

DATA SHEET

NAME OF MEDICINE

RISPERDAL CONSTA®

Risperidone prolonged release microspheres formulation for intramuscular injection

25 mg/2mL

37.5 mg/2mL

50 mg/2mL

DESCRIPTION

RISPERDAL CONSTA is an extended release microspheres formulation of risperidone micro-encapsulated in polyglactin for intramuscular injection, in strengths of 25mg, 37.5mg and 50mg when suspended in 2mL diluent. The diluent contains carmellose sodium 40 mPa.s, anhydrous citric acid, sodium phosphate-dibasic dihydrate, polysorbate 20, sodium chloride, sodium hydroxide and water for injection.

USES

Actions

Risperidone belongs to the benzisoxazole derivatives class of antipsychotic agents.

Risperidone is a selective monoaminergic antagonist having a high affinity for serotonergic 5-HT₂ and dopaminergic D₂ receptors. Risperidone binds also to alpha₁-adrenergic receptors and, with lower affinity, to H₁-histamine and alpha₂-adrenergic receptors. Risperidone has no affinity for cholinergic receptors. The antipsychotic activity of risperidone is considered to be attributable to both risperidone and its active metabolite 9-hydroxy risperidone.

Central dopamine D₂ receptor antagonism is considered to be the mechanism of action by which conventional neuroleptics improve the positive symptoms of schizophrenia, but also induce extrapyramidal symptoms and release of prolactin.

Although risperidone antagonises dopamine D₂ receptors and causes release of prolactin, it is less potent than classical neuroleptics for depression of motor activity and for induction of catalepsy in animals.

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.

Due to the alpha-blocking activity of RISPERDAL (risperidone), orthostatic hypotension can occur, especially during the initial dose-titration period. This alpha-blocking activity may also induce nasal mucosal swelling, which is probably related to the observed incidence of rhinitis associated with the use of RISPERDAL.

Antagonism of serotonergic and histaminergic receptors may induce body weight gain.

In controlled clinical trials, RISPERDAL was found to improve positive symptoms (such as hallucinations, delusions, thought disturbances, hostility, suspiciousness), as well as negative symptoms (such as blunted affect, emotional and social withdrawal, poverty of

speech). RISPERDAL may also alleviate affective symptoms (such as depression, guilt feelings, anxiety) associated with schizophrenia.

Pharmacokinetics

Disposition of risperidone after administration of RISPERDAL CONSTA

After a single intramuscular (i.m) 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. Following i.m. injection the main release of drug starts from 3 weeks 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

The combination of the release profile and the dosage regimen (i.m. 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.

The absorption of risperidone from RISPERDAL CONSTA is presumably complete following breakdown of the microspheres.

Risperidone is rapidly distributed following oral administration. The volume of distribution is 1-2 L/kg. In plasma, risperidone is bound to albumin and alpha₁-acid glycoprotein. The plasma protein binding of risperidone is 90% and that of 9-hydroxy-risperidone is 77%.

Risperidone plus 9-hydroxy risperidone 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.

After repeated i.m. injections with 25 or 50 mg RISPERDAL CONSTA every two weeks, median trough and peak plasma concentrations of risperidone plus 9-hydroxy risperidone 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.

In vitro data suggests that drugs that inhibit the metabolism of risperidone to 9-hydroxyrisperidone by inhibition of cytochrome P450 2D6 would increase the plasma concentration of risperidone and lower the plasma concentration of 9-hydroxyrisperidone. Drugs metabolised by other P450 isoenzymes are only weak inhibitors of risperidone metabolism *in vitro*. Although *in vitro* studies suggest that risperidone can inhibit cytochrome P450 2D6, substantial inhibition of the clearance of drugs metabolised by this enzymatic pathway would not be expected at therapeutic risperidone plasma concentrations. However, clinical data to confirm this expectation are not available.

Risperidone has an elimination half-life of about 3 hours in extensive metabolisers and 17 hours in poor metabolisers. Clinical studies do not suggest that poor and extensive metabolisers have different rates of adverse effects.

One week after administration of oral risperidone, 70% of the dose is excreted in the urine and 14% in faeces. In urine, risperidone and 9-hydroxyrisperidone represent 35-45% of the dose.

A single-dose study with oral risperidone showed higher active plasma concentrations and a reduced clearance of risperidone plus 9-hydroxy risperidone 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 apparent relationship between the plasma concentrations of risperidone plus 9-hydroxy risperidone 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.

INDICATIONS

RISPERDAL CONSTA is indicated for the treatment of schizophrenia and other psychotic disorders. These include first episode psychoses, acute schizophrenic exacerbations, chronic schizophrenia and other psychotic conditions, in which positive symptoms (such as hallucinations, delusions, thought disturbances, hostility, suspiciousness), and/or negative symptoms (such as blunted affect, emotional and social withdrawal, poverty of speech) are prominent.

RISPERDAL CONSTA also alleviates affective symptoms (such as depression, guilt-feelings, anxiety) associated with schizophrenia. In addition, RISPERDAL CONSTA also appears effective in maintaining the clinical improvement during continuation therapy in patients who have shown an initial response to treatment with this agent.

RISPERDAL CONSTA is indicated for maintenance treatment to prevent the recurrence of mood episodes of bipolar disorder.

DOSAGE AND ADMINISTRATION

Treatment initiation: For risperidone naïve patients, it is recommended to establish tolerability with immediate release oral formulations of risperidone prior to initiating treatment with RISPERDAL CONSTA.

For those patients stabilized on a fixed dose of oral risperidone for 2 weeks or more, the following conversion scheme should be considered: Patients treated with a dosage of 4 mg or less oral risperidone should receive the recommended dose of 25 mg RISPERDAL CONSTA once every 2 weeks. After an adequate trial at the recommended dose, some patients may benefit from higher doses of 37.5 mg and/or 50 mg of RISPERDAL CONSTA. Patients treated with oral risperidone doses higher than 4 mg per day may be considered for RISPERDAL CONSTA doses of 37.5 mg and up to 50 mg once every 2 weeks, after a trial at the recommended dose of 25 mg once every 2 weeks.

RISPERDAL CONSTA should be administered every two weeks by deep intramuscular deltoid or gluteal injection using the enclosed 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** and **ADVERSE EFFECTS**). This product does not contain an antimicrobial agent. It is for single use in one patient only. Any residue is to be discarded.

Adults

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. No additional benefit was observed with 75 mg in clinical trials in patients with schizophrenia. Doses above 50 mg were not studied in patients with bipolar disorder. Doses higher than 50 mg every 2 weeks are not recommended.

Sufficient antipsychotic coverage should be ensured during the three-week lag period following the first RISPERDAL CONSTA injection (see **Pharmacokinetics**). Patients should be closely monitored during the treatment initiation period.

After the first 3 weeks of RISPERDAL CONSTA treatment, oral risperidone should be discontinued in the majority of the patients. Under clinical surveillance, there is no need to taper the oral antipsychotic doses before its discontinuation. However, if clinically appropriate, oral risperidone 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 assessed and, if there is continuing need for oral supplementation, consideration should be given to increasing the dose of RISPERDAL CONSTA.

Upward dosage adjustment should not be made more frequently than every 4 weeks. The effect of this dose adjustment should not be anticipated earlier than 3 weeks after the first injection with the higher dose.

Elderly

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 **Pharmacokinetics**).

RISPERDAL is well tolerated in the elderly.

Hepatic and renal impairment

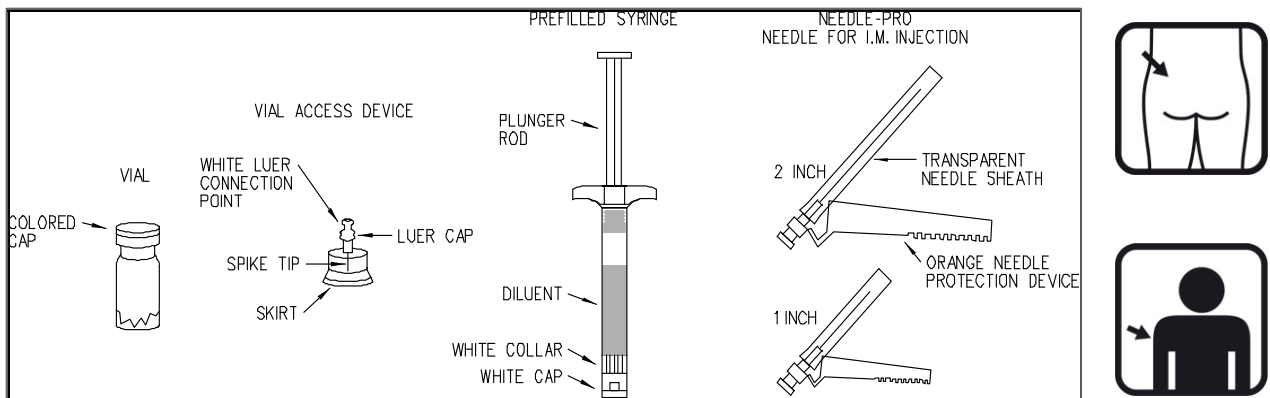
RISPERDAL CONSTA has not been studied in hepatically and renally impaired patients.

In case hepatically or renally impaired patients would 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 1mg 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.

Instruction for use and handling

RISPERDAL CONSTA requires close attention to the step-by-step 'Instructions for Use' to help ensure successful administration and help avoid difficulties in the use of the kit.

RISPERDAL CONSTA in the vial must **only** be reconstituted in the diluent in the syringe supplied in the dose pack and must be administered with **only** the appropriate needle supplied in the dose pack for gluteal (2-inch needle) or deltoid (1-inch needle) administration. Do not substitute any components in the dose pack. To assure that the intended dose of risperidone is delivered, the full contents from the vial must be administered. Administration of partial contents may not deliver the intended dose of risperidone. It is recommended to administer immediately after reconstitution.

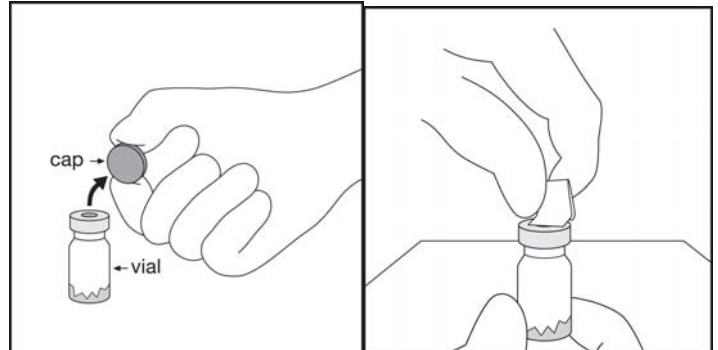


Remove the dose pack of RISPERDAL CONSTA from the refrigerator and allow it to come to room temperature for approximately 30 minutes prior to reconstitution.

Contents of the dose pack:

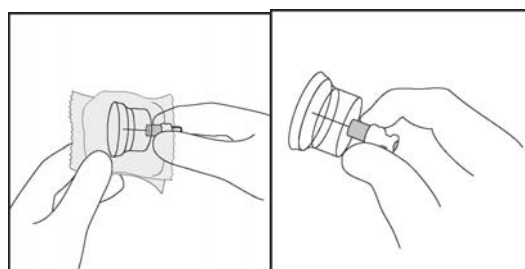
- One vial containing RISPERDAL CONSTA extended release microspheres
- One Alaris™ SmartSite® Needle-Free Vial Access Device for reconstitution
- One prefilled syringe containing the diluent for RISPERDAL CONSTA
- Two needles for intramuscular injection (a 21G UTW 1-inch safety needle with Needle-Pro® safety device for deltoid administration and a 20G TW 2-inch safety needle with Needle-Pro® safety device for gluteal administration)

1. Flip off the plastic coloured cap from the vial. Do not remove the grey rubber stopper. Wipe the top of the grey rubber stopper with an alcohol wipe and allow to dry.



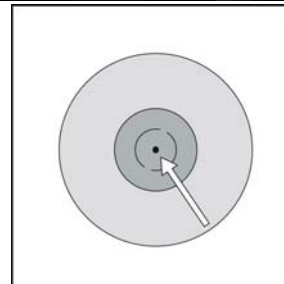
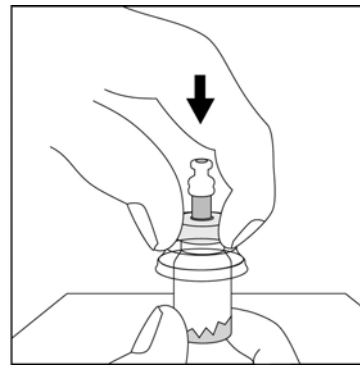
2. Peel back the blister pouch and remove the SmartSite® Needle-Free Vial Access Device by holding between the white luer cap and the skirt.

Do not touch the spike tip of the access device at any time.



3. **It is very important that the SmartSite® Needle-Free Vial Access Device be placed on the vial correctly or the diluent could leak upon transfer to the vial.**

Place the vial on a hard surface. Hold the base of the vial. Orient the SmartSite® Needle-Free Vial Access Device vertically over the vial so that the spike tip is at the center of the vial's rubber stopper.

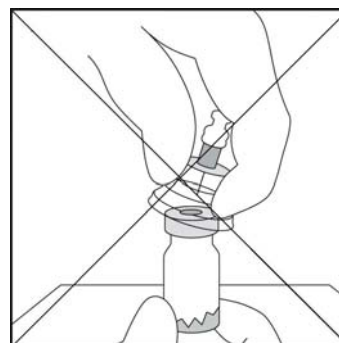


With a straight downward push, press the spike tip of the SmartSite® Needle-Free Vial Access Device through the centre of the vial's rubber stopper until the device securely snaps onto the vial top.

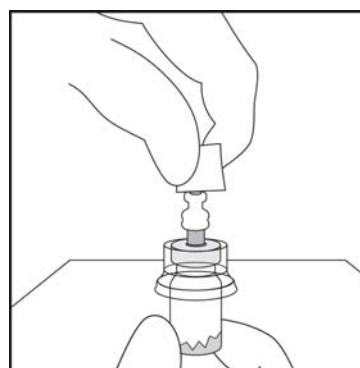
Correct



Incorrect



4. **Hold the base of the vial** and swab the syringe connection point (blue circle) of the SmartSite® Needle-Free Vial Access Device with an alcohol wipe and allow to dry prior to attaching the syringe to the SmartSite® Needle-Free Vial Access Device .



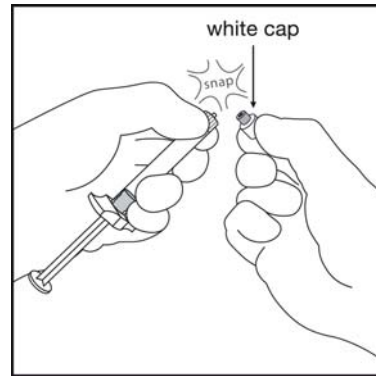
5. The prefilled syringe has a white tip consisting of 2 parts: a white collar

and a smooth white cap. To open the syringe, hold the syringe by the white collar and **snap** off the smooth white cap (**DO NOT TWIST OR CUT OFF THE WHITE CAP**). Remove the white cap together with the rubber tip cap inside.

For all syringe assembly steps, hold the syringe only by the white collar located at the tip of the syringe.

Holding the white collar will help to prevent the white collar from getting detached and ensure a good connection to the syringe.

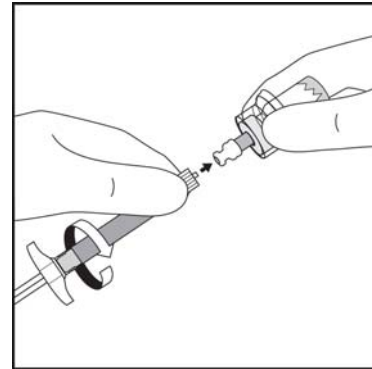
Be careful not to overtighten components when assembling. Overtightening connections may cause syringe component parts to loosen from the syringe body.



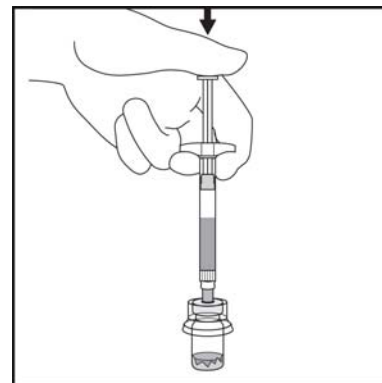
6. While holding the **white collar** of the syringe, insert and **press** the syringe tip into the blue circle of the SmartSite[®] Needle-Free Vial Access Device and **twist** in a clockwise motion to secure the connection of the syringe to the SmartSite[®] Needle-Free Vial Access Device (avoid over twisting).

Hold the skirt of the SmartSite[®] Needle-Free Vial Access Device during attachment to prevent it from spinning.

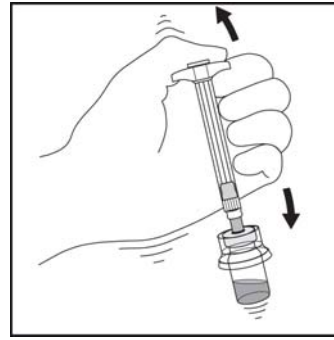
Keep the syringe and the SmartSite[®] Needle-Free Vial Access Device aligned.



7. Inject the entire contents of the syringe containing the diluent into the vial.



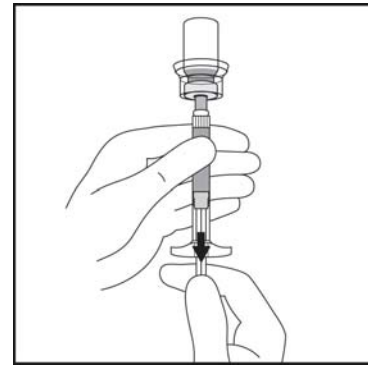
8. Shake the vial **VIGOROUSLY** while holding the plunger rod down with the thumb for a minimum of 10 seconds to ensure a homogeneous suspension. When properly mixed the suspension appears uniform, thick, and milky in color. The microspheres will be visible in liquid, but no dry microspheres remain.



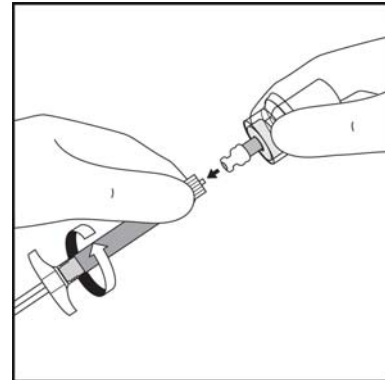
DO NOT STORE THE VIAL AFTER RECONSTITUTION OR THE SUSPENSION MAY SETTLE.

9. Invert the vial completely and **SLOWLY** withdraw the entire content of the suspension from the vial into the syringe.

Tear the section of the vial label at the perforation and apply the detached label to the syringe for identification purposes.



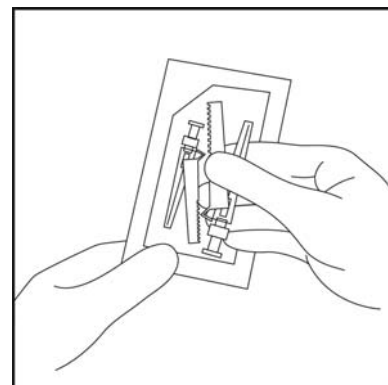
10. While holding the **white collar** of the syringe, unscrew the syringe from the SmartSite[®] Needle-Free Vial Access Device. Discard both the vial and vial access device appropriately.



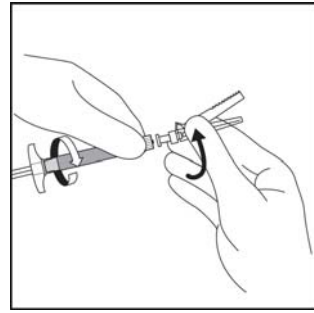
11. Open the needle pack and select the appropriate needle provided with the kit. Do **NOT** touch the connection part of the needle, only touch the transparent sheath of the needle:

For **GLUTEAL** injection, select the **20G TW 2-inch** needle (longer needle with **yellow** coloured hub).

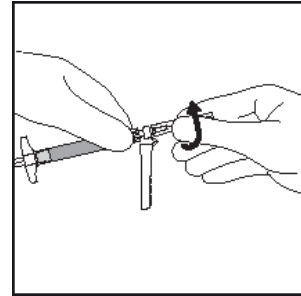
For **DELTOID** injection, select the **21G UTW 1-inch** needle (shorter needle with **green** coloured hub).



12. To prevent contamination, be careful not to touch the orange Needle-Pro[®] safety device's luer connector. While holding the **white collar** of the syringe, attach the luer connection of the orange Needle-Pro[®] safety device to the syringe with an easy clockwise twisting motion.

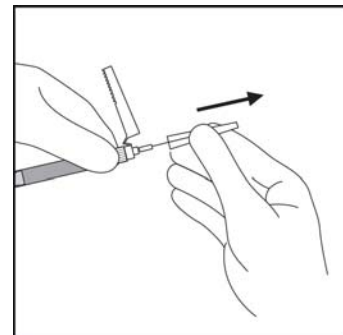


13. While continuing to hold the **white collar** of the syringe, grasp the transparent needle sheath and seat the needle firmly on the orange Needle-Pro[®] safety device with a push and a clockwise twist. **Seating the needle will help ensure a secure connection between the needle and the orange Needle-Pro[®] safety device while conducting the following steps.**



14. **RESUSPENSION OF RISPERDAL CONSTA WILL BE NECESSARY PRIOR TO ADMINISTRATION, AS SETTLING WILL OCCUR OVER TIME ONCE PRODUCT IS RECONSTITUTED. RESUSPEND THE MICROSPHERES IN THE SYRINGE BY SHAKING VIGOROUSLY.**

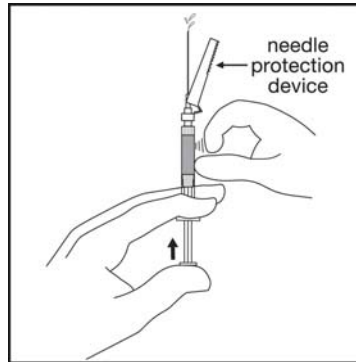
15. While holding the **white collar** of the syringe, pull the transparent needle sheath straight away from the needle. **DO NOT TWIST** the sheath as the luer connections may be loosened.



16. Tap the syringe gently to make any air bubbles rise to the top.

Remove air in syringe by depressing the plunger rod, carefully and slowly, while holding the needle in an upright position. Inject the entire contents of the syringe intramuscularly into the selected gluteal or deltoid muscle of the patient immediately. Gluteal injection should be made into the upper-outer quadrant of the gluteal area.

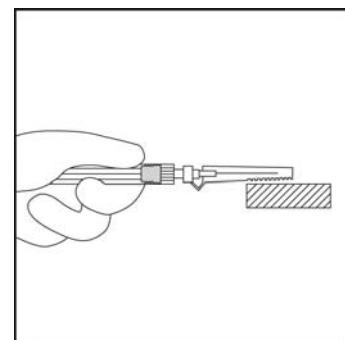
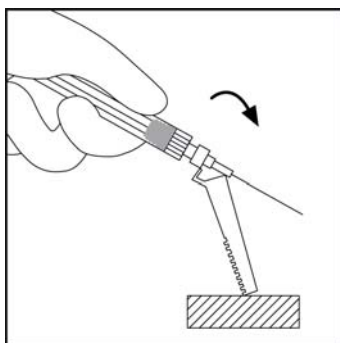
DO NOT ADMINISTER INTRAVENOUSLY.



WARNING: To avoid a needle stick injury with a contaminated needle:

- Do not use free hand to press the Needle-Pro[®] safety device over the needle.
- Do not intentionally disengage the Needle-Pro[®] safety device
- Do not attempt to straighten the needle or engage Needle-Pro[®] safety device if the needle is bent or damaged
- Do not mishandle the Needle-Pro[®] safety device as it may cause the needle to protrude from the Needle-Pro[®] safety device.

17. After injection is completed, press the needle into the orange Needle-Pro[®] safety device using a one-handed technique. Perform a one-handed technique by GENTLY pressing the orange Needle-Pro[®] safety device against a flat surface. AS THE ORANGE NEEDLE-PRO[®] SAFETY DEVICE IS PRESSED, THE NEEDLE WILL FIRMLY ENGAGE INTO THE ORANGE NEEDLE-PRO[®] SAFETY DEVICE. Visually confirm that the needle is fully engaged into the orange Needle-Pro[®] safety device before discarding. Discard needle appropriately. Also discard the other (unused) needle provided in the dose pack.



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.

CONTRAINDICATIONS

RISPERDAL CONSTA is contraindicated in patients with a known hypersensitivity to the drug or any of its excipients.

WARNINGS AND PRECAUTIONS

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% (40/1009) for RISPERDAL treated patients compared to 3.1% (22/712) for placebo-treated patients. The mean age (range) of patients who died was 86 years (range 67-100).

Concomitant use with Frusemide

In the oral RISPERDAL placebo-controlled trials in elderly patients with dementia, a higher incidence of mortality was observed in patients treated with frusemide plus risperidone (7.3% [15/206]; mean age 89 years, range 75-97) compared to treatment with risperidone alone (3.1% [25/803]; mean age 84 years, range 70-96) or frusemide alone (4.1% [5/121]; mean age 80 years, range 67-90). The Odds Ratio (95% exact confidence interval) was 1.82 (0.65, 5.14). The increase in mortality was observed in two of the four clinical trials.

No pathophysiological mechanism has been clearly identified to explain this finding and no consistent pattern for cause of death was observed. Nevertheless, caution should be exercised and the risks and benefits of this combination should be considered prior to the decision to treat. 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

In placebo-controlled trials in elderly patients with dementia, there was a significantly higher incidence of cerebrovascular adverse events, such as stroke (including fatalities) and transient ischaemic attacks in patients (mean age 85 years, range 73-97) treated with oral RISPERDAL compared to patients treated with placebo. The pooled data from six placebo-controlled trials in mainly elderly patients (>65 years of age) with dementia showed that cerebrovascular adverse events (serious and non-serious combined) occurred in 3.3% (33/989) of patients treated with risperidone and 1.2% (8/693) of patients treated with placebo. The Odds Ratio (95% exact confidence interval) was 2.96 (1.33,7.45).

Alpha-blocking activity

Due to the alpha-blocking activity of risperidone, orthostatic hypotension can occur, especially during the initial dose-titration period. Clinically significant hypotension has been observed postmarketing with concomitant use of risperidone and antihypertensive treatment. The risk-benefit of further treatment with RISPERDAL CONSTA should be assessed if clinically relevant orthostatic hypotension persists with oral treatment.

Patients with a history of clinically significant cardiac disorders were excluded from clinical trials. Risperidone should be used with caution in patients with known cardiovascular disease (e.g. heart failure, myocardial infarction, conduction abnormalities) and other conditions (such as dehydration, hypovolaemia, hypokalaemia or cerebrovascular disease). In these patients the dosage should be gradually increased.

Tardive Dyskinesia

A syndrome consisting of potentially irreversible, involuntary dyskinetic movements may develop in patients treated with conventional neuroleptics. Although this syndrome of TD appears to be most prevalent in the elderly, especially elderly females, it is impossible to predict at the onset of treatment which patients are likely to develop TD.

It has been suggested that the occurrence of parkinsonian side effects is a predictor for the development of TD. In clinical studies, the observed incidence of drug-induced Parkinsonism was lower with risperidone than with haloperidol. In the optimal clinical dose-range, the difference between risperidone and haloperidol was significant. Therefore the risk of developing tardive dyskinesia may be less with RISPERDAL. The risk of developing TD and the likelihood that it will become irreversible are believed to increase as the duration of treatment and the total cumulative dose of antipsychotic drugs administered to the patient increase. However, the syndrome can develop, although less commonly, after relatively brief periods of treatment at low doses. There is no known treatment for an established case of TD. The syndrome may remit partially or completely if antipsychotic drug treatment is withdrawn.

Antipsychotic drug treatment itself, however, may suppress the signs and symptoms of TD, thereby masking the underlying process. The effect of symptom suppression upon the long-term course of TD is unknown. In view of these considerations, RISPERDAL CONSTA should be prescribed in a manner that is most likely to minimise the risk of TD. As with any antipsychotic drug, RISPERDAL CONSTA should be reserved for patients who appear to be obtaining substantial benefit from the drug. In such patients, the smallest dose and the shortest duration of treatment should be sought. The need for continued treatment should be reassessed periodically. If signs and symptoms of TD appear in a patient on antipsychotics, drug discontinuation should be considered. However, some patients may require treatment despite the presence of this syndrome.

Neuroleptic Malignant Syndrome

This is a potentially fatal symptom complex that has been reported in association with antipsychotic drugs, including risperidone.

Clinical manifestations of NMS are hyperthermia, muscle rigidity, altered mental status (including catatonic signs) and evidence of autonomic instability (irregular pulse or blood pressure, tachycardia, cardiac arrhythmias and diaphoresis). Additional signs may include elevated creatine phosphokinase (CPK) levels, myoglobinuria (rhabdomyolysis), and acute renal failure.

In arriving at a diagnosis, it is important to identify cases where the clinical presentation includes both serious medical illness (eg pneumonia, systemic infection, etc.) and untreated or inadequately treated extrapyramidal signs and symptoms (EPS). Other important considerations in the differential diagnosis include central anticholinergic toxicity, heat stroke, drug fever, and primary central nervous system pathology.

The management of NMS should include: 1) immediate discontinuation of all antipsychotic drugs and other drugs not essential to concurrent therapy. After the last administration of RISPERDAL CONSTA, plasma levels of risperidone are measurable for at least 6 weeks; 2) intensive symptomatic treatment and medical monitoring; and 3) treatment of any concomitant serious medical problems for which specific treatments are available. There is

no general agreement about specific pharmacological treatment regimens for uncomplicated NMS.

If a patient requires antipsychotic drug treatment after recovery from NMS, the potential reintroduction of drug therapy should be carefully considered. The patient should be carefully monitored, since recurrences of NMS have been reported.

Physicians should weigh the risks versus 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.

Patients with Epilepsy

Classical neuroleptics are known to lower the seizure threshold. RISPERDAL CONSTA has not been studied in patients who also have epilepsy. In clinical trials, seizures have occurred in a few risperidone treated patients. Therefore, caution is recommended when treating patients having a history of seizures or other predisposing factors.

Hyperglycaemia and Diabetes Mellitus

Hyperglycaemia, in some cases extreme and associated with ketoacidosis or hyperosmolar coma or death, has been reported in patients treated with atypical antipsychotics including RISPERDAL CONSTA. 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 hyperglycaemia-related adverse events is not completely understood. However, epidemiological studies suggest an increased risk of treatment-emergent hyperglycaemia-related adverse events in patients treated with atypical antipsychotics. Precise risk estimates for hyperglycaemia related adverse events in patients treated with atypical antipsychotics are not available.

Patients with an established diagnosis of diabetes mellitus who are started on atypical antipsychotics should be monitored regularly for worsening of glucose control. Patients with risk factors for diabetes mellitus (e.g., obesity, family history of diabetes) who are starting treatment with atypical antipsychotics should undergo fasting blood glucose testing at the beginning of treatment and periodically during treatment. Any patient treated with atypical antipsychotics should be monitored for symptoms of hyperglycaemia including polydipsia, polyuria, polyphagia, and weakness. Patients who develop symptoms of hyperglycaemia during treatment with atypical antipsychotics should undergo fasting blood glucose testing. In some cases, hyperglycaemia has resolved when the atypical antipsychotic was discontinued; however, some patients required continuation of anti-diabetic treatment despite discontinuation of the suspect drug.

Dysphagia

Oesophageal dysmotility and aspiration have been associated with antipsychotic drug use. Aspiration pneumonia is a common cause of morbidity and mortality in patients with advanced Alzheimer's dementia. Risperdal and other antipsychotic drugs should be used cautiously in patients at risk for aspiration pneumonia.

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.

Premenopausal women with secondary amenorrhoea

Premenopausal women who develop secondary amenorrhoea of greater than six months duration should receive appropriate preventive therapy to avoid hypo-oestrogenic bone loss.

Administration

Care must be taken to avoid inadvertent injection of RISPERDAL CONSTA into a blood vessel (see **ADVERSE EFFECTS**).

Carcinogenicity

Risperidone was administered in the diet to Swiss albino mice for 18 months and to Wistar rats for 25 months at doses equivalent to 0.3, 1.3 and 5 times the maximum human dose of 10 mg/day (mice) or 0.6, 2.5 and 10 times the maximum human dose (rats) on a mg/m² basis. There were statistically significant increases in pituitary gland adenomas in female mice and endocrine pancreas adenomas in male rats at the two highest dose levels, and in mammary gland adenocarcinomas at all dose levels in female mice and female rats and at the highest dose in male rats.

Antipsychotic drugs have been shown to chronically elevate prolactin levels in rodents. Serum prolactin levels were not measured during the risperidone carcinogenicity studies; however, measurements during subchronic toxicity studies showed that risperidone elevated serum prolactin levels 5 to 6-fold in mice and rats at the same doses used in the carcinogenicity studies. An increase in mammary, pituitary and endocrine pancreas neoplasms has been found in rodents after chronic administration of other dopamine receptor antagonists and is considered to be prolactin mediated.

In a 2 year IM carcinogenicity study in rats, increased incidences of mammary gland adenocarcinoma, pancreatic islet-cell adenoma, adrenal gland pheochromocytoma, pituitary gland adenoma and renal corticotubular adenoma were observed with systemic exposure (plasma AUC) to risperidone plus 9-hydroxyrisperidone) about twice that anticipated in humans at the maximal recommended clinical dose of RISPERDAL CONSTA. Increased incidences of mammary adenocarcinoma were also observed at doses for which the plasma AUC of risperidone plus 9-hydroxy risperidone was less than anticipated clinical exposure, a no-effect dose for this finding was not determined. Elevated plasma concentrations of prolactin were present after one year of treatment, but the relationship between the renal tubular tumours and prolactin is uncertain. The increase in pheochromocytomas was associated with hypercalcemia but there was no evidence for a causal relationship. However, pheochromocytomas associated with hypercalcemia is a common finding in rats and is likely to be of low relevance to humans.

The relevance for human risk of the findings of prolactin-mediated endocrine tumours in rodents is unknown. In controlled clinical trials, RISPERDAL elevated serum prolactin levels more than haloperidol, although to date neither clinical studies nor epidemiological studies have shown an association between chronic administration of these drugs and mammary tumorigenesis. However, since tissue culture experiments indicate that approximately one-third of human breast cancers are prolactin dependent *in vitro*, RISPERDAL should be used cautiously in patients with previously detected breast cancer or in patients with pituitary tumours. Possible manifestations associated with elevated prolactin levels are amenorrhoea, galactorrhoea and menorrhagia (see **ADVERSE EFFECTS**).

Local irritation at the injection site was observed in dogs and rats after administration of RISPERDAL CONSTA. In a 2 year IM carcinogenicity study in rats, no increased incidence of injection site tumours was seen in either the vehicle or active drug groups.

Genotoxicity

No evidence of genotoxicity was observed in assays for DNA damage, gene mutations or chromosomal damage.

Effects on Fertility

Risperidone impaired mating, but not fertility, in Wistar rats at doses 0.2 to 5 times the maximum human dose on a mg/m² basis. The effect appeared to be in females since the oestrus cycle in rats was disrupted by risperidone and impaired mating behaviour was not noted when males only were treated. In repeat dose toxicity studies in Beagle dogs, risperidone at dose of 1 to 17 times the maximum human dose on a mg/m² basis was associated with adverse effects on the male reproductive system (inhibited ejaculation, incomplete spermatogenesis, reduced sperm motility and concentration, reduced gonadal and prostatic weight, prostatic immaturity, decreased serum testosterone). Serum testosterone and sperm parameters partially recovered but remained decreased after treatment was discontinued. No-effect doses were not determined in either rat or dog.

Use in pregnancy - Category C

Risperidone has only been taken by a limited number of pregnant women or women of childbearing age. No increases in the frequency of malformation or other direct or indirect harmful effects on the human fetus have been observed. In rats and rabbits, oral administration of risperidone during the period of organogenesis did not increase the incidence of malformations in offspring at doses of up to 10 times the maximum human dose on a mg/m² basis. In an embryofetal development study in rats, intramuscular administration of RISPERDAL CONSTA delayed ossification in the metatarsals and mandible at risperidone plus 9-hydroxy risperidone levels less than those achieved at the maximal human dose. This is unlikely to be clinically relevant. There was no effect on the incidence of malformations.

Non-teratogenic class effect: Neonates exposed to antipsychotic drugs (including RISPERDAL CONSTA) during the third trimester of pregnancy are at risk of experiencing extrapyramidal neurological disturbances and/or withdrawal symptoms following delivery. There have been post-market reports of agitation, hypertonia, hypotonia, tremor, somnolence, respiratory distress, and feeling disorder in these neonates. These complications have varied in severity; while in some cases symptoms have been self-limited; in other cases neonates have required additional medical treatment or monitoring.

RISPERDAL CONSTA should be used during pregnancy only if the anticipated benefit outweighs the risk and the administered dose and duration of treatment should be as low and as short as possible.

Use during lactation

It has been demonstrated that risperidone and 9-hydroxyrisperidone are excreted in human breast milk. It is recommended that women receiving RISPERDAL should not breast feed. Risperidone and 9-hydroxyrisperidone are excreted in milk in lactating dogs. In rats, administration of risperidone during late gestation and lactation was associated with an increase in pup deaths during the first 4 days of lactation at doses 0.2 to 5 times the maximum human dose on a mg/m² basis. A no-effect dose was not determined. It is not known whether these deaths were due to a direct effect on the foetuses or pups or to effects on the dams. In one such study there was an increase in stillborn rat pups at a dose 2.5 times the maximum human dose on a mg/m² basis.

Use in patients with hepatic and renal impairment

RISPERDAL CONSTA has not been studied in hepatically and renally impaired patients. In case hepatically or renally impaired patients would require treatment with RISPERDAL CONSTA, a starting dose of 0.5mg b.i.d. oral risperidone is recommended during the first week. The second week 1 mg b.i.d. or 2 mg o.d. can be given. If an oral dose of at least 2 mg is well tolerated, an intramuscular injection of 25mg RISPERDAL CONSTA can be administered every 2 weeks.

Use in children

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

However, 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.

Effects on mental alertness

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.

Weight gain

Patients may be advised to refrain from excessive eating in view of the possibility of weight gain.

ADVERSE EFFECTS

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 drug reactions (ADRs) reported by $\geq 2\%$ 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 $\geq 2\%$ 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
Hypoesthesia	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.

Double-Blind, Placebo-Controlled Data – Bipolar Disorder

Adverse drug reactions (ADRs) reported by $\geq 1\%$ of RISPERDAL CONSTA-treated patients with bipolar disorder in the 24-month double-blind, placebo-controlled period in one monotherapy recurrence prevention trial are shown in Table 2.

Table 2. Adverse Drug Reactions Reported by $\geq 1\%$ of Bipolar Disorder Patients Treated with RISPERDAL CONSTA as Monotherapy in a 24-Month Double-Blind, Placebo-Controlled Trial		
System/Organ Class Adverse Reaction	RISPERDAL CONSTA (N=154) %	Placebo (N=149) %
Infections and infestations		
Viral infection	2	1
Metabolism and nutrition disorders		
Hyperglycaemia	1	0
Psychiatric disorders		
Libido decreased	1	0
Nervous system disorders		
Dizziness	3	1
Parkinsonism ^a	1	0
Dyskinesia ^a	1	0
Akathisia ^a	1	0
Cardiac disorders		
Bundle branch block right	1	0
Vascular disorders		
Hypertension	3	1
Gastrointestinal disorders		
Diarrhoea	2	1
Reproductive system and breast disorders		
Erectile dysfunction	1	0
Sexual dysfunction	1	0
Investigations		
Weight increased	5	1
Electrocardiogram QT prolonged	1	1

^a Parkinsonism includes hypokinesia and muscle rigidity; Dyskinesia includes dyskinesia and muscle twitching; Akathisia includes akathisia and restlessness.

Adverse drug reactions (ADRs) reported by $\geq 1\%$ of RISPERDAL CONSTA-treated patients with bipolar disorder in the 52-week double-blind, placebo-controlled period in one adjunctive therapy recurrence prevention trial are shown in Table 3.

Table 3. Adverse Drug Reactions Reported by $\geq 1\%$ of Bipolar Disorder Patients Treated with RISPERDAL CONSTA as Adjunctive Therapy in a 52-Week Double-Blind, Placebo-Controlled Trial		
System Organ Class Adverse Reaction	RISPERDAL[®] CONSTA[®] + Treatment as Usual^a (N=72) %	Placebo + Treatment as Usual^a (N=67) %
Infections and infestations		
Upper respiratory tract infection	6	3
Urinary tract infection	3	1
Metabolism and nutrition disorders		
Decreased appetite	6	1
Increased appetite	4	0
Anorexia	1	0
Psychiatric disorders		
Libido decreased	1	0
Nervous system disorders		
Tremor	23	16
Hypokinesia	7	0
Sedation	6	0
Disturbance in attention	4	0

Dyskinesia	4	3
Bradykinesia	3	0
Cogwheel rigidity	1	0
Drooling	1	0
Muscle twitching	1	0
Posture abnormal	1	0
Tardive dyskinesia	1	0
Eye disorders		
Visual acuity reduced	3	0
Vascular disorders		
Orthostatic hypotension	3	0
Respiratory, thoracic and mediastinal disorders		
Cough	4	1
Musculoskeletal and connective tissue disorders		
Muscle rigidity	11	6
Arthralgia	4	3
Muscle twitching	1	0
Reproductive system and breast disorders		
Amenorrhoea	4	1
Menstrual Disorder	1	0
General disorders and administration site conditions		
Gait abnormal	4	0
Investigations		
Weight increased	7	1
^a Adjunctive therapy to patients treated with Treatment as Usual (TAU), i.e. other psychotropic medications, including benzodiazepines, selective serotonin reuptake inhibitors (SSRIs), atypical antipsychotics (including olanzepine), valproate, and/or lithium.		

Other Clinical Trial Data

ADRs reported by < 2% of the RISPERDAL CONSTA-treated patients in the 12-week, double-blind, placebo-controlled schizophrenia trial, by <1% of the RISPERDAL CONSTA-treated patients in the 24-month double-blind, placebo-controlled period of the monotherapy bipolar disorder trial, and by <1% of the RISPERDAL CONSTA-treated patients in the 52-week double-blind, placebo-controlled period of the adjunctive therapy bipolar disorder trial are shown in Table 4. Table 4 also includes ADRs reported at any rate in RISPERDAL CONSTA-treated patients who participated in other studies, including double-blind, active-controlled and open-label studies in schizophrenia and in the open-label phases in bipolar disorder studies.

<p>Table 4. Adverse Drug Reactions Reported by < 2% of RISPERDAL CONSTA-Treated Patients in the 12-Week Double-Blind, Placebo-Controlled Schizophrenia Trial, by < 1% of RISPERDAL[®] CONSTA[®]-Treated Patients in the 24-Month Double-Blind, Placebo-Controlled Period of the Monotherapy Bipolar I Disorder Trial, by <1% of RISPERDAL[®] CONSTA[®]-Treated Patients in the 52-Week Double-Blind, Placebo-Controlled Phase of the Adjunctive Therapy Bipolar Disorder Trial, or At Any Rate in Other Studies, Including Double-Blind, Active-Controlled and Open-Label Studies in Schizophrenia and in the Open-Label Phases in Bipolar Disorder Studies.</p>
<p>Infections and Infestations Nasopharyngitis, Influenza, Bronchitis, Rhinitis, Respiratory tract infection,, Ear infection, Pneumonia, Lower respiratory tract infection, Pharyngitis, Sinusitis, Infection, Localized infection, Cystitis, Gastroenteritis, Subcutaneous abscess</p> <p>Blood and Lymphatic System Disorders Anemia, Neutropenia</p> <p>Immune System Disorders Hypersensitivity</p> <p>Endocrine Disorders Hyperprolactinemia</p> <p>Psychiatric Disorders Insomnia, Anxiety, Agitation, , Sleep disorder, Depression, Initial insomnia, ,Nervousness</p> <p>Nervous System Disorders</p>

Coordination abnormal, Dystonia, Lethargy, Paresthesia, Dizziness postural, Hypersomnia, Convulsion, Akinesia, Dysarthria

Eye Disorders

Conjunctivitis

Ear and Labyrinth Disorders

Ear pain, Vertigo

Cardiac Disorders

Tachycardia, Atrioventricular block first degree, Palpitations, Sinus bradycardia, Bundle branch block left, Bradycardia, Sinus tachycardia

Vascular Disorders

Hypotension

Respiratory, Thoracic and Mediastinal Disorders

Nasal congestion, Pharyngolaryngeal pain, Dyspnea, Rhinorrhea

Gastrointestinal Disorders

Vomiting, Abdominal pain upper, Abdominal pain, Stomach discomfort, Gastritis

Skin and Subcutaneous Disorders

Rash, Eczema, Pruritis generalized, Pruritis

Musculoskeletal, Connective Tissue, and Bone Disorders

Back pain, Myalgia, Musculoskeletal chest pain, Buttock pain, Muscular weakness, Neck pain

Renal and Urinary Disorders

Urinary incontinence

Reproductive System and Breast Disorders

Galactorrhea, Oligomenorrhea, Ejaculation disorder, Gynecomastia, Breast discomfort, Menstruation irregular, Menstruation delayed

General Disorders and Administration Site Conditions

Injection site pain, Chest discomfort, Chest pain, Influenza like illness, Sluggishness, Malaise, Induration, Injection site induration, Injection site swelling Injection site reaction, Face edema

Investigations

Blood prolactin increased, Alanine aminotransferase increased, Electrocardiogram abnormal, Gamma-glutamyl transferase increased, Blood glucose increased, Hepatic enzyme increased, Aspartate aminotransferase increased, Glucose urine present

Injury, Poisoning and Procedural Complications

Fall, Procedural pain

The following is a list of additional ADRs that have been reported with oral risperidone:

Infections and Infestations: Tonsillitis, Eye infection, Cellulitis, Otitis media, Onychomycosis, Acarodermatitis, Bronchopneumonia, Tracheobronchitis, Otitis media chronic

Blood and Lymphatic Disorders: Granulocytopenia

Immune System Disorders: Drug hypersensitivity

Metabolism and Nutrition Disorders: Polydipsia

Psychiatric Disorders: Blunted affect, Confusional state, Middle insomnia, Listless, Anorgasmia

Nervous System Disorders: Hypertonia, Balance disorder, Unresponsive to stimuli, Depressed level of consciousness, Movement disorder, Parkinsonian rest tremor, Transient ischemic attack, Cerebrovascular accident, Masked facies, Speech disorder, Loss of consciousness, Muscle contractions involuntary, Cerebral ischemia, Cerebrovascular disorder, Neuroleptic malignant syndrome, Diabetic coma, Head titubation

Eye Disorders: Ocular hyperemia, Eye discharge, Eye rolling, Eyelid edema, Eye swelling, Eyelid margin crusting, Dry eye, Lacrimation increased, Photophobia, Glaucoma,

Ear and Labyrinth Disorders: Tinnitus

Cardiac Disorders: Atrioventricular block

Vascular Disorders: Flushing

Respiratory, Thoracic, and Mediastinal Disorders: Epistaxis, Wheezing, Pneumonia aspiration, Dysphonia, Productive cough, Pulmonary congestion, Respiratory tract congestion, Rales, Respiratory disorder, Hyperventilation, Nasal edema

Gastrointestinal Disorders: Dysphagia, Fecaloma, Abdominal discomfort, Fecal incontinence, Lip swelling, Cheilitis, Aptyalism

Skin and Subcutaneous Tissue Disorders: Erythema, Skin discoloration, Skin lesion, Skin disorder, Rash erythematous, Rash papular, Hyperkeratosis, Dandruff, Seborrheic dermatitis, Rash generalised, Rash maculo-papular

Musculoskeletal, Connective Tissue, and Bone Disorders: Joint stiffness, Rhabdomyolysis, Torticollis

Renal and Urinary Disorders: Enuresis, Dysuria, Pollakiuria

Reproductive System and Breast Disorders: Vaginal discharge, Retrograde ejaculation, Ejaculation failure, Breast enlargement

General Disorders and Administration Site Conditions: Thirst, Feeling abnormal, Gait disturbance, Pitting edema, Edema, Chills, Discomfort, Generalised edema, Drug withdrawal syndrome, Peripheral coldness,

Investigations: Body temperature increased, Heart rate increased, Eosinophil count increased, White blood cell count decreased, Hemoglobin decreased, Blood creatine phosphokinase increased, Hematocrit decreased, Body temperature decreased, Blood pressure decreased, Transaminases increased

Postmarketing Data

Adverse events first identified as ADRs during postmarketing experience with risperidone based on spontaneous reporting rates are included in Table 5. 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

Table 5. Adverse Drug Reactions Identified During Postmarketing Experience with Risperidone by Frequency Category Estimated from Spontaneous Reporting Rates

Blood and Lymphatic Disorders	
<i>Very rare</i>	Agranulocytosis
<i>Very rare</i>	Thrombocytopenia ^a
Immune System Disorders	
<i>Very rare</i>	Anaphylactic reaction
Endocrine Disorders	
<i>Very rare</i>	Inappropriate antidiuretic hormone secretion
Metabolism and Nutrition Disorders	
<i>Very rare</i>	Blood cholesterol increased, Blood triglycerides increased
<i>Very rare</i>	Diabetic ketoacidosis, Diabetes mellitus, Hypoglycaemia
<i>Very rare</i>	Water intoxication
Nervous System Disorders	
<i>Very rare</i>	Dysgeusia
Psychiatric Disorders	
<i>Very rare</i>	Mania
Eye Disorders	
<i>Very rare</i>	Retinal artery occlusion ^b
Cardiac Disorders	
<i>Very rare</i>	Atrial fibrillation
Respiratory, Thoracic, and Mediastinal Disorders	
<i>Very rare</i>	Sleep apnea syndrome
Gastrointestinal Disorders	
<i>Very rare</i>	Intestinal obstruction
<i>Very rare</i>	Pancreatitis
Hepatobiliary Disorders	
<i>Very rare</i>	Jaundice

Skin and Subcutaneous Tissue Disorders

Very rare Angioedema^c

Very rare Alopecia

Renal and Urinary Disorders

Very rare Urinary retention

Pregnancy, Puerperium and Perinatal Conditions

Very rare Drug withdrawal syndrome neonatal

Reproductive System and Breast Disorders

Very rare Priapism

General Disorders and Administration Site Conditions

Very rare Hypothermia

Very rare Injection site reaction including injection site abscess, cellulitis, cyst, haematoma, necrosis, nodule, and ulcer^d

^a Search terms included Thrombocytopenia, Platelet count decreased, Plateletcrit decreased, Platelet production decreased

^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)

^c Search terms included Angioneurotic oedema, C1 esterase deficiency acquired, Circumoral oedema, Eyelid edema, Face edema, Hereditary angioedema, Laryngeal oedema, Laryngotracheal oedema, Oculo-respiratory syndrome, Oedema mouth, Periorbital edema, Small bowel angioedema, Tongue oedema

^d These events were reported as serious. Isolated cases required surgical intervention.

INTERACTIONS

Given the primary CNS effects of risperidone, it should be used with caution in combination with other centrally acting medicines.

Risperidone may antagonise the effects of levodopa and other dopamine agonists.

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

As with other antipsychotics, caution should be exercised when RISPERDAL CONSTA is prescribed in combination with other medicines thought to prolong the QT interval or medicines known to cause electrolyte imbalance.

Inhibitors of hepatic metabolism of risperidone.

Carbamazepine has been shown to decrease the plasma levels of risperidone plus 9-hydroxy risperidone. Similar effects may be observed with other CYP 3A4 hepatic enzyme inducers. When carbamazepine or other CYP 3A4 hepatic enzyme inducers are initiated or discontinued, the physician should re-evaluate the dosing of RISPERDAL CONSTA.

Fluoxetine and paroxetine, CYP 2D6 inhibitors, increase the plasma concentration of risperidone but less so of 9-hydroxy risperidone. When concomitant fluoxetine or paroxetine is initiated or discontinued, the physician should re-evaluate the dosing of RISPERDAL CONSTA.

Topiramate modestly reduced the bioavailability of risperidone, but not that of risperidone plus 9-hydroxy risperidone.

Quinidine, phenothiazines, tricyclic antidepressants and some beta-blockers may increase the plasma concentrations of risperidone but not those of risperidone plus 9-hydroxy risperidone (see **Pharmacokinetics**).

In patients with schizophrenia receiving risperidone 3mg twice daily for 28 days, the addition of amitriptyline initially at 50mg twice daily, increasing to 100mg twice daily for the last 6 days of the study produced relative increases in the 0-12 hr AUC of 1.21 ± 0.35 , 1.15 ± 0.36 and 1.16 ± 0.34 and C_{max} of 1.17 ± 0.33 , 1.11 ± 0.43 and 1.11 ± 0.38 for risperidone, 9-hydroxy-risperidone and risperidone plus 9-hydroxy risperidone respectively. These modest increases do not necessitate dose modification.

In volunteer studies, a single 1mg risperidone dose was administered with cimetidine 400mg twice daily or ranitidine 150mg twice daily. Cimetidine produced a relative increase in AUC 0-Inf of 1.95 ± 0.78 , 1.01 ± 0.25 and 1.15 ± 0.28 for risperidone, 9-hydroxy-risperidone and risperidone plus 9-hydroxy risperidone respectively. Relative C max increases were 1.90 ± 0.95 , 0.95 ± 0.21 and 1.24 ± 0.27 . Co-administration of ranitidine produced a relative increase of 1.35 ± 0.32 , 1.23 ± 0.44 and 1.25 ± 0.39 in the AUC 0-Inf and of Cmax of 1.45 ± 0.61 , 1.28 ± 0.37 and 1.36 ± 0.35 . Dose modification is not considered to be necessary.

Erythromycin, a CYP3A4 inhibitor, does not change the pharmacokinetics of risperidone and risperidone plus 9-hydroxy risperidone. The cholinesterase inhibitors galantamine and donepezil, do not show a clinically relevant effect on the pharmacokinetics of risperidone and risperidone plus 9-hydroxy risperidone.

Risperidone does not show a clinically relevant effect on the pharmacokinetics of lithium, valproate, digoxin or topiramate.

In vitro studies, in which risperidone was given in the presence of various, highly protein-bound agents, indicated that clinically relevant changes in protein binding would not occur either for RISPERDAL or for any of the drugs tested.

See Warnings section regarding increased mortality in elderly dementia patients concomitantly receiving frusemide.

OVERDOSAGE

Symptoms

In general, reported signs and symptoms have been those resulting from an exaggeration of the known pharmacological effects of risperidone. These include drowsiness and sedation, tachycardia and hypotension, and extrapyramidal symptoms.

QT prolongation and convulsions have been reported. Torsades de pointes has been reported in association with combined overdose of oral risperidone and paroxetine.

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 RISPERDAL CONSTA. 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. Due to the lag period with absorption of RISPERDAL CONSTA, adverse effects may not be seen for 2-6 weeks after the overdose.

PRESENTATION AND STORAGE CONDITIONS

RISPERDAL CONSTA contains either 25 mg, 37.5 mg or 50 mg risperidone and is presented as a white to off-white free-flowing powder in a 5mL vial and a prefilled syringe containing 2mL diluent, together with:

- One Alaris™ SmartSite® Needle-Free Vial Access Device for reconstitution and
- Two Needle-Pro® 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).

Before reconstitution, 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° for no more than 7 days prior to administration. Do not expose unrefrigerated product to temperatures above 25°C.

After reconstitution, the product should be used immediately. The maximum allowable storage time at room temperature is 6 hours. If the product is not used right away it should be shaken vigorously to re-suspend. Do not refrigerate or refreeze.

MEDICINE CLASSIFICATION

Prescription Medicine

FURTHER INFORMATION

Clinical trials

Schizophrenia

The effectiveness of RISPERDAL CONSTA (25 mg and 50 mg) in the management of the manifestations of psychotic disorders (schizophrenia/schizoaffective) was established in one 12-week, placebo-controlled trial in adult psychotic inpatients and outpatients who met the DSM-IV criteria for schizophrenia (RIS-USA-121 – see figure 1).

Further trials included a 12 week non-inferiority comparative trial in stable patients with schizophrenia, in which RISPERDAL CONSTA was shown to be as effective as the oral tablet formulation (RIS-INT-61). 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 and outpatients who met the DSM-IV criteria for schizophrenia or schizoaffective disorder (RIS-INT-57-see figure 2). Over time efficacy was maintained with RISPERDAL CONSTA.

These efficacy trials used the internationally recognised PANSS scale. The total score (30 items) is divided into subscales: 8 items covering positive symptoms (e.g. hallucinations and delusions), 7 covering negative symptoms (e.g. blunted affect), 7 covering disorganised thought, 4 covering uncontrolled hostility/excitement and 4 covering anxiety/depression. Each item is scored on a seven point item-specific Likert scale ranging from 1 to 7.

The safety information is available in the safety section of this document.

Figure 1. Change from Baseline to Endpoint in Total PANSS (Positive and Negative Syndrome Scale) Score in Schizophrenic Patients During a 12-Week, Placebo-Controlled Trial (RIS-USA-121) (Last Observation Carried Forward)

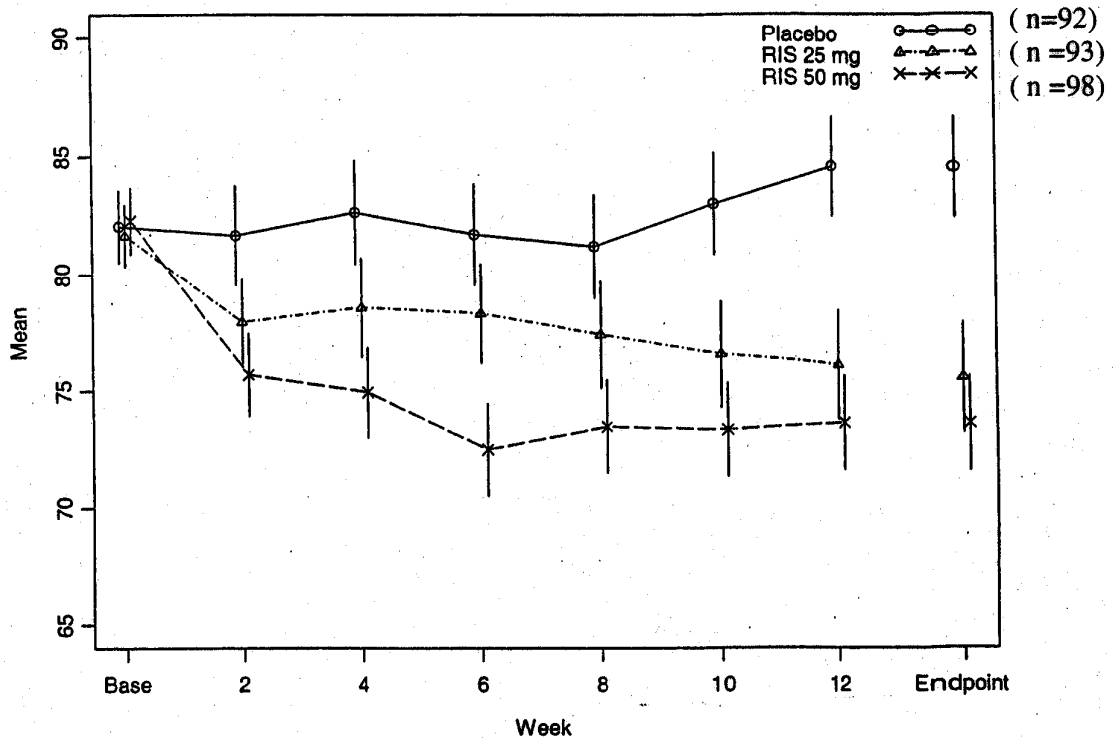
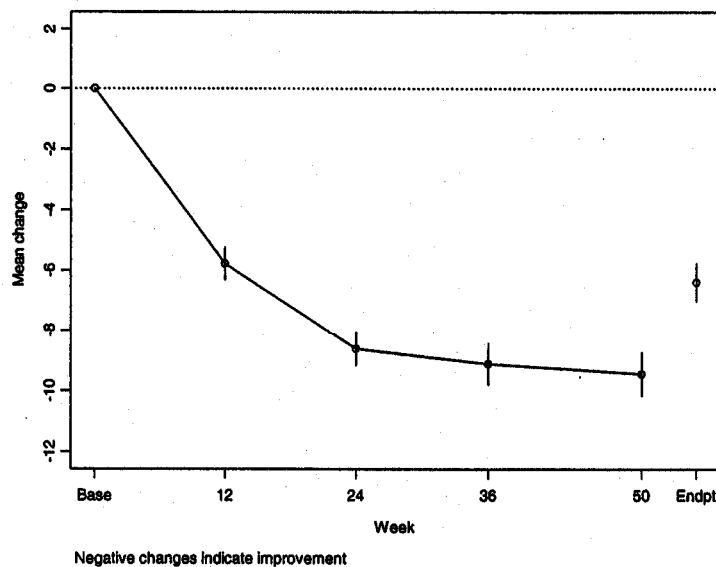


Figure 2.

Mean Change in Total PANSS (Positive and Negative Syndrome Scale) Score in Patients with Schizophrenia and Schizoaffective Disorder in a 50-Week, Open-Label Trial (RIS-INT-57) (Observed Case, All Treatments Combined) (n = 725)



Bipolar disorder:

In a 24-month placebo-controlled trial (RIS-BIM-3003) in patients with Bipolar Disorder Type I who achieved remission on RISPERDAL CONSTA during a stabilisation phase prior to randomisation, RISPERDAL CONSTA as monotherapy demonstrated superiority over placebo in preventing recurrence of a mood episode. The majority of relapses were due to manic rather than depressive symptoms. There are insufficient data to know whether RISPERDAL CONSTA is effective in delaying the time to occurrence of depression in patients with Bipolar Disorder Type I.

In another trial (RIS-BIP-302), a 52-week placebo-controlled trial included patients with Bipolar Disorder Type I or II who had at least 4 episodes of mood disorder requiring psychiatric/clinical intervention in the 12 months prior to study entry (at least 2 of which were in the 6 months prior to study entry) and who had achieved remission on RISPERDAL CONSTA as adjunctive therapy to their usual treatments for bipolar disorder (including mood stabilisers, antidepressants, and/or anxiolytics) prior to randomisation. RISPERDAL CONSTA as adjunctive therapy to treatment-as-usual demonstrated superiority over placebo plus treatment-as-usual in preventing recurrence of a mood episode.

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