Holding the white collar, snap off the white cap.

Do not twist or cut off the white cap.

Do not touch syringe tip. This will result in contamination.



The broken-off cap can be discarded.

vial adapter
Hold vial adapter by skirt to keep stationary.

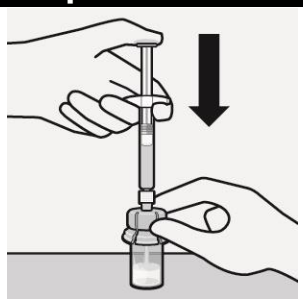
Hold syringe by white collar then insert tip into the luer opening of the vial adapter.

Do not hold the glass syringe barrel. This may cause the white collar to loosen or detach.

Attach the syringe to the vial adapter with a firm clockwise twisting motion until it feels snug.

Do not over-tighten. Over-tightening may cause the syringe tip to break.

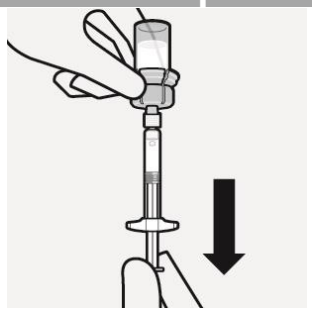
Step 2 Reconstitute microspheres



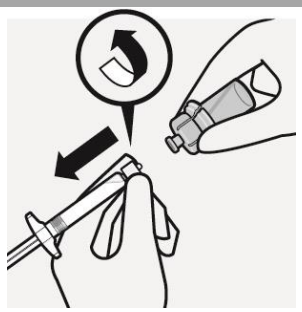
Inject diluent
Inject entire amount of diluent from syringe into the vial.

Suspend microspheres in diluent
Continuing to hold down the plunger rod, shake vigorously for at least 10 seconds, as shown.

Check the suspension. When properly mixed,



Transfer suspension to syringe
Invert vial completely. Slowly pull plunger rod down to withdraw entire contents from the vial into the syringe.



Remove vial adapter
Hold white collar on the syringe and unscrew from vial adapter.

Tear section of the vial label at the perforation. Apply

Vial contents will now be under pressure.
Keep holding the plunger rod down with thumb.

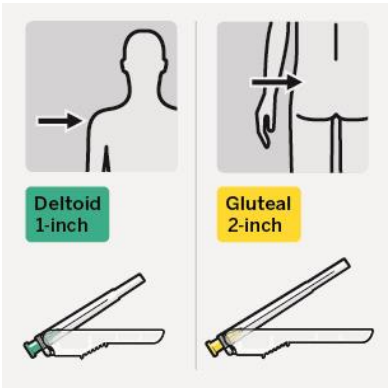
the suspension appears uniform, thick and milky in color. Microspheres will be visible in the liquid.

Immediately proceed to the next step so suspension does not settle.

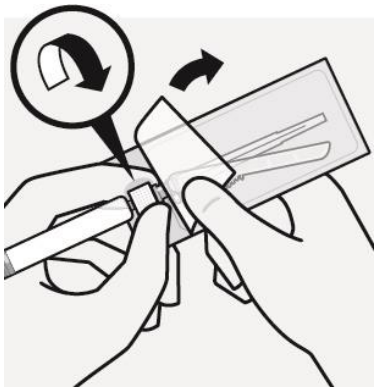
detached label to the syringe for identification purposes.

Discard both vial and vial adapter appropriately.

Step 3 Attach needle



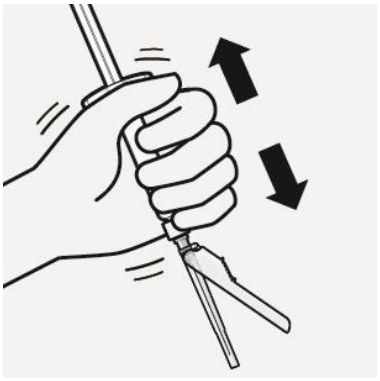
Select appropriate needle
Choose needle based on injection location (gluteal or deltoid).



Attach needle
Peel blister pouch open part way and use to grasp the base of the needle, as shown.

Holding the white collar on the syringe, attach syringe to needle luer connection with a firm clockwise twisting motion until snug.

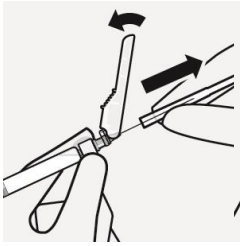
Do not touch needle luer opening. This will result in contamination.



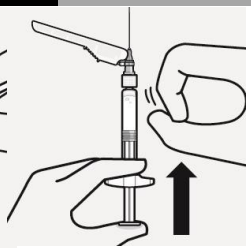
Resuspend microspheres
Fully remove the blister pouch.

Just before injection, shake syringe vigorously again, as some settling will have occurred.

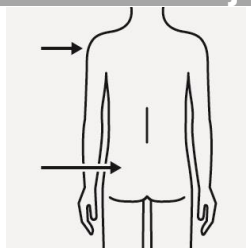
Step 4 — Inject dose



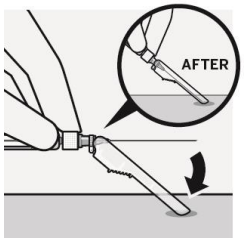
Remove transparent needle protector
Move the needle safety device back towards the syringe, as shown. Then hold white collar on syringe and carefully pull the transparent



Remove air bubbles
Hold needle upright and tap gently to make any air bubbles rise to the top. Slowly and carefully press plunger rod upward to remove air.



Inject
Immediately inject entire contents of syringe intramuscularly (IM) into the gluteal or deltoid muscle of the patient.
Gluteal injection should be made into the upper-outer quadrant of the gluteal area.



Secure needle in safety device
Using one hand, place needle safety device at a 45 degree angle on a hard, flat surface. Press down with a firm, quick motion until needle is fully engaged in safety device.

Avoid needle stick injury:

Properly dispose of needles
Check to confirm needle safety device is fully engaged. Discard in an approved sharps container.
Also discard the unused needle provided in the dose pack.

needle protector straight off.

Do not twist transparent needle protector, as the luer connection may loosen.

Do not administer intravenously.

Do not use two hands.

Do not intentionally disengage or mishandle the needle safety device.

Do not attempt to straighten the needle or engage the safety device if the needle is bent or damaged.

PRODUCT REGISTRANT

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