RISPERDAL CONSTA®

risperidone

NEW ZEALAND DATA SHEET

1. PRODUCT NAME

RISPERDAL CONSTA 25 mg/2 ml Suspension for injection

RISPERDAL CONSTA 37.5 mg/2 ml Suspension for injection

RISPERDAL CONSTA 50 mg/2 ml Suspension for injection

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

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.

For a full list of excipients, see **section 6.1**.

3. PHARMACEUTICAL FORM

Powder and solvent for prolonged-release suspension for injection.

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 Vial Adapter for reconstitution (referred as Vial Adapter), and
- Two Terumo SurGuard 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).

4. CLINICAL PARTICULARS

4.1 Therapeutic 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 effect, 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.

4.2 Dose and method of 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 **sections 4.4** and **4.8**). 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 **section 5.2**). 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.

Special populations

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 **section 5.2**).

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.

4.3 Contraindications

RISPERDAL CONSTA is contraindicated in patients with a known hypersensitivity to the drug or any of its excipients. See **section 6.1**.

4.4 Special warnings and precautions for use

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).

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.

Leukopenia, Neutropenia, and Agranulocytosis

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

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

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

Venous thromboembolism

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

Tardive Dyskinesia/extrapyramidal symptoms

A syndrome consisting of potentially irreversible, involuntary dyskinetic, rhythmical movements, predominantly of the tongue and/or face, 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.

Extrapyramidal symptoms and psychostimulants

Caution is warranted in patients receiving both psychostimulants (e.g. methylphenidate) and risperidone concomitantly, as extrapyramidal symptoms could emerge when adjusting one or both medications. Gradual withdrawal of one or both treatments should be considered (see **section 4.5**).

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 of such symptoms and signs as, left untreated, akathisia is associated with poor compliance and an increased risk of relapse.

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 (e.g. 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.

Parkinson's Disease and Dementia with Lewy Bodies

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.

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 **sections 4.2** and **4.8**).

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 (see **sections 4.3** and **4.8**).

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.

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

Seizures

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

Intraoperative Floppy Iris Syndrome

Intraoperative Floppy Iris Syndrome (IFIS) has been observed during cataract surgery in patients treated with medicines with alpha1a-adrenergic antagonist effect, including RISPERDAL CONSTA (see **section 4.8**).

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

Suicide

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

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 **section 4.8**).

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/m^2 basis) the maximum human oral dose in adolescents.

Weight gain

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

4.5 Interactions with other medicines and other forms of interactions

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

Pharmacodynamic-related Interactions

Centrally-acting Drugs and Alcohol

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

Levodopa and Dopamine Agonists

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

Psychostimulants

The combined use of psychostimulants (e.g. methylphenidate) with risperidone can lead to the emergence of extrapyramidal symptoms upon change of either or both treatments (see **section 4.4**).

Drugs with Hypotensive Effects

Clinically significant hypotension has been observed post-marketing with concomitant use of risperidone and antihypertensive treatment.

Drugs Known to Prolong the QT interval

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.

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, see below). When concomitant paroxetine or another strong CYP2D6 inhibitor, especially at higher doses, is initiated or discontinued, the physician should re-evaluate the dosing of RISPERDAL CONSTA.

CYP3A4 and/or P-gp Inhibitors

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

CYP3A4 and/or P-gp Inducers

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

Highly Protein-bound Drugs

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

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

Examples

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

Antibacterials:

- Erythromycin, a moderate 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 plasma concentrations of the active antipsychotic fraction.

Anticholinesterases:

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

Antiepileptics:

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

Antifungals:

- Itraconazole, a strong CYP3A4 inhibitor and a P-gp inhibitor, at a dosage of 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 plasma concentrations of risperidone and decreased the plasma concentrations of 9-hydroxyrisperidone.

Antipsychotics:

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

Antivirals:

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

Beta Blockers:

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

Calcium Channel Blockers:

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

Digitalis Glycosides:

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

Diuretics:

- Furosemide: See **section 4.4** regarding increased mortality in elderly patients with dementia concomitantly receiving furosemide and oral RISPERDAL.

Gastrointestinal Drugs:

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

Lithium:

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

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.
- Paroxetine, a strong CYP2D6 inhibitor, increases the plasma concentrations of risperidone, but, at dosages up to 20 mg/day, less so of the active antipsychotic fraction. However, higher doses of paroxetine may elevate concentrations of the risperidone active antipsychotic fraction.
- 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, doses higher than 100 mg/day of sertraline or fluvoxamine may elevate concentrations of the risperidone active antipsychotic fraction.
- Tricyclic antidepressants may increase the plasma concentrations of risperidone but not those of the active antipsychotic fraction. Amitriptyline does not affect the pharmacokinetics of risperidone or the active antipsychotic fraction (see **section 5.2**).

In patients with schizophrenia receiving risperidone 3mg twice daily for 28 days, the addition of amitriptyline initially at 50 mg 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 400 mg twice daily or ranitidine 150mg twice daily. Cimetidine produced a relative increase in $AUC_{0\text{-}Inf}$ 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 $AUC_{0\text{-}Inf}$ and of C_{max} of 1.45±0.61, 1.28±0.37 and 1.36±0.35. Dose modification is not considered to be necessary.

4.6 Fertility, pregnancy & lactation

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^2 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^2 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.

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

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/m^2 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/m^2 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^2 basis.

4.7 Effects on ability to drive and use machines

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

4.8 Undesirable 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 ≥ 2% of RISPERDAL CONSTA-treated patients with schizophrenia in one 12-week double-blind, placebo-controlled trial are shown in **Table 1**.

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

System/Organ Class Adverse Reaction	**RISPERDAL CONSTA 25 mg (n=99) %**	**RISPERDAL CONSTA 50 mg (n=103) %**	**Placebo (n=98) %**
Infections and Infestations			
Upper respiratory tract infection	2	0	1
Nervous System Disorders			
Headache	15	21	12
Parkinsonism*	8	15	9
Dizziness	7	11	6
Akathisia*	4	11	6
Somnolence	4	4	0
Tremor	0	3	0
Sedation	2	2	3
Syncope	2	1	0
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

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

System/Organ Class Adverse Reaction	RISPERDAL CONSTA (N=154) %	Placebo (N=149) %
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 ≥ 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 ≥ 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 rigidty	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

System Organ Class Adverse Reaction	RISPERDAL CONSTA + Treatment as Usual[a] (N=72) %	Placebo + Treatment as Usual [a] (N=67) %
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

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.

ADRs reported with risperidone and/or paliperidone by ≥ 2% of RISPERDAL CONSTA-treated subjects with schizophrenia are shown in **Table 4a**.

Table 4a. ADRs Reported with Risperidone and/or Paliperidone by ≥ 2% of RISPERDAL CONSTA-treated Subjects with Schizophrenia (The Terms within each System Organ Class are Sorted Alphabetically)

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

System/Organ Class Adverse Reaction
* **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**.

Table 4b. ADRs Reported with Risperidone and/or Paliperidone by < 2% of RISPERDAL CONSTA-treated Subjects with Schizophrenia (The Terms within each System Organ Class are Sorted Alphabetically)

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

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**.

Table 4c. 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)

System/Organ Class Adverse Reaction
Infections and Infestations Acarodermatitis, Bronchitis, Cellulitis, Cystitis, Eye infection, Localised infection, Onychomycosis, Pneumonia, Respiratory tract infection, Subcutaneous abscess, Tonsillitis, Urinary tract infection, Viral infection
Blood and Lymphatic System Disorders Anaemia, Eosinophil count increased, Haematocrit decreased, Neutropenia, White blood cell count decreased
Immune System Disorders Anaphylactic reaction
Endocrine Disorders Glucose urine present, Hyperprolactinaemia
Metabolism and Nutrition Disorders Anorexia, Blood cholesterol increased, Blood triglycerides increased, Hyperglycaemia, Hyperinsulinaemia, Polydipsia
Psychiatric Disorders Anorgasmia, Blunted affect, Sleep disorder
Nervous System Disorders Balance disorder, Cerebrovascular accident, Cerebrovascular disorder, Convulsion*, Coordination abnormal, Depressed level of consciousness, Diabetic coma, Dystonia*, Head titubation, Loss of consciousness, Neuroleptic malignant syndrome, Psychomotor hyperactivity, Tardive dyskinesia, Unresponsive to stimuli
Eye Disorders Conjunctivitis, Dry eye, Eye movement disorder, Eye rolling, Eyelid margin crusting, Glaucoma, Lacrimation increased, Ocular hyperaemia
Ear and Labyrinth Disorders Tinnitus, Vertigo
Cardiac Disorders Atrioventricular block, Postural orthostatic tachycardia syndrome, Sinus arrhythmia
Vascular Disorders Flushing, Hypotension, Orthostatic hypotension
Respiratory, Thoracic and Mediastinal Disorders Dysphonia, Epistaxis, Hyperventilation, Pneumonia aspiration, Pulmonary congestion, Rales, Respiratory disorder, Respiratory tract congestion
Gastrointestinal Disorders Cheilitis, Dysphagia, Faecal incontinence, Faecaloma, Flatulence, Gastroenteritis, Intestinal obstruction, Swollen tongue
Hepatobiliary disorders Transaminases increased
Skin and Subcutaneous Disorders Drug eruption, Eczema, Erythema, Hyperkeratosis, Skin discolouration, Skin lesion, Urticaria
Musculoskeletal, Connective Tissue, and Bone Disorders Blood creatine phosphokinase increased, Joint swelling, Neck pain, Posture abnormal, Rhabdomyolysis
Renal and Urinary Disorders Dysuria, Pollakiuria
Reproductive System and Breast Disorders Breast discharge, Breast engorgement, Breast enlargement, Gynaecomastia, Menstrual disorder*, Menstruation delayed, Sexual dysfunction, Vaginal discharge

System/Organ Class Adverse Reaction
General Disorders and Administration Site Conditions Body temperature decreased, Body temperature increased, Chills, Discomfort, Drug withdrawal syndrome, Face oedema, Induration, Malaise, Peripheral coldness, Thirst **Injury, Poisoning and Procedural Complications** Fall, Procedural pain
* **Convulsion includes:** Grand mal convulsion; **Dystonia includes:** blepharospasm, cervical spasm, emprosthotonus, facial spasm, hypertonia, laryngospasm, muscle contractions involuntary, myotonia, oculogyration, opisthotonus, oropharyngeal spasm, pleurothotonus, risus sardonicus, tetany, tongue paralysis, tongue spasm, torticollis, trismus; **Menstrual disorder includes:** Menstruation irregular, Oligomenorrhoea

Post-marketing Data

Adverse events first identified as ADRs during post-marketing experience with risperidone and/or paliperidone 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
Not Known Cannot be estimated from the available data.

Table 5. Adverse Drug Reactions Identified During Post-marketing 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	Catatonia, Mania, Somnambulism; Sleep-related eating disorder
Eye Disorders	
Very rare	Retinal artery occlusion[a], 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, ileus
Hepatobiliary Disorders	
Very rare	Jaundice
Skin and Subcutaneous Tissue Disorders	
Very rare	Alopecia, Angioedema, Stevens-Johnson syndrome/Toxic epidermal necrolysis

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 [b]
[a]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 post-marketing experience in patients who have previously tolerated oral risperidone.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Healthcare professionals are asked to report any suspected adverse reactions

https//nzphvc.otago.ac.nz/reporting/

4.9 Overdose

Symptoms and Signs

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.

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

Treatment

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

There is no specific antidote to 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.

For advice on the management of overdose please contact the National Poisons Centre on 0800 POISON (0800 764766).

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Other antipsychotics, ATC code: N05AX08
Mechanism of action

Risperidone belongs to the benzisoxazole derivatives class of antipsychotic agents.

Risperidone is a selective monoaminergic antagonist having a high affinity for serotoninergic 5-HT_2 and dopaminergic D_2 receptors. Risperidone binds also to $alpha_1$-adrenergic receptors and, with lower affinity, to H_1-histamine and $alpha_2$-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_2 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_2 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 serotoninergic 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.

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)

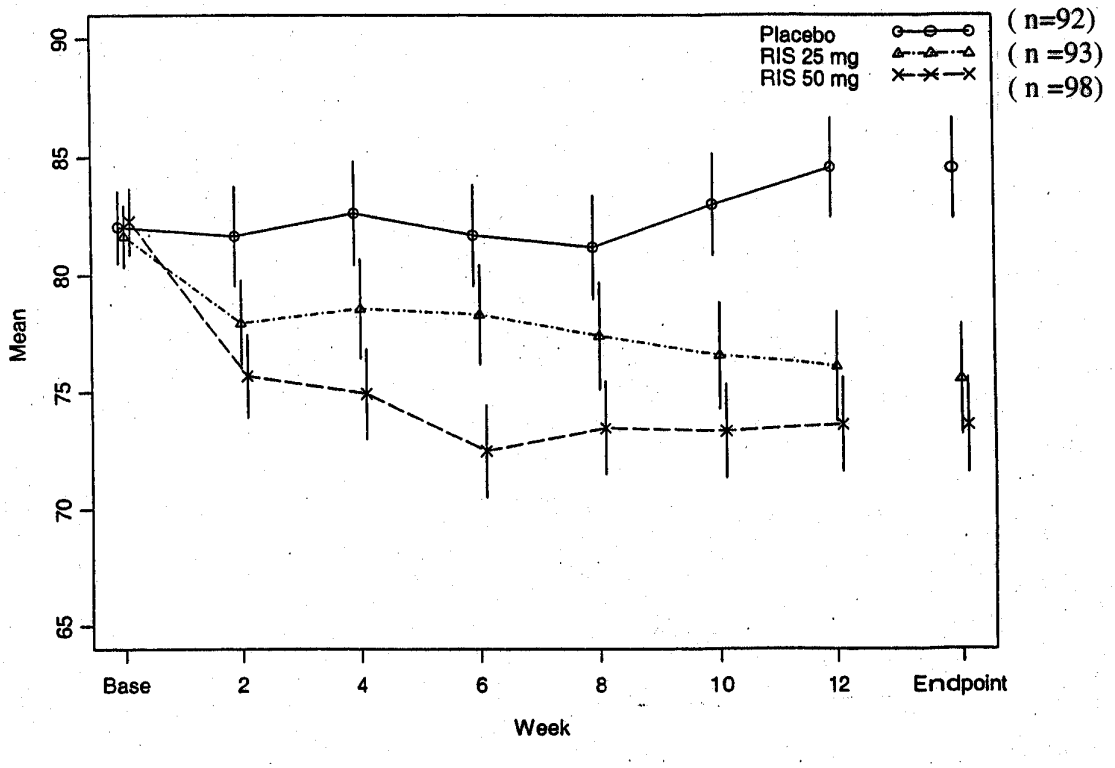
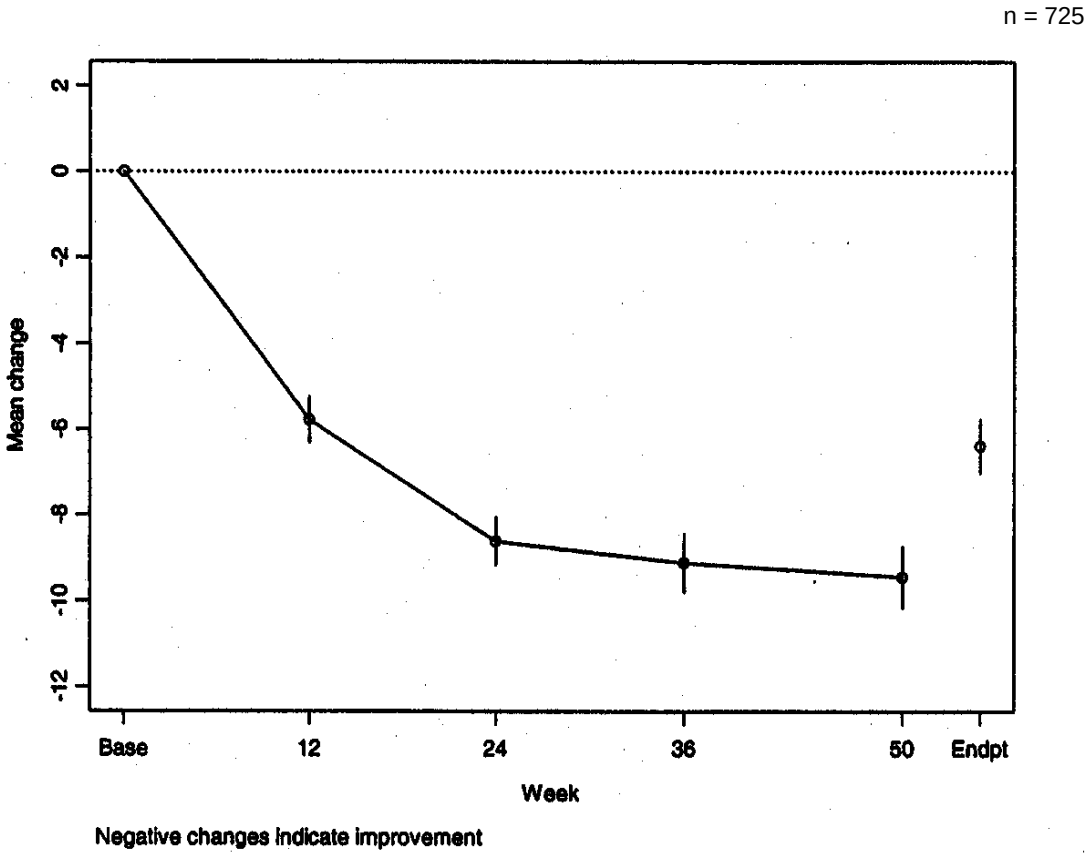


Figure 2. Mean Change in Total PANSS (Positive and Negative Syndrome Scale) Score in Patients with Schizophrenia and Schizoaffective Disorder in a 50-Week, Open-label Trial (RIS-INT-57) (Observed Case, All Treatments Combine)



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. RISPDERDAL CONSTA as adjunctive therapy to treatment-as-usual demonstrated superiority over placebo plus treatment-as-usual in preventing recurrence of a mood episode.

5.2 Pharmacokinetic properties

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 $alpha_1$-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.

5.3 Preclinical safety data

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^2 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 phaeochromocytoma, 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 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, 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 **section 4.8**).

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.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipient

Powder for suspension for injection

Polyglactin

Diluent

Carmellose sodium 40 mPa.s

Anhydrous citric acid

Dibasic sodium phosphate dihydrate

Polysorbate 20

Sodium chloride

Sodium hydroxide

Water for injection.

6.2 Incompatibilities

This medicinal product must not be mixed with other medicinal products except those mentioned in **section 6.6**.

6.3 Shelf Life

36 months stored at 2° to 8°C.

6 hours reconstituted stored at or below 25°C. See **section 6.4**.

6.4 Special precautions for storage

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°C 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.

6.5 Nature and contents of container

Contents of the dose pack:

- One vial containing RISPERDAL CONSTA extended release microspheres
- One Vial Adapter for reconstitution (referred as Vial Adapter)
- One prefilled syringe containing the diluent for RISPERDAL CONSTA
- 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)

6.6 Special precautions for disposal and other 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.

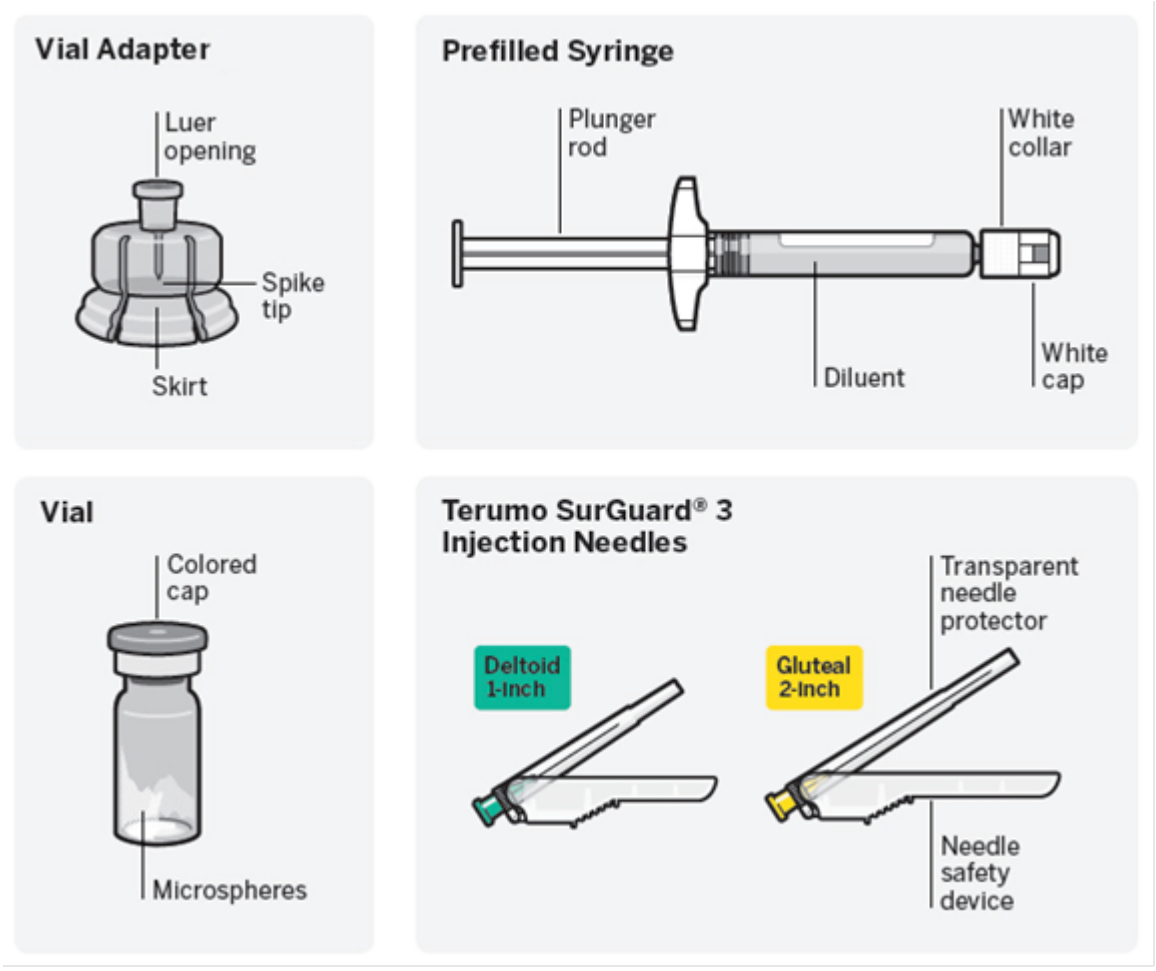
Proper dosing

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.

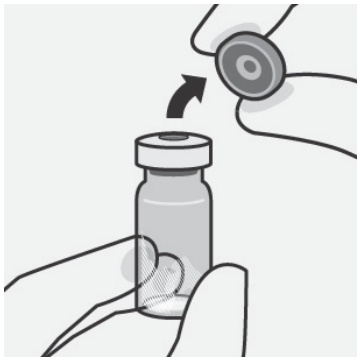
Dose pack contents



Step 1 Assemble components

Connect vial adapter to vial

Remove cap from vial

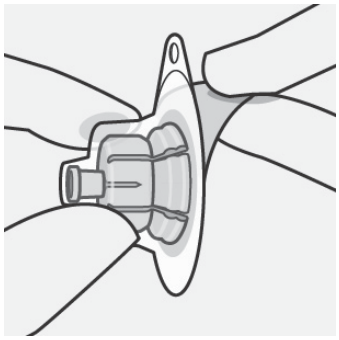


Flip off coloured cap from vial. Wipe top of the grey stopper with an alcohol swab.

Allow to air dry.

Do not remove grey rubber stopper.

Prepare vial adapter



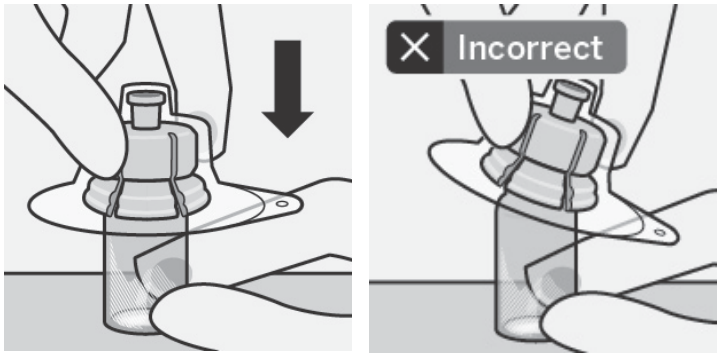
Hold sterile blister as shown.

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

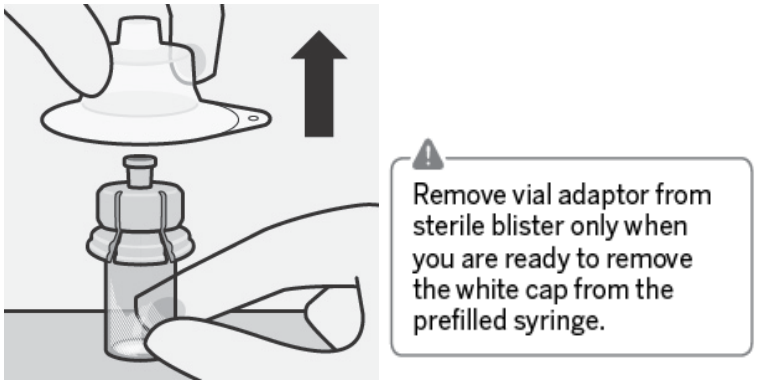


Place vial on a hard surface and hold by the base. Center vial adapter over the grey rubber stopper. Push vial adapter straight down onto vial top until it snaps securely into place.

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

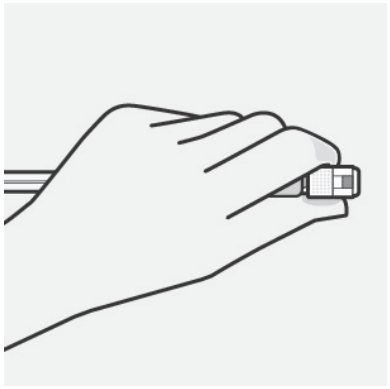


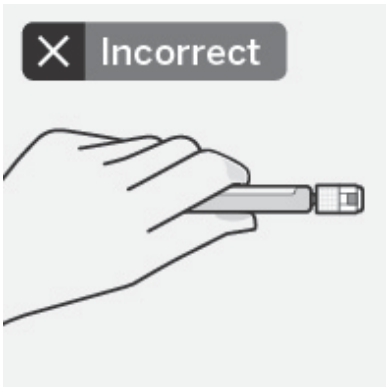
Keep vial vertical to prevent leakage. Hold base of vial and pull up on the sterile blister to remove.

Do not shake.

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

Use proper grip

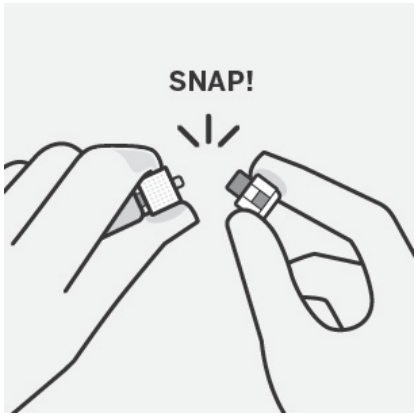




Hold by white collar at the tip of the syringe.

Do not hold syringe by the glass barrel during assembly.

Remove cap



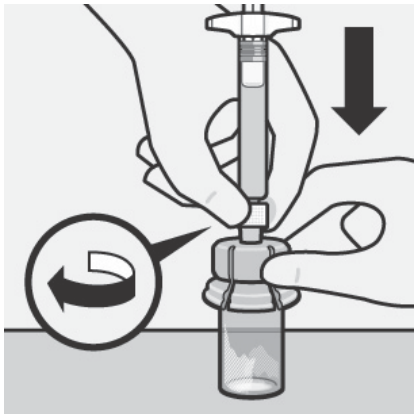
Holding the white collar, snap off the white cap.

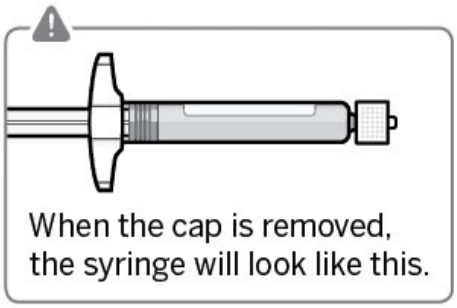
Do not twist or cut off the white cap.

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.

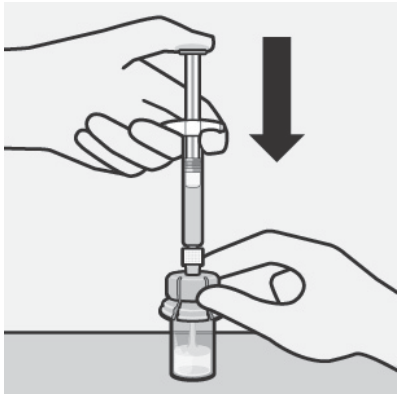
Do not hold the glass syringe barrel. This may cause the white collar to loosen or detach.

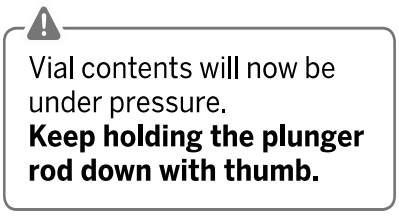
Attach the syringe to the vial adapter with a firm clockwise twisting motion until it feels snug.

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

Step 2 Reconstitute microspheres

Inject diluent





Inject entire amount of diluent from syringe into the vial.

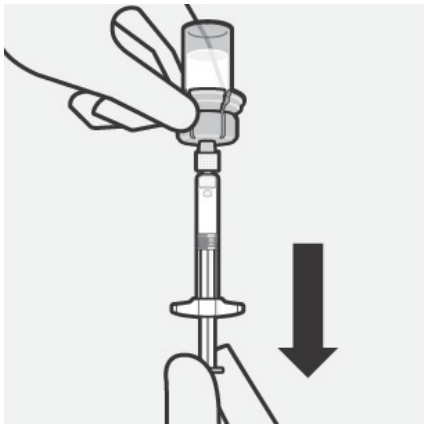
Suspend microspheres in diluent

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.

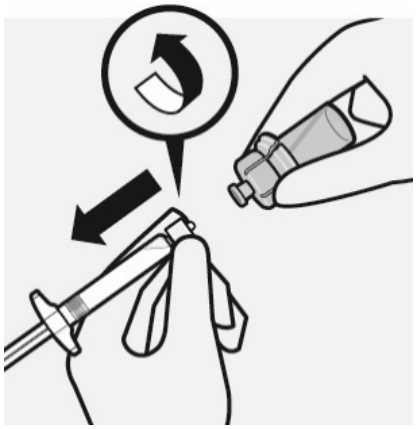
Immediately proceed to the next step so suspension does not settle.

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



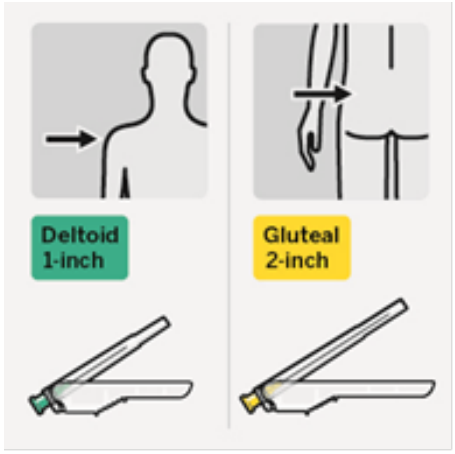
Hold white collar on the syringe and unscrew from vial adapter.

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.

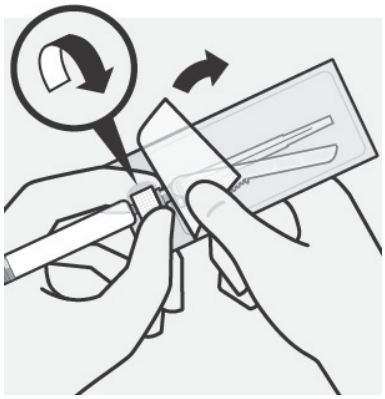
Step 3 Attach needle

Select appropriate needle



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

Attach needle

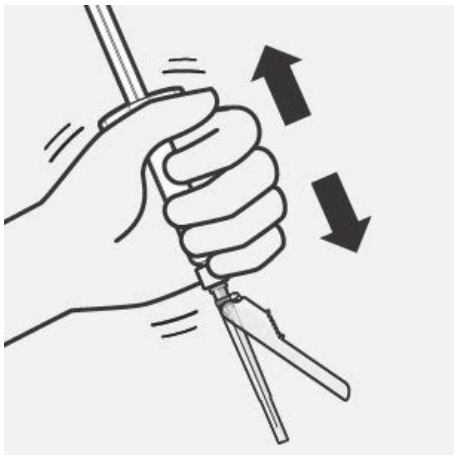


Peel blister pouch open part way and use to grasp the base of the needle, as shown.

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

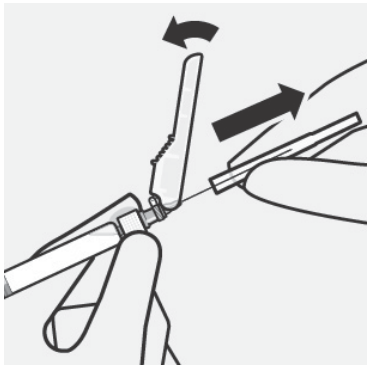


Fully remove the blister pouch.

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

Step 4 Inject dose

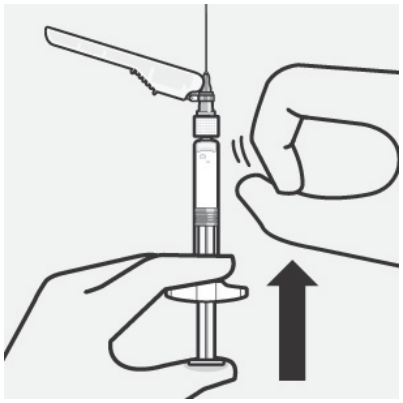
Remove transparent needle protector



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.

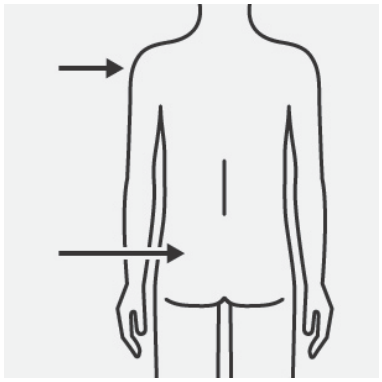
Do not twist transparent needle protector, as the luer connection may loosen.

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

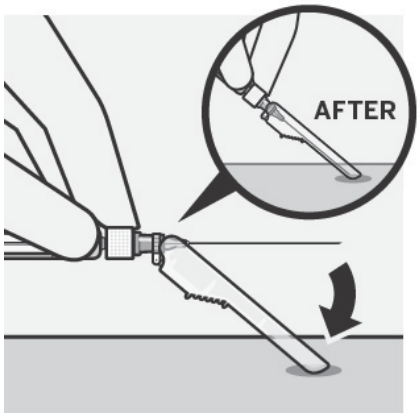


Immediately inject entire contents of syringe intramuscularly (IM) into the gluteal or deltoid muscle of the patient.

Gluteal injection should be made into the upper-outer quadrant of the gluteal area.

Do not administer intravenously.

Secure needle in safety device



Using <u>one hand</u>, 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.

7. MEDICINE SCHEDULE

Prescription Medicine

8. SPONSOR

Janssen-Cilag (New Zealand) Ltd

Auckland, NEW ZEALAND

Telephone: 0800 800 806

Fax: (09) 588 1398

Email: medinfo@janau.jnj.com

9. DATE OF FIRST APPROVAL

25 mg/2 mL – 2 October 2003

37.5 mg/2 mL & 50 mg/2 mL – 15 August 2002

10. DATE OF REVISION OF THE TEXT

29 June 2020

Summary table of changes

Section changes	Summary of new information
4.8	Addition of adverse reaction SJS/TEN in Table 5.