

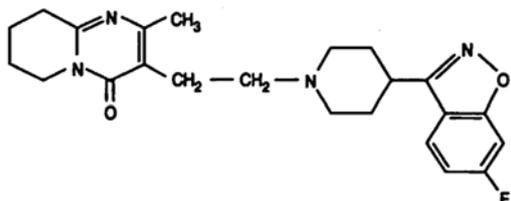
# RISPERDAL CONSTA<sup>®</sup>

## PRODUCT INFORMATION

### NAME OF THE MEDICINE

Risperidone is a white to off white crystalline powder, practically insoluble in water, freely soluble in methylene chloride, sparingly soluble in ethanol (96%) and dissolves in dilute acid solutions.

Risperidone is chemically identified as 3-[2-[4-(6-fluoro-1,2-benzisoxazol-3-yl)-1-piperidiny] ethyl]-6,7,8,9-tetrahydro-2-methyl-4H-pyrido[1,2-a]pyrimidin-4-one, and has the following structural formula:



CAS-106266-06-2

C<sub>23</sub>H<sub>27</sub>FN<sub>4</sub>O<sub>2</sub>

MW=410.49

### 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, anhydrous citric acid, dibasic sodium phosphate dihydrate, polysorbate 20, sodium chloride, sodium hydroxide and water for injections.

### PHARMACOLOGY

#### Pharmacodynamics

Risperidone is a selective monoaminergic antagonist with a high affinity for serotonergic 5-HT<sub>2</sub> and dopaminergic D<sub>2</sub> receptors. Risperidone binds also to alpha<sub>1</sub>-adrenergic receptors, and with lower affinity, to H<sub>1</sub>-histaminergic and alpha<sub>2</sub>-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 D<sub>2</sub> 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 D<sub>2</sub> 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 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 risperidone.

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

In controlled clinical trials, risperidone 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). Risperidone 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 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 alphas<sub>2</sub>-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 metabolisers, respectively, and 3.2 and 3.3 L/h in poor metabolisers of CYP2D6, respectively.

After repeated i.m. injections with 25 or 50mg 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 P4502D6, 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.

An oral, single-dose study showed higher active plasma concentrations and a slower elimination of 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 unbound risperidone was somewhat increased by about 35% due to diminished concentration of both  $\alpha_1$ -acid glycoprotein and albumin.

#### *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.

## **CLINICAL TRIALS**

### ***Schizophrenia***

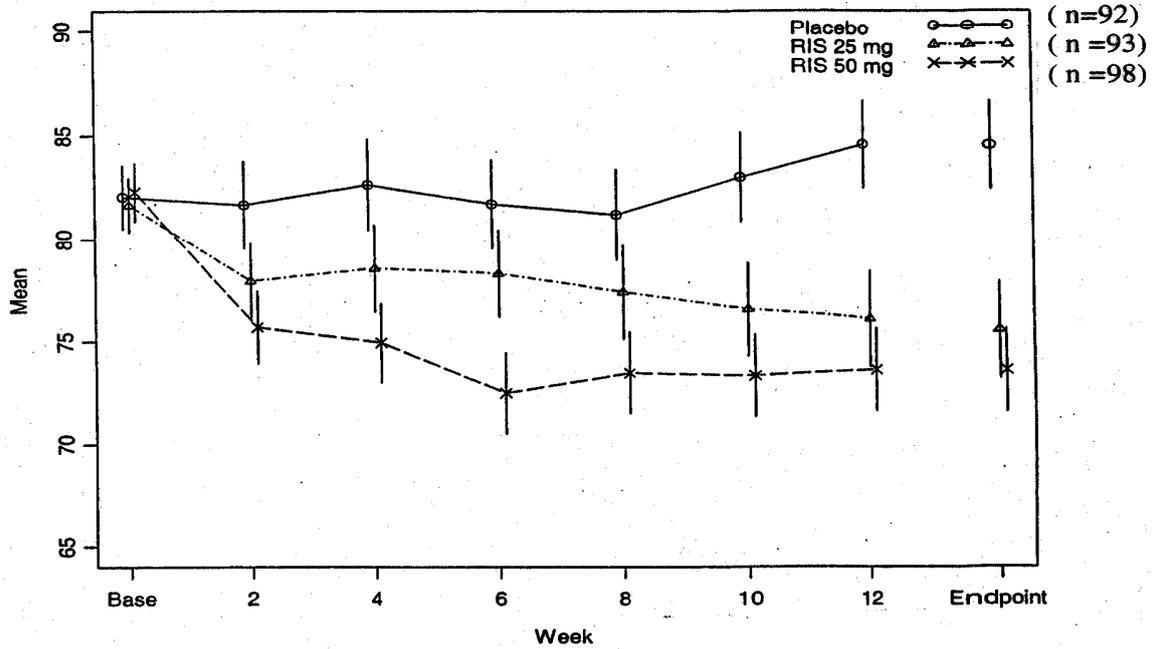
The effectiveness of RISPERDAL CONSTA (25 mg and 50 mg) in the management of the manifestations of psychotic disorders (schizophrenia/schizoaffective) was established in one 12-week, placebo-controlled trial in adult psychotic inpatients and outpatients who met the DSM-IV criteria for schizophrenia (RIS-USA-121-see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

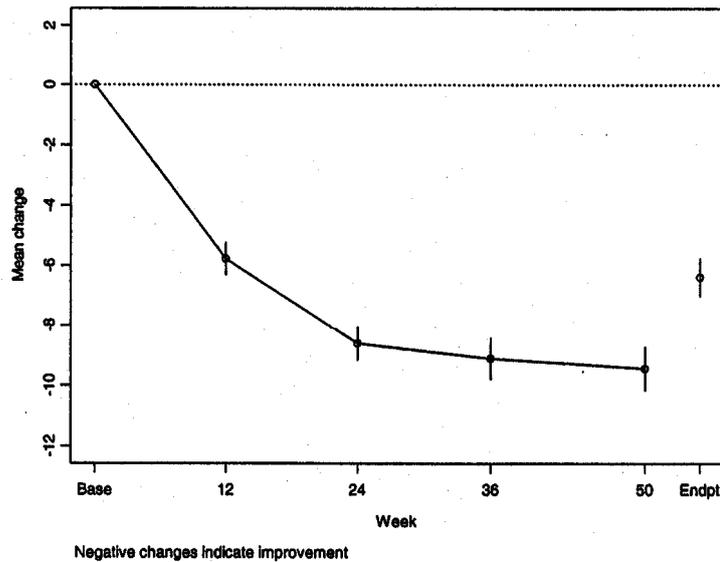
The safety information is available in the safety section of this document.

**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.**

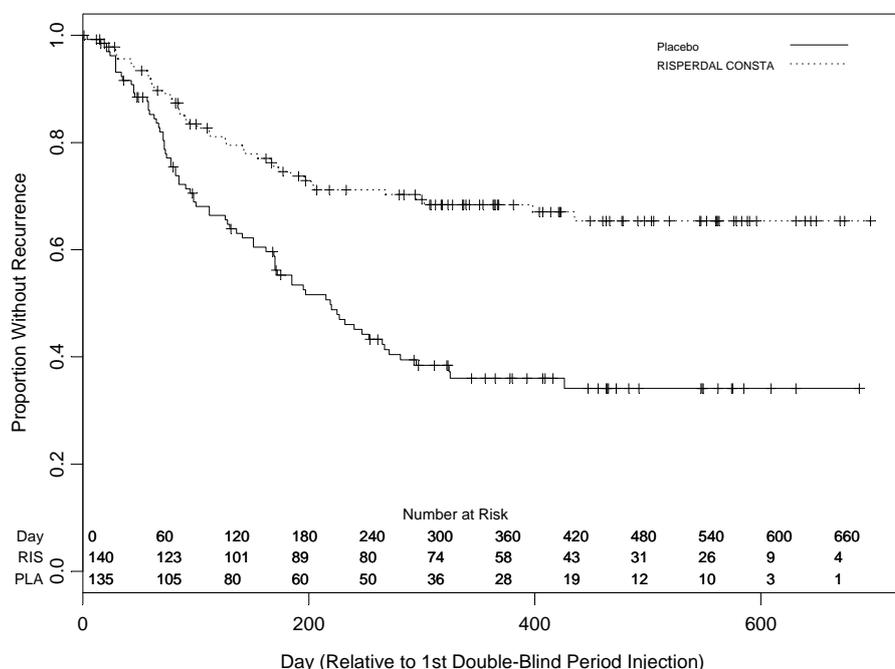
**Mean Change in Total PANSS (Positive and Negative Syndrome Scale) Score in Patients with Schizophrenia and Schizoaffective Disorder in a 50-Week, Open-Label Trial (RIS-INT-57) (Observed Case, All Treatments Combined) (n = 725)**



## Bipolar I disorder

In a pivotal 24-month placebo-controlled trial (RIS-BIM-3003) male and female patients aged 18 to 65 with Bipolar Disorder Type I who achieved remission on RISPERDAL CONSTA during an open-label 26-week initial stabilisation phase were randomised to receive either RISPERDAL CONSTA as monotherapy or placebo during a 2-year, double-blind treatment period. A total of 559 patients were enrolled in the study, of which a total of 303 subjects (54%) were randomly assigned to double-blind treatment with RISPERDAL CONSTA (n=154) or placebo (n=149). Patients receiving RISPERDAL CONSTA demonstrated superiority over placebo in preventing recurrence of a mood episode. There was a statistically significant difference ( $p < 0.001$ ; log-rank test) between treatment groups in the time to recurrence during double-blind treatment in favour of RISPERDAL CONSTA, with 30% of patients experiencing a recurrence in the RISPERDAL CONSTA group versus 56% in the placebo group during the 2-year double-blind follow-up period. The relative reduction in risk of recurrence, as reflected by the treatment:placebo hazard ratio [95% CI], was 0.40 [0.27, 0.59]. The majority of recurrences were due to manic rather than depressive symptoms. RISPERDAL CONSTA was not effective in delaying the time to occurrence of a depressed mood episode.

**Figure 3. Kaplan-Meier Curves of Time to Recurrence in Double-Blind Period (Study RIS-BIM-3003)**



In a supporting 52-week placebo-controlled study (RIS-BIP-302), male and female patients, aged 18 to 70, with primarily Bipolar disorder Type I (87%, with 13% Bipolar Disorder Type 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) were enrolled. Patients entered a 16-week open-label stabilization period prior to randomisation and received RISPERDAL CONSTA as adjunctive therapy to their usual treatments for bipolar disorder. The usual treatments for bipolar disorder included one or more of the following: valproic acid derivatives, lithium carbonate, lamotrigine, benzodiazepines, and/or antidepressants (serotonin reuptake inhibitors, serotonin-norepinephrine reuptake inhibitors, tricyclic antidepressants, mirtazapine, bupropion, trazodone). Patient taking carbamazepine, oxcarbazepine, paroxetine or fluoxetine were excluded from the study. A total of 275 patients were enrolled, of which 139 (51%) patients were randomized to receive either RISPERDAL CONSTA plus treatment-as-usual (n=72) or placebo plus treatment-as-usual (n=67) in the 52-week double-blind follow-up period. Treatment-as-usual was valproate or lithium (or both) for 89% of patients in the RISPERDAL CONSTA group and 96% of patients in the placebo group. There was a statistically significant difference ( $p < 0.004$ ; log-rank test) between treatment groups in the time to recurrence during double-blind treatment in favour of RISPERDAL

CONSTA, with 22% of patients in the RISPERDAL CONSTA group versus 48% in the placebo group experiencing a recurrence. RISPERDAL CONSTA as adjunctive therapy to treatment-as-usual demonstrated superiority over placebo plus treatment-as-usual in preventing recurrence of both elevated and depressed mood episodes.

## INDICATIONS

RISPERDAL CONSTA is indicated for:

- Treatment of schizophrenia and related psychoses.
- Adjunctive maintenance treatment with lithium or sodium valproate in treatment refractory patients with bipolar I disorder who have at least 4 relapses in a 12 month period.
- Monotherapy for maintenance treatment to prevent the recurrence of manic or mixed episodes of bipolar I disorder in patients with a manic or mixed episode, following stabilisation with oral risperidone.

## CONTRAINDICATIONS

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

## PRECAUTIONS

### *Elderly Patients with Dementia*

Overall Mortality:

Elderly patients with dementia treated with atypical antipsychotic medicines have an increased mortality compared to placebo in a meta-analysis of 17 controlled trials of atypical antipsychotic medicines, including risperidone. In placebo-controlled trials with oral risperidone in this population, the incidence of mortality was 4.0% (40/1009) for risperidone treated patients and 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 risperidone 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 risperidone

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).

### *Orthostatic Hypotension*

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.

### *Akathisia*

The presentation of akathisia may be variable and comprises subjective complaints of restlessness and an overwhelming urge to move and either distress or motor phenomena such as pacing, swinging of the legs while seated, rocking from foot to foot, or both. Particular attention should be paid to the monitoring for such symptoms and signs as, left untreated, akathisia is associated with poor compliance and an increased risk of relapse.

### *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<sup>9</sup>/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 preventative measures undertaken.

### *Tardive dyskinesia (TD)*

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 risperidone. 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 medicines 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 medicine 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, medicine discontinuation should be considered. However, some patients may require treatment despite the presence of this syndrome.

### *Neuroleptic Malignant Syndrome (NMS)*

This is a potentially fatal symptom complex that has been reported in association with antipsychotic medicines, 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 medicines and other medicines 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 medicine 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.

### *Parkinson's Disease and Dementia with Lewy Bodies*

Physicians should weigh the risks versus benefits when prescribing antipsychotics, including risperidone, 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 **DOSE AND ADMINISTRATION** and **ADVERSE EFFECTS**).

If hypersensitivity reactions occur, discontinue use of RISPERDAL CONSTA; initiate general supportive measures as clinically appropriate and monitor the patient until signs and symptoms resolve (**CONTRAINDICATIONS** and **ADVERSE EFFECTS**).

### *Seizures*

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

### *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 medicine.

### *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 post-marketing surveillance.

### *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 overdose with certain drugs or of conditions such as intestinal obstruction, Reye's syndrome, and brain tumour.

### *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.

### *Suicide*

The possibility of a suicide attempt is inherent in schizophrenia, and close supervision of high-risk patients should accompany therapy.

### *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 RISPREDAL CONSTA (see **ADVERSE EFFECTS**).

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 alpha 1 blocking therapy prior to cataract surgery has not been established and must be weighed against the risk of stopping the antipsychotic therapy.

### *Effects on mental alertness*

RISPREDAL CONSTA may interfere with activities requiring mental alertness. Therefore, patients should be advised not to drive or operate machinery until their individual susceptibility is known.

### *Administration*

Care must be taken to avoid inadvertent injection of RISPREDAL 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/m<sup>2</sup> 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 medicines 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-hydroxy risperidone about twice that anticipated in humans at the maximal recommended clinical dose of RISPREDAL 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 phaeochromocytomas was associated with hypercalcemia but there was no evidence for a causal relationship. However, phaeochromocytomas 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, risperidone 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 medicines and mammary tumorigenesis. However, since tissue culture experiments indicate that approximately one-third of human breast cancers are prolactin dependent *in vitro*, risperidone 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/m<sup>2</sup> 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/m<sup>2</sup> 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 the elderly**

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

### **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 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.

*\*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.*

In an embryo fetal 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 feeding 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 risperidone 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/m<sup>2</sup> 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/m<sup>2</sup> basis.

## **Use in children**

RISPERDAL CONSTA has not been studied in adolescents and children younger than 18 years. There are also insufficient nonclinical data to adequately define the safety of risperidone in young children. A 39-day oral toxicity study with juvenile rats noted increased pup mortality, a delay in physical development and, in a small proportion of animals, impairment of auditory startle, at exposures (plasma AUC) less than that at the maximum recommended oral paediatric dose (6 mg/day). The clinical relevance of these findings for children of 5 years and above is uncertain, given the relative immaturity of the rat pups upon commencement of treatment. A 40-week oral toxicity study with juvenile dogs noted delayed sexual maturation, probably secondary to hormonal changes. Long bone growth was slightly reduced at exposures (plasma AUC) of 3 fold and greater those at the maximum dose in children and adolescents (6 mg/day); exposure at the no-effect dose was similar to human exposure.

## **INTERACTIONS WITH OTHER MEDICINES**

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 medicines or alcohol.

### Levodopa and Dopamine Agonists

Risperidone may antagonise the effect of levodopa and other dopamine-agonists.

### 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 metabolised through CYP2D6, and to a lesser extent through CYP3A4. Both risperidone and its active metabolite 9-hydroxyrisperidone 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 or fluoxetine). (See also section **SSRIs and Tricyclic antidepressants**).

### 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.

Carbamazepine has been shown to decrease the plasma levels the active antipsychotic fraction.

### Highly Protein-bound Drugs

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 risperidone or for any of the medicines tested.

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 CYP3A4 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 risperidone active antipsychotic fraction  $C_{max}$  by 41% and  $AUC_{last}$  by 45%, following a single dose of risperidone 1mg.

#### 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 levels of the active antipsychotic fraction of risperidone.
- Topiramate modestly reduced the bioavailability of risperidone, but not that of the active antipsychotic fraction. Therefore, this interaction is unlikely to be of clinical significance.
- Risperidone does not show a clinically relevant effect on the pharmacokinetics of valproate.

#### Antifungals:

- Itraconazole, a strong CYP3A4 inhibitor and a P-gp inhibitor, at a dosage of 200 mg/day increased the plasma concentrations of the active antipsychotic fraction by about 70%, at risperidone doses of 2 to 8 mg/day.
- Ketoconazole, a strong CYP3A4 inhibitor and a P-gp inhibitor, at a dosage of 200 mg/day increased the risperidone AUC by 67%, and decreased the 9-hydroxyrisperidone AUC by 49%, following a single dose of risperidone 2mg. However, maximal CYP3A4 inhibition may not have been achieved in this study.

#### 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; Protease inhibitors are moderate to strong CYP3A4 inhibitors; ritonavir is also a weak CYP2D6 inhibitor and tipranavir is also a strong CYP2D6 inhibitor. Protease inhibitors therefore may 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, at a dose of 240mg/day, increased the risperidone  $C_{max}$  and AUC by 1.8-fold, and the active antipsychotic fraction  $C_{max}$  by 1.3-fold and AUC by 1.4-fold, following a single dose of risperidone 1mg.

#### Digitalis Glycosides:

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

#### Diuretics:

- Frusemide: See section **PRECAUTIONS** regarding increased mortality in elderly patients with dementia concomitantly receiving frusemide.

#### Gastrointestinal Drugs:

- H<sub>2</sub>-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.

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.

#### Lithium:

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

#### Sodium Channel Blockers:

- Quinidine may increase the plasma concentrations of risperidone but not those of the active antipsychotic fraction.

#### SSRIs and Tricyclic Antidepressants:

- Fluoxetine, a strong CYP2D6 inhibitor, increases the plasma concentration of risperidone, but less so of the active antipsychotic fraction. Co-administration of fluoxetine produced relative increases of 1.63±0.43, 1.54±0.54 and 1.40±0.24 in C<sub>min</sub>, C<sub>max</sub> and AUC<sub>0-12hr</sub> of risperidone plus 9-hydroxy risperidone. Administration of paroxetine 20mg/day for 4 weeks to patients stabilised on 4-8mg risperidone/day produced a relative increase of 1.51±0.34 in C<sub>min</sub> of risperidone plus 9-hydroxy risperidone.
- Paroxetine, is a strong CYP2D6 inhibitor. At paroxetine doses of 10mg/day the plasma concentration of risperidone increased by 4-fold, without a significant increase in the active antipsychotic fraction (1.3-fold). Dosages of paroxetine of 20mg/day resulted in a 7-fold increase in the concentration of risperidone, and a non-significant increase in the active antipsychotic fraction (1.6-fold). Paroxetine 40mg/day resulted in a significant increase in the concentrations of both risperidone (10-fold) and the active antipsychotic fraction (1.8-fold). Doses of risperidone of 4mg/day were used in this study. When concomitant fluoxetine or paroxetine is initiated or discontinued, the physician should re-evaluate the dose of risperidone.
- Sertraline, a weak inhibitor of CYP2D6, and fluvoxamine, a weak inhibitor of CYP3A4, at dosages up to 100 mg/day are not associated with clinically significant changes in concentrations of the risperidone active antipsychotic fraction. However, the concentrations of the active antipsychotic fraction increased by 42% in 2 patients treated with sertraline 150mg/day, and by 26% in 5 patients treated with fluvoxamine 200mg/day. Doses of risperidone used were 4-6mg/day in the sertraline study and 3-6mg/day in the fluvoxamine study.
- 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.

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  $1.21\pm 0.35$ ,  $1.15\pm 0.36$  and  $1.16\pm 0.34$  and  $C_{max}$  of  $1.17\pm 0.33$ ,  $1.11\pm 0.43$  and  $1.11\pm 0.38$  for risperidone, 9-hydroxy-risperidone and risperidone plus 9-hydroxy risperidone respectively. These modest increases do not necessitate dose modification.

## 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) %
<b>Infections and Infestations</b>			
Upper respiratory tract infection	2	0	1
<b>Nervous System Disorders</b>			
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
<b>Eye Disorders</b>			
Vision blurred	2	3	0
<b>Respiratory, Thoracic And Mediastinal Disorders</b>			
Cough	4	2	3
Sinus congestion	2	0	0
<b>Gastrointestinal Disorders</b>			
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
<b>Skin And Subcutaneous Tissue Disorders</b>			
Acne	2	2	0
Dry skin	2	0	0
<b>Musculoskeletal and Connective Tissue Disorders</b>			
Pain in extremity	6	2	1
<b>General Disorders And Administration Site Conditions</b>			
Fatigue	3	6	0
Asthenia	0	3	0
Edema peripheral	2	3	1
Pain	4	1	0
Pyrexia	2	1	0
<b>Investigations</b>			
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.

<b>Table 2.</b> 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		
<b>System/Organ Class</b> Adverse Reaction	<b>RISPERDAL CONSTA (N=154) %</b>	<b>Placebo (N=149) %</b>
<b>Infections and infestations</b>		
Viral infection	2	1
<b>Metabolism and nutrition disorders</b>		
Hyperglycaemia	1	0
<b>Psychiatric disorders</b>		
Libido decreased	1	0
<b>Nervous system disorders</b>		
Dizziness	3	1
Parkinsonism <sup>a</sup>	1	0
Dyskinesia <sup>a</sup>	1	0
Akathisia <sup>a</sup>	1	0
<b>Cardiac disorders</b>		
Bundle branch block right	1	0
<b>Vascular disorders</b>		
Hypertension	3	1
<b>Gastrointestinal disorders</b>		
Diarrhoea	2	1
<b>Reproductive system and breast disorders</b>		
Erectile dysfunction	1	0
Sexual dysfunction	1	0
<b>Investigations</b>		
Weight increased	5	1
Electrocardiogram QT prolonged	1	1

<sup>a</sup> 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

<b>System Organ Class Adverse Reaction</b>	<b>RISPERDALCONSTA + Treatment as Usual<sup>a</sup> (N=72) %</b>	<b>Placebo + Treatment as Usual<sup>a</sup> (N=67) %</b>
<b>Infections and infestations</b>		
Upper respiratory tract infection	6	3
Urinary tract infection	3	1
<b>Metabolism and nutrition disorders</b>		
Decreased appetite	6	1
Increased appetite	4	0
Anorexia	1	0
<b>Psychiatric disorders</b>		
Libido decreased	1	0
<b>Nervous system disorders</b>		
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
<b>Eye disorders</b>		
Visual acuity reduced	3	0
<b>Vascular disorders</b>		
Orthostatic hypotension	3	0
<b>Respiratory, thoracic and mediastinal disorders</b>		
Cough	4	1
<b>Musculoskeletal and connective tissue disorders</b>		
Muscle rigidity	11	6
Arthralgia	4	3
Muscle twitching	1	0
<b>Reproductive system and breast disorders</b>		
Amenorrhoea	4	1
Menstrual Disorder	1	0
<b>General disorders and administration site conditions</b>		
Gait abnormal	4	0
<b>Investigations</b>		
Weight increased	7	1

<sup>a</sup> 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

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. This subsection includes additional ADRs reported with risperidone and/or paliperidone in clinical trials.

<p><b>Table 4a.</b> ADRs Reported with Risperidone and/or Paliperidone by <math>\geq 2\%</math> of RISPERDAL CONSTA-treated Subjects with Schizophrenia (The Terms within each System Organ Class are Sorted Alphabetically)</p>
<p><b>System/Organ Class</b> Adverse Reaction</p> <p><b>Psychiatric disorders</b> Agitation, Anxiety, Depression, Insomnia*</p> <p><b>Nervous System Disorders</b> Akathisia*, Parkinsonism*</p> <p><b>Cardiac disorders</b> Tachycardia</p> <p><b>Respiratory, thoracic and mediastinal disorders</b> Nasal congestion</p> <p><b>Gastrointestinal disorders</b> Abdominal discomfort, Diarrhoea, Vomiting</p> <p><b>Skin and subcutaneous tissue disorders</b> Rash</p> <p><b>Musculoskeletal and Connective Tissue Disorders</b> Back pain, Muscle spasms, Musculoskeletal pain</p> <p><b>General disorders and administration site conditions</b> Oedema*</p>

\* **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.

ADRs reported with risperidone and/or paliperidone by  $< 2\%$  of RISPERDAL CONSTA-treated subjects with schizophrenia are shown in Table 4b.

<p><b>Table 4b.</b> ADRs Reported with Risperidone and/or Paliperidone by <math>&lt; 2\%</math> of RISPERDAL CONSTA-treated Subjects with Schizophrenia (The Terms within each System Organ Class are Sorted Alphabetically)</p>
<p><b>System/Organ Class</b> Adverse Reaction</p> <p><b>Immune system disorders</b> Hypersensitivity</p> <p><b>Metabolism and nutrition disorders</b> Decreased appetite, increased appetite</p> <p><b>Psychiatric disorders</b> Confusional state, libido decreased, nightmare</p> <p><b>Nervous system disorders</b> Dizziness postural, Dysarthria, Dyskinesia*, Paraesthesia</p> <p><b>Eye disorders</b> Photophobia</p> <p><b>Ear and labyrinth disorders</b> Ear pain</p> <p><b>Cardiac disorders</b> Bradycardia, Conduction disorder, Electrocardiogram abnormal, Electrocardiogram QT prolonged, Palpitations</p> <p><b>Respiratory, thoracic and mediastinal disorders</b> Dyspnoea, Pharyngolaryngeal pain, Wheezing</p> <p><b>Hepatobiliary disorders</b> Gamma-glutamyltransferase increased, Hepatic enzyme increased</p>

<p><b>Skin and subcutaneous tissue disorders</b> Pruritus, Seborrhoeic dermatitis, Skin disorder</p> <p><b>Musculoskeletal and connective tissue disorders</b> Joint stiffness, Muscular weakness</p> <p><b>Renal and urinary disorders</b> Urinary incontinence</p> <p><b>Reproductive system and breast disorders</b> Breast discomfort, Ejaculation disorder, Erectile dysfunction, Galactorrhoea</p> <p><b>General disorders and administration site conditions</b> Chest discomfort, Feeling abnormal, Injection site reaction</p>
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\* **Dyskinesia includes:** athetosis, chorea, choreoathetosis, movement disorder, muscle twitching, myoclonus

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 are shown in Table 4c.

<p><b>Table 4c.</b> 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. (The Terms within each System Organ Class are Sorted Alphabetically)</p>
<p><b>System/Organ Class</b> Adverse Reaction</p> <p><b>Infections and Infestations</b> Acarodermatitis, Bronchitis, Cellulitis, Cystitis, Eye infection, Localised infection, Onychomycosis, Pneumonia, Respiratory tract infection, Subcutaneous abscess, Tonsillitis, Urinary tract infection, Viral infection</p> <p><b>Blood and Lymphatic System Disorders</b> Anaemia, Eosinophil count increased, Haematocrit decreased, Neutropenia, White blood cell count decreased</p> <p><b>Immune System Disorders</b> Anaphylactic reaction</p> <p><b>Endocrine Disorders</b> Glucose urine present, Hyperprolactinaemia</p> <p><b>Metabolism and Nutrition Disorders</b> Anorexia, Blood cholesterol increased, Blood triglycerides increased, Hyperglycaemia, Hyperinsulinaemia, Polydipsia</p> <p><b>Psychiatric Disorders</b> Anorgasmia, Blunted affect, Sleep disorder</p> <p><b>Nervous System Disorders</b> 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</p> <p><b>Eye Disorders</b> Conjunctivitis, Dry eye, Eye movement disorder, Eye rolling, Eyelid margin crusting, Glaucoma, Lacrimation increased, Ocular hyperaemia</p> <p><b>Ear and Labyrinth Disorders</b> Tinnitus, Vertigo</p> <p><b>Cardiac Disorders</b> Atrioventricular block, Postural orthostatic tachycardia syndrome, Sinus arrhythmia</p> <p><b>Vascular Disorders</b> Flushing, Hypotension, Orthostatic hypotension</p> <p><b>Respiratory, Thoracic and Mediastinal Disorders</b> Dysphonia, Epistaxis, Hyperventilation, Pneumonia aspiration, Pulmonary congestion, Rales, Respiratory disorder, Respiratory tract congestion</p> <p><b>Gastrointestinal Disorders</b> Cheilitis, Dysphagia, Faecal incontinence, Faecaloma, Flatulence, Gastroenteritis, Intestinal obstruction, Swollen tongue</p> <p><b>Hepatobiliary disorders</b> Transaminases increased</p>

<p><b>Skin and Subcutaneous Disorders</b> Drug eruption, Eczema, Erythema, Hyperkeratosis, Skin discolouration, Skin lesion, Urticaria</p> <p><b>Musculoskeletal, Connective Tissue, and Bone Disorders</b> Blood creatine phosphokinase increased, Joint swelling, Neck pain, Posture abnormal, Rhabdomyolysis</p> <p><b>Renal and Urinary Disorders</b> Dysuria, Pollakiuria</p> <p><b>Reproductive System and Breast Disorders</b> Breast discharge, Breast engorgement, Breast enlargement, Gynaecomastia, Menstrual disorder*, Menstruation delayed, Sexual dysfunction, Vaginal discharge</p> <p><b>General Disorders and Administration Site Conditions</b> Body temperature decreased, Body temperature increased, Chills, Discomfort, Drug withdrawal syndrome, Face oedema, Induration, Malaise, Peripheral coldness, Thirst</p> <p><b>Injury, Poisoning and Procedural Complications</b> Fall, Procedural pain</p>
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\* **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

## Postmarketing Data

Adverse events first identified as ADRs during postmarketing experience with risperidone and/or 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 and/or Paliperidone by Frequency Category Estimated from Spontaneous Reporting Rates with Risperidone

### Blood and Lymphatic Disorders

*Very rare* Agranulocytosis, Thrombocytopenia

### Endocrine Disorders

*Very rare* Inappropriate antidiuretic hormone secretion

### Metabolism and Nutrition Disorders

*Very rare* Diabetes mellitus, Diabetic ketoacidosis, Hypoglycaemia, Water intoxication, Blood cholesterol increased, Blood triglycerides increased

### Nervous System Disorders

*Very rare* Dysgeusia

### Psychiatric Disorders

*Very rare* Mania

### Eye Disorders

*Very rare* Retinal artery occlusion<sup>a</sup>, Floppy iris syndrome (intraoperative)

### Cardiac Disorders

*Very rare* Atrial fibrillation

### Vascular Disorders

*Very rare* Deep vein thrombosis, Pulmonary embolism

### Respiratory, Thoracic, and Mediastinal Disorders

*Very rare* Sleep apnoea syndrome

### Gastrointestinal Disorders

*Very rare* Pancreatitis, ilues

### Hepatobiliary Disorders

*Very rare* Jaundice

**Skin and Subcutaneous Tissue Disorders**

*Very rare* Alopecia, Angioedema

**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, Injection site abscess, Injection site cellulitis, Injection site cyst, Injection site haematoma, Injection site necrosis, Injection site ulcer

<sup>a</sup> 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)

There have also been reports of benign pituitary adenoma that were temporally related, but not necessarily causally related, to risperidone therapy.

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.

## 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.**

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. Prior to each administration, the site of injection should be examined for any signs of inflammation. If such signs exist, an alternative site should be chosen for injection. Do not administer intravenously (see **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 25mg intramuscularly 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**).

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 **Pharmacokinetic**).

### *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 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*

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

## **Instruction for use and handling**

### **Important information**

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

#### **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**

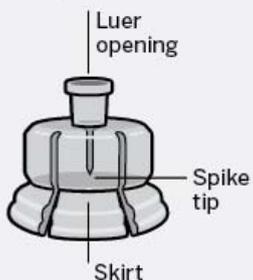
**Do not reuse.** Medical devices require specific material characteristics to perform as intended. These characteristics have been verified for single use only. Any attempt to re-process the device for subsequent re-use may adversely affect the integrity of the device or lead to deterioration in performance.

Contents of the dose pack:

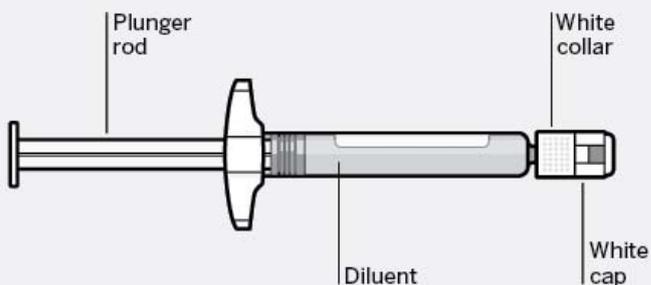
- One vial containing RISPERDAL CONSTA extended release microspheres
- One West-Medimop Vial Adapter<sup>®</sup> for reconstitution (referred as Vial Adapter)
- One prefilled syringe containing the diluent for RISPERDAL CONSTA
- Two Terumo SurGuard<sup>®</sup>-3 Needles for intramuscular injection (a 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)

## Dose pack contents

### West-Medimop Vial Adapter®



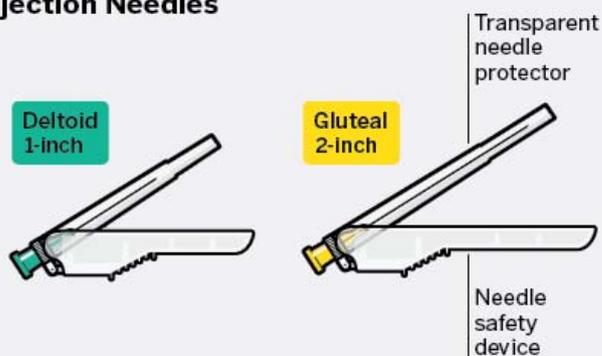
### Prefilled Syringe



### Vial



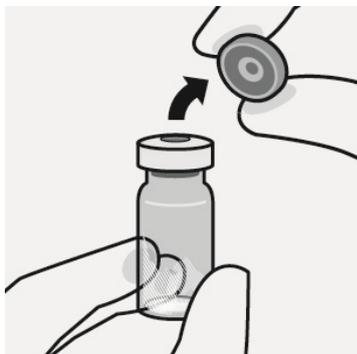
### Terumo SurGuard®-3 Injection Needles



## Step 1 Assemble components

Connect vial adapter to vial

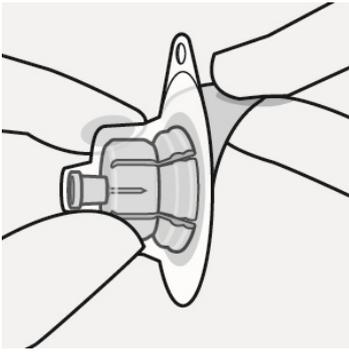
Remove cap from vial



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



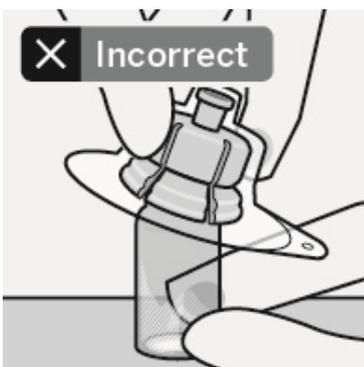
Hold sterile blister as shown.  
Peel back and remove paper backing.  
**Do not** remove vial adapter from blister.  
**Do not** touch spike tip at any time. This will result in contamination.

### Connect vial adapter to vial



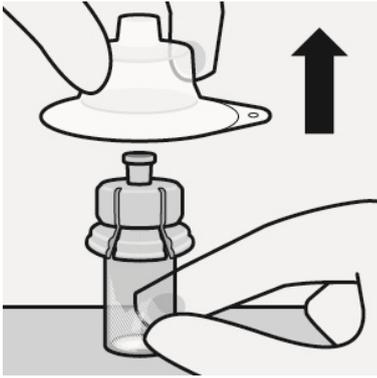
Place vial on a hard surface and hold by the base. Center vial adapter over the grey rubber stopper. Push vial adapter straight down onto vial top until it snaps securely into place.

**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

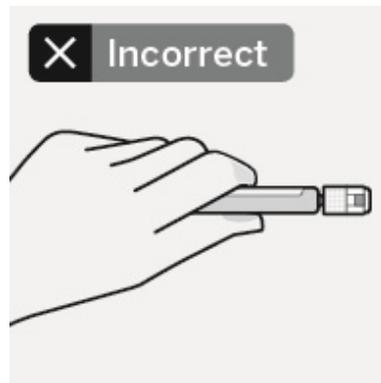
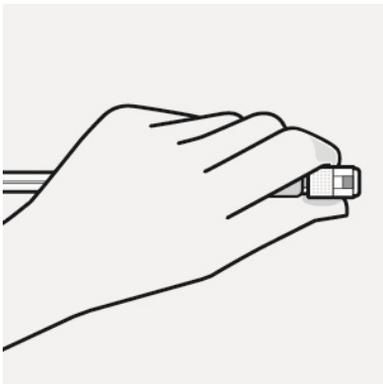


**Remove vial adaptor from sterile blister only when you are ready to remove the white cap from the prefilled syringe.**

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

**Do not** shake.

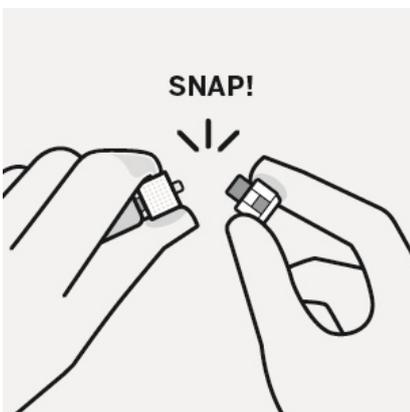
**Do not** touch exposed luer opening on vial adapter. This will result in contamination.



## Use proper grip

Hold by white collar at the tip of the syringe.

**Do not** hold syringe by the glass barrel during assembly.

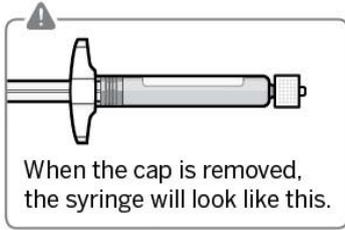


## Remove cap

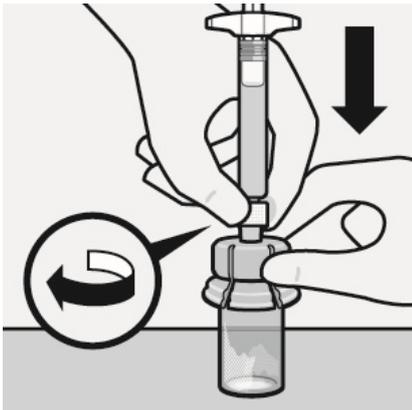
Holding the white collar, snap off the white cap.

**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.



### Connect syringe to vial adapter

Hold vial adapter by skirt to keep stationary.

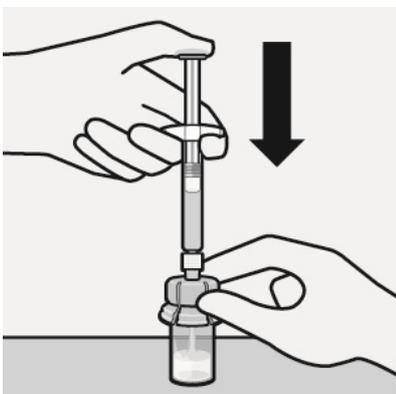
Hold syringe by white collar then insert tip into the luer opening of the vial adapter.

**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



Vial contents will now be under pressure.

**Keep holding the plunger rod down with thumb.**

### Inject diluent

Inject entire amount of diluent from syringe into the vial.

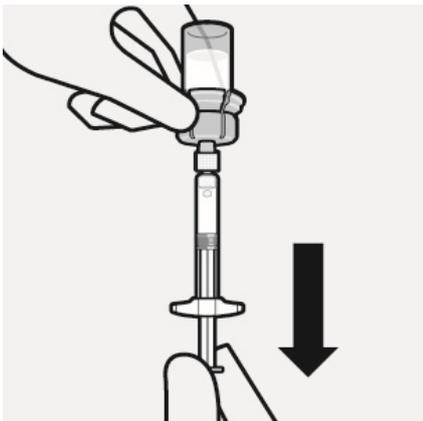


### **Suspend microspheres in diluent**

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

Check the suspension. When properly mixed, the suspension appears uniform, thick and milky in colour. Microspheres will be visible in the liquid.

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



### **Transfer suspension to syringe**

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



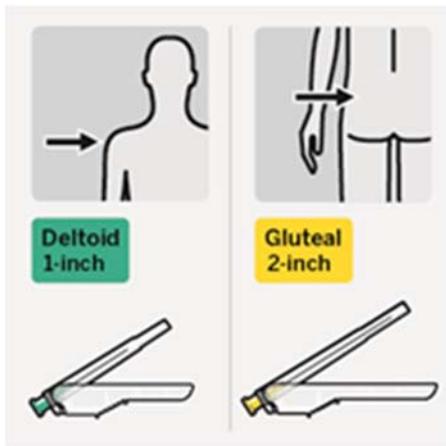
### Remove vial adapter

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

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

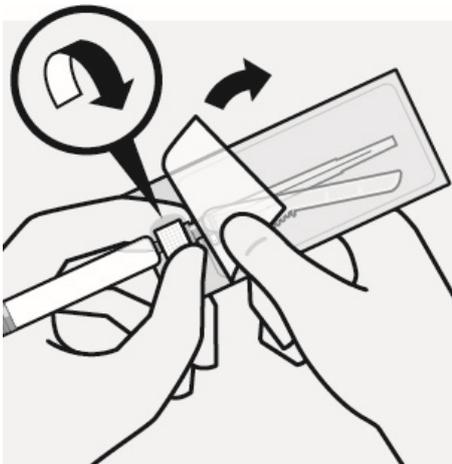
Discard both vial and vial adapter appropriately.

### Step 3 Attach needle



### Select appropriate needle

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

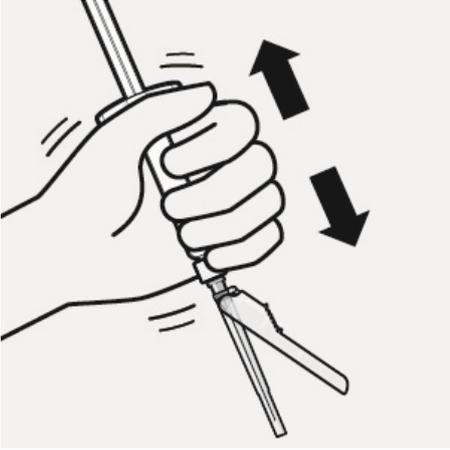


### Attach needle

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.

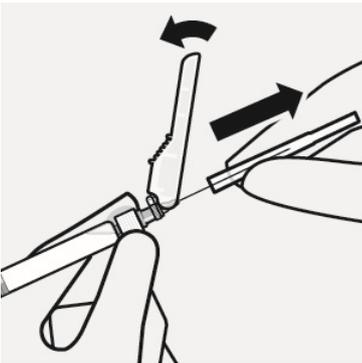


### Resuspend microspheres

Fully remove the blister pouch.

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

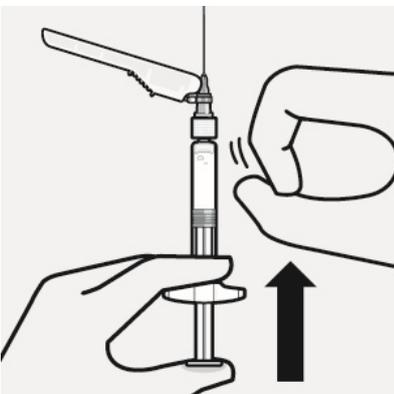
## Step 4 Inject dose



### Remove transparent needle protector

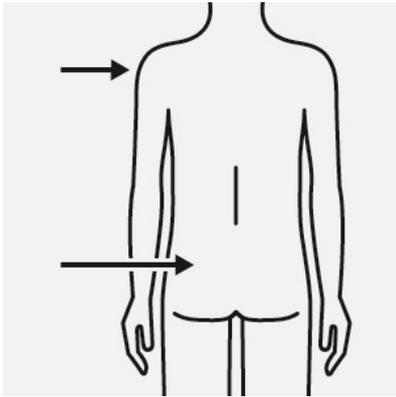
Move the needle safety device back towards the syringe, as shown. Then hold white collar on syringe and carefully pull the transparent needle protector straight off.

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



### 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.

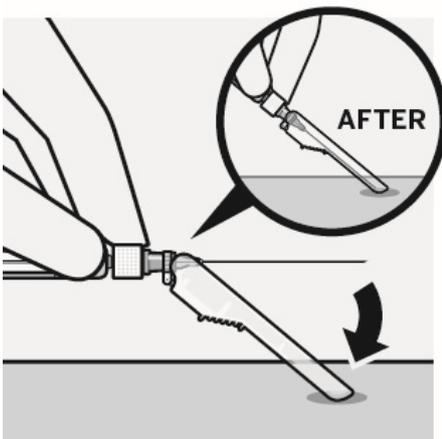


### Inject

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.

**Do not administer intravenously.**



### 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:

**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.



### **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.

## **OVERDOSAGE**

### **Symptoms:**

In general, reported signs and symptoms have been those resulting from an exaggeration of 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.

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

As strategies for the management of overdose are continually evolving, it is advisable to contact the Poisons Information Centre to determine the latest recommendations for the management of an 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 West-Medimop Vial Adapter® for reconstitution (referred as Vial Adapter) and

- 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 medicines only).

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.

Keep out of the reach of children.

## **NAME AND ADDRESS OF THE SPONSOR**

JANSSEN-CILAG Pty Ltd  
1-5 Khartoum Road Macquarie Park NSW 2113 Australia  
NZ Office: Auckland, New Zealand

## **POISON SCHEDULE OF THE MEDICINE**

S4 - Prescription Only Medicine

**DATE OF FIRST INCLUSION ON THE ARTG:** 04 April 2003

**DATE OF MOST RECENT AMENDMENT:** 06 December 2017

Please note change(s) presented as *\*italicised text* in Product Information