AUSTRALIAN PRODUCT INFORMATION - RISVAN® (RISPERIDONE) MODIFIED RELEASE POWDER FOR INJECTION AND DILUENT

1 NAME OF THE MEDICINE

Risperidone

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

RISVAN 75 mg powder and diluent for prolonged-release suspension for injection

One (1) pre-filled syringe with the modified release powder for injection contains 75 mg of risperidone.

RISVAN 100 mg powder and diluent for prolonged-release suspension for injection

One (1) pre-filled syringe with the modified release powder for injection contains 100 mg risperidone.

For the full list of excipients, see Section 6.1 List of excipients.

3 PHARMACEUTICAL FORM

Modified release, powder for injection

RISVAN is a modified release powder for injection of risperidone and appears as a white to white-yellowish non-aggregated powder contained within a pre-filled syringe.

Diluent for reconstitution

The diluent appears as a clear solution free of visible particles contained within a pre-filled syringe.

4 CLINICAL PARTICULARS

4.1 THERAPEUTIC INDICATIONS

RISVAN is indicated for the treatment of schizophrenia in adults for whom tolerability and effectiveness has been established with oral risperidone.

4.2 DOSE AND METHOD OF ADMINISTRATION

Dosage

Adults

RISVAN should be administered every 28 days by intramuscular (IM) injection.

RISVAN should be initiated according to the patient's clinical context:

Patients with history of previous response to Risperidone who are currently stabilised with oral antipsychotics (mild to moderate psychotic symptoms).

Patients stabilised with oral risperidone can be switched to RISVAN without previous titration. Patients stabilised on other oral antipsychotics (different from risperidone) should be titrated with oral risperidone before initiating treatment with RISVAN. The duration of the titration period should be sufficiently long (at least 6 days) to confirm the tolerability and responsiveness to risperidone.

Patients never treated before with oral Risperidone

Patients who are candidates to receive RISVAN and have NOT been previously treated with risperidone, the tolerability and responsiveness to risperidone must be confirmed with a period of oral risperidone treatment before initiating treatment with RISVAN. The duration of the titration period is recommended to be at least 14 days.

Switching from oral risperidone to RISVAN

The recommended doses of oral risperidone and RISVAN needed to maintain a similar active moiety steady-state exposure are as follows:

Previous oral risperidone dose of 3 mg/day to RISVAN injection 75 mg every 28 days
Previous oral risperidone dose of 4 mg/day or higher to RISVAN injection 100 mg every 28 days

RISVAN must be initiated approximately 24 hours after the last oral risperidone dose. Dose adjustments of RISVAN may be made every 28 days. A maintenance dose of RISVAN 75 mg every 28 days is generally recommended. However, some patients may benefit from RISVAN 100 mg every 28 days, according to the patient's clinical response and tolerability. Neither a loading dose nor any supplemental oral risperidone is recommended when using RISVAN.

Switching from Risperidone bi-weekly long-acting injection to RISVAN

When switching from Risperidone bi-weekly long-acting injection, RISVAN should be initiated in place of the next regularly scheduled injection of risperidone bi-weekly long-acting injection (i.e., two weeks after the last risperidone bi-weekly long-acting injection). RISVAN should then be continued at 28-day intervals. No oral concomitant risperidone is recommended.

When switching patients previously stabilised on risperidone bi-weekly long-acting injection to RISVAN, the recommended dose to maintain a similar active moiety steady-state exposure is as follows:

Risperidone bi-weekly long acting 37.5 mg to RISVAN injection 75 mg every 28 days
Risperidone bi-weekly long acting 50 mg to RISVAN injection 100 mg every 28 days

Switching from RISVAN to oral risperidone
When switching patients from RISVAN injection back to oral risperidone therapy, the prolonged release characteristics of the formulation must be considered. In general, it is recommended to start oral risperidone treatment 28 days after the last RISVAN administration.

Missed doses
Avoiding missed doses
To avoid a missed 28-day dose, patients may be given the injection up to 3 days before the 28-day time point. If a dose is delayed by 1 week, the median trough concentration decreases by approximately 50% during that week. The clinical relevance of this is unknown. If the dose is delayed, the next 28-day interval injection should be scheduled according to the last injection date.

Special populations

Elderly
Efficacy and safety of RISVAN in elderly > 65 years have not been established for the RISVAN prolonged-release suspension for injection. RISVAN should be used with caution in elderly.
Tolerability to ≥ 3 mg daily oral risperidone should be reliably established prior to administration of RISVAN.

In general, recommended dosing of risperidone for elderly patients with normal renal function is the same as for adult patients with normal renal function. However, if it is considered clinically appropriate, starting with 75 mg RISVAN should be considered (see Renal impairment below for dosing recommendations in patients with renal impairment).

Renal impairment
RISVAN has not been systematically studied in patients with renal impairment.
For patients with mild renal impairment (creatinine clearance 60 to 89 mL/min) no dose adjustment is required for RISVAN.
RISVAN is not recommended in patients with moderate to severe renal impairment (creatinine clearance < 60 mL/min).

Hepatic impairment
RISVAN has not been systematically studied in patients with hepatic impairment.
Patients with impaired hepatic function have increases in plasma concentration of the free fraction of risperidone.

RISVAN should be used with caution in these groups of patients. A careful titration with oral risperidone (halving starting doses and slowing titration) before initiating treatment with RISVAN at a dose of 75 mg is recommended if tolerability of an oral dose of at least 3 mg is confirmed.

Paediatric population

The safety and efficacy of RISVAN in children and adolescents less than 18 years have not been established. No data are available.

Use in one patient on one occasion only. Contains no antimicrobial preservative.

RISVAN is only intended for intramuscular use and should not be administered intravenously or subcutaneously (see Sections 4.4 and 6.6) or by any other route. It should be administered by a healthcare professional.

RISVAN should be administered by deep intramuscular deltoid or gluteal injection using the appropriate sterile needle. For deltoid administration, the 1-inch needle should be used alternating injections between the two deltoid muscles. For gluteal administration, the 2-inch needle should be used alternating injections between the two gluteal muscles.

The pre-filled syringe of RISVAN powder should be reconstituted with the pre-filled syringe of accompanying diluent immediately prior to administration by injection.

The reconstitution process should be done accordingly to the Instructions for Use. An incorrect reconstitution could affect the correct dissolution of the powder and in case of administration a higher peak of risperidone could appear in the initial hours (overdose) and a lower AUC of the entire dose treatment (underdose).

INSTRUCTIONS FOR USE

RISVAN 75 mg modified release powder for injection

Important information

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

Use components provided

The components in the kit box are specifically designed for use with RISVAN.
RISVAN must be reconstituted only with the diluent supplied in the kit box.

Do not substitute ANY components of the kit box.

Administer dose immediately after reconstitution. For intramuscular use only after reconstitution.

Proper dosing

The entire content of the reconstituted syringe must be administered to ensure intended dose of RISVAN is delivered.

Single use device

1. CHECK CONTENTS

Working on a clean surface, open the sachets and discard the desiccant pack.
The kit box of RISVAN contains:

- One aluminium foil pouch with a RISVAN pre-filled syringe with a WHITE plunger rod and WHITE finger flange. The syringe is marked with 

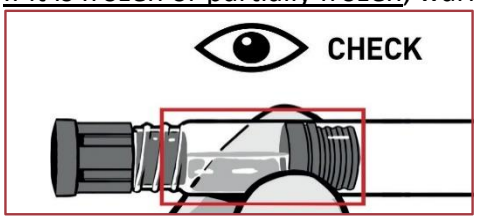
.

- One aluminium foil pouch with DILUENT for RISVAN pre-filled syringe with a TRANSPARENT plunger rod and a RED finger flange. The syringe is marked with S .
- Two administration needles (21G, 1 inch for deltoid [green cap] and a 20G, 2 inch for gluteus [yellow cap]).

Discard the kit if any component is damaged.
In the event of any foreign particulate matter and/or variation of physical aspect is observed, do not administer RISVAN.

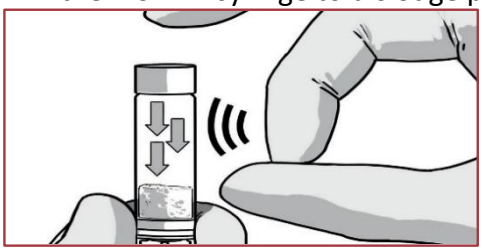
1.1 Inspect diluent syringe

ENSURE that DILUENT syringe content flows normally as a liquid.
If it is frozen or partially frozen, warm it until it is completely thawed.



1.2 Dislodge powder syringe

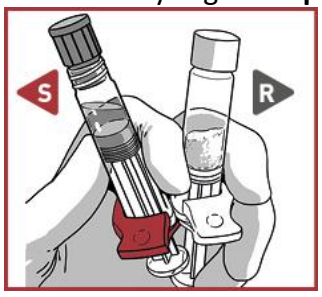
TAP the RISVAN syringe to dislodge potential packed powder near the cap.



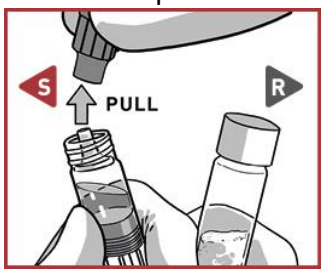
2 CONNECT THE SYRINGES

2.1 Uncap syringes in upright position:

Hold both syringes in **upright position to prevent loss of product**.



PULL the cap off the Diluent syringe.



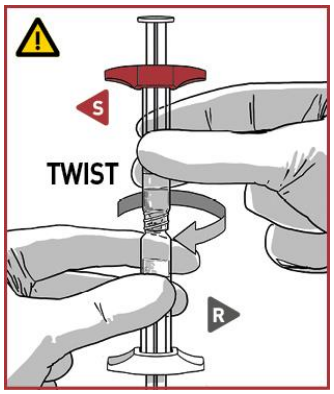
TWIST and PULL the Powder syringe cap off.

2.2 Connect the syringes:

Pick the diluent syringe S that has the coloured finger flange and place it on TOP of the powder syringe R, or slightly lean it when connecting.

TWIST the syringes together until you feel a slight resistance.

Make sure that Powder syringe R is in the upright position to prevent loss of product.



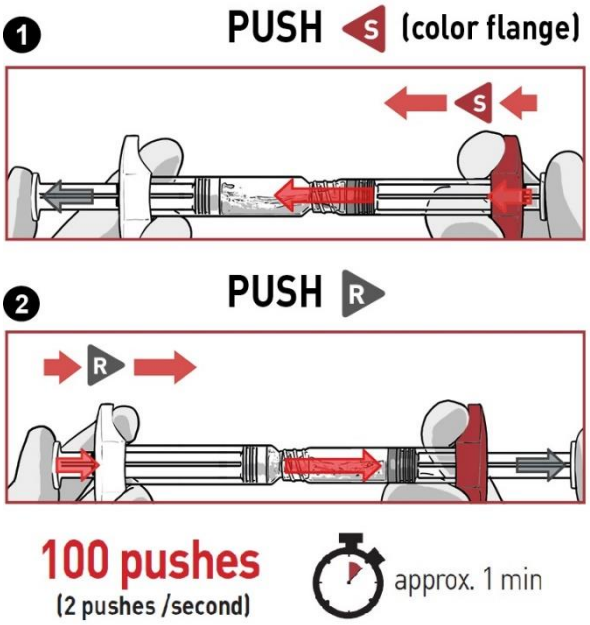
3 MIX THE CONTENTS

STOP AND READ THIS SECTION BEFORE STARTING OR THE MEDICINE MAY NOT CORRECTLY RECONSTITUTE.

- **PUSH VIGOROUSLY** the diluent content towards the Powder syringe.
- **DO NOT WAIT for powder wetting** and **QUICKLY** start mixing contents by **pushing the plungers FAST and alternately for 100 pushes (2 pushes within 1 second, approximately 1 minute).**
- **ENSURE medicine is passing between both syringes** for a properly mixing: **medicine is viscous** and **you will need to apply force** when pressing on the plunger rods.

Mix for at least **100 pushes** by doing alternately

❶ followed by ❷.



Make sure medicine is passing between both syringes.

When medicine is correctly mixed, the appearance will be a uniform suspension off white to yellowish colour and **thick consistency**.

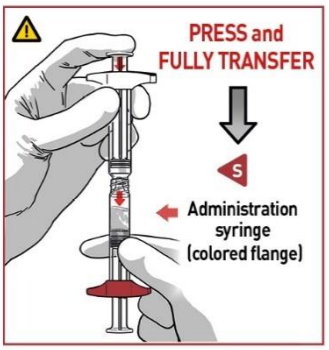
Once reconstituted, proceed immediately to prepare the injection syringe for administration to avoid loss of homogeneity.

4 PREPARE INJECTION SYRINGE

4.1 Transfer medicine:

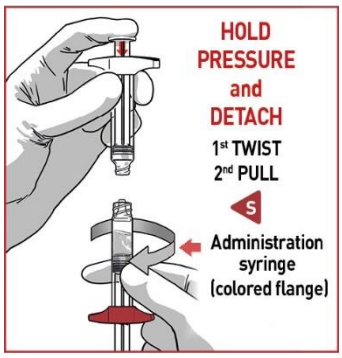
Place downward pressure on the **R** plunger rod and transfer all the content into the **S** syringe that has attached the **coloured finger flange.**

Make sure all the content is transferred.



4.2 Detach syringes:

Once the medicine is fully transferred, separate the two syringes by untwisting.
RISVAN should be **administered immediately to avoid loss of homogeneity.**



4.3 Attach the sterile needle with safety shield

Choose the proper needle:

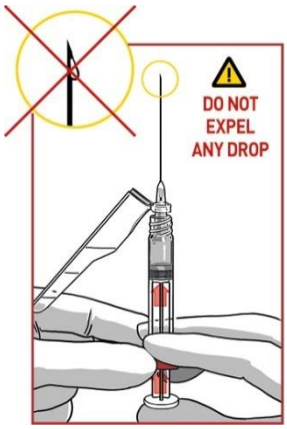
- Deltoid: 21G, 1 inch for deltoid (green cap).
- Gluteus: 20G, 2 inches for gluteus (yellow cap).

Attach it using a clockwise twisting motion. **Do not over-tighten.**

4.4 Remove exceeding air:

Remove needle cover and push out the excess of air (only big bubbles) from the syringe barrel.

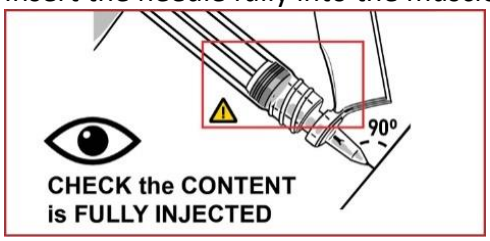
DO NOT expel any drops of medicine.
If medicine is seen at the needle tip, pull back slightly on the plunger to prevent medicine spillage.



5 ADMINISTER AND DISPOSE

5.1 Inject medicine:

Insert the needle fully into the muscle. **DO NOT INJECT BY ANY OTHER ROUTE.**

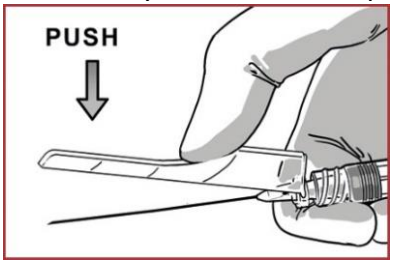


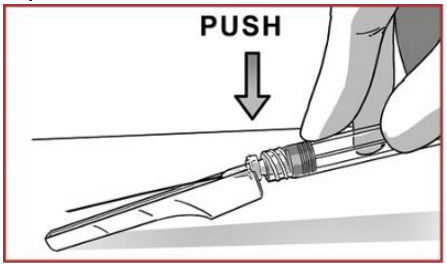
THICK MEDICINE. MAKE SURE TO FULLY INJECT IT.

- **The injection time is longer than usual due to the viscosity of the medicine.**
- **Wait a few seconds before removing the needle.**
- **Avoid inadvertent injection into a blood vessel.**

5.2 Dispose medicine:

Cover the needle pressing on the needle guard using a finger or a flat surface and dispose immediately in a secure sharp's disposal container.





In Australia, any unused medicine or waste material should be disposed of in accordance with local requirements (see section 6.6).

INSTRUCTIONS FOR USE

RISVAN 100 mg modified release powder for injection

Important information
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Use components provided
The components in the kit box are specifically designed for use with RISVAN.
RISVAN must be reconstituted only with the diluent supplied in the kit box.

Do not substitute ANY components of the kit box.

Administer dose immediately after reconstitution. For intramuscular use only after reconstitution.

Proper dosing
The entire content of the reconstituted syringe must be administered to ensure intended dose of RISVAN is delivered.

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The kit box of RISVAN contains:

- One aluminium foil pouch with a RISVAN pre-filled syringe with a WHITE plunger rod and WHITE finger flange. The syringe is marked with 

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- One aluminium foil pouch with DILUENT for RISVAN pre-filled syringe with a TRANSPARENT plunger rod and a BLUE finger flange. The syringe is marked with 

- Two administration needles (21G, 1 inch for deltoid [green cap] and a 20G, 2 inch for gluteus [yellow cap]).

Discard the kit if any component is damaged.
In the event of any foreign particulate matter and/or variation of physical aspect is observed, do not administer RISVAN.

1.1 Inspect diluent syringe

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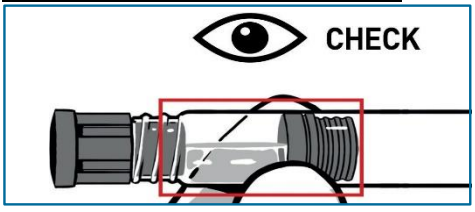


1.2 Dislodge powder syringe

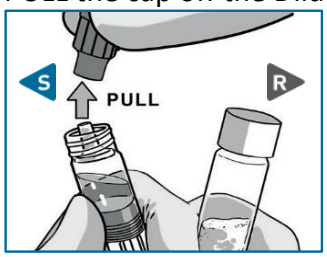
TAP the RISVAN syringe to dislodge potential packed powder near the cap.

2 CONNECT THE SYRINGES

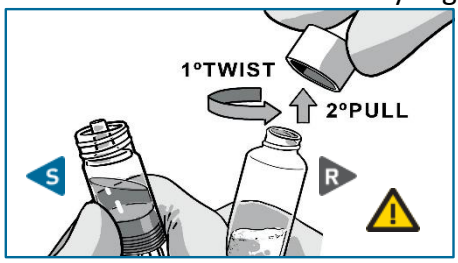
2.1 Uncap syringes in upright position:

Hold both syringes in **upright position to prevent loss of product**.

PULL the cap off the Diluent syringe.



TWIST and PULL the Powder syringe cap off.



2.2 Connect the syringes:

Pick the diluent syringe Sthat has the **coloured finger flange** and place it on TOP of the powder syringe R, or slightly lean it when connecting.
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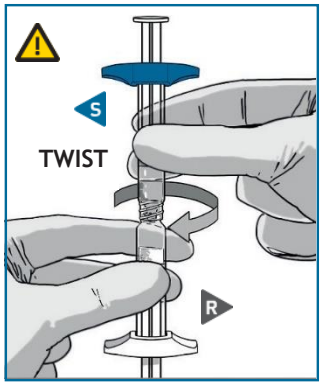

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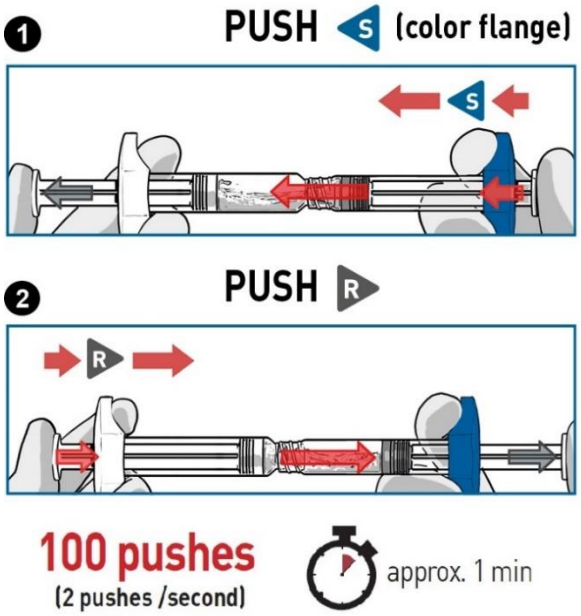


Make sure medicine is passing between both syringes.

When medicine is correctly mixed, the appearance will be a uniform suspension off white to yellowish colour and **thick consistency**.

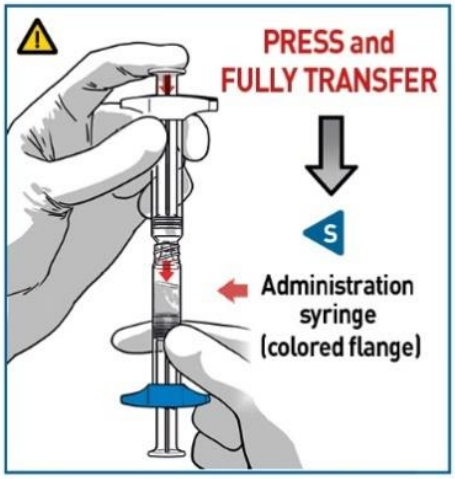
Once reconstituted, proceed immediately to prepare the injection syringe for administration to avoid loss of homogeneity.

4 PREPARE INJECTION SYRINGE

4.1 Transfer medicine:

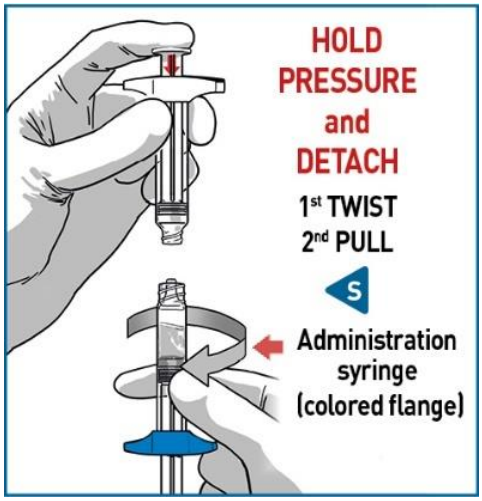
Place downward pressure on the **R** plunger rod and transfer all the content into the **S** syringe that has attached the **coloured finger flange.**

Make sure all the content is transferred.



4.2 Detach syringes:

Once the medicine is fully transferred, separate the two syringes by untwisting. RISVAN should be **administered immediately to avoid loss of homogeneity.**



4.3 Attach the safety needle with safety shield.

Choose the proper needle:

- Deltoid: 21G, 1 inch for deltoid (green cap).
- Gluteus: 20G, 2 inches for gluteus (yellow cap).

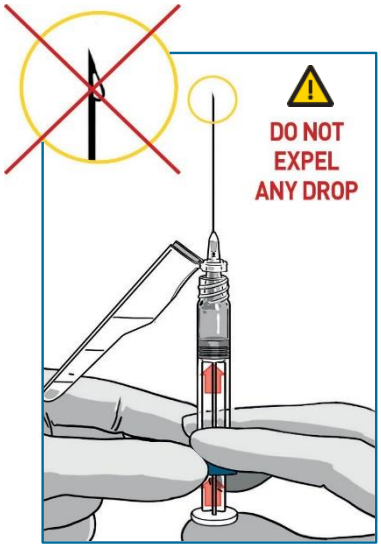
Attach it using a clockwise twisting motion. **Do not over-tighten.**

4.4 Remove exceeding air:

Remove needle cover and push out the excess of air (only big bubbles) from the syringe barrel.

DO NOT expel any drops of medicine.

If medicine is seen at the needle tip, pull back slightly on the plunger to prevent medicine spillage.



5 ADMINISTER AND DISPOSE

5.1 Inject medicine:

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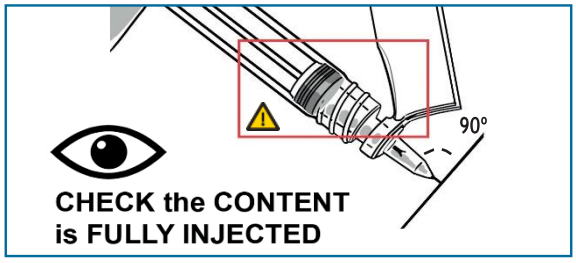
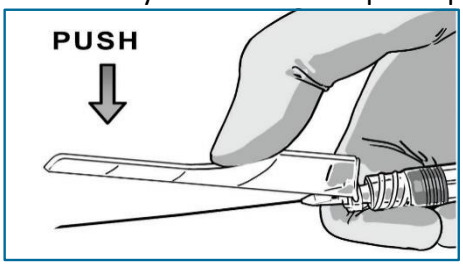


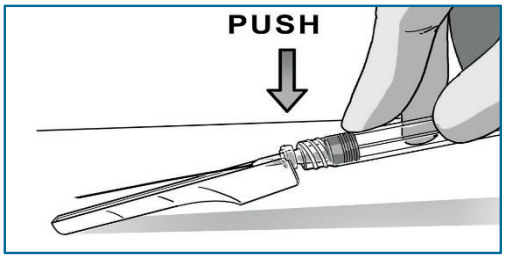
THICK MEDICINE. MAKE SURE TO FULLY INJECT IT.

- **The injection time is longer than usual due to the viscosity of the medicine.**
- **Wait a few seconds before removing the needle.**
- **Avoid inadvertent injection into a blood vessel.**

5.2 Dispose medicine:

Cover the needle pressing on the needle guard using a finger or a flat surface and dispose immediately in a secure sharp's disposal container.





In Australia, any unused medicine or waste material should be disposed of in accordance with local requirements (see section 6.6).

4.3 CONTRAINDICATIONS

Hypersensitivity to the active substance or to any of the excipients listed in Section 6.1 List of excipients.

4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE

For risperidone-naive patients, it is recommended to establish tolerability with oral risperidone prior to initiating treatment with RISVAN (see Section 4.2 Dose and method of administration). Consideration should be given to the prolonged release nature of the medicinal product and the long elimination half-life of risperidone when assessing treatment needs and the potential need to be able to discontinue treatment.

Use in the elderly patients with dementia

Increased mortality in elderly people with dementia

RISVAN has not been studied in elderly patients with dementia, hence it is not indicated for use in this group of patients. In a meta-analysis of 17 controlled trials of atypical antipsychotics, including risperidone, elderly patients with dementia treated with atypical antipsychotics have an increased mortality compared to placebo. In placebo-controlled trials with oral risperidone in this population, the incidence of mortality was 4% for risperidone- treated patients compared to 3.1% for placebo-treated patients. The odds ratio (95% exact confidence interval) was 1.21 (0.7; 2.1). The mean age (range) of patients who died was 86 years (range 67-100). Data from two large observational studies showed that elderly people with dementia who are treated with conventional antipsychotics are also at a small increased risk of death compared with those who are not treated. There are insufficient data to give a firm estimate of the precise magnitude of the risk and the cause of the increased risk is not known. The extent to which the findings of increased mortality in observational studies may be attributed to the antipsychotic active substance as opposed to some characteristic(s) of the patients is not clear.

Concomitant use with furosemide

In the risperidone placebo-controlled trials in elderly patients with dementia, a higher incidence of mortality was observed in patients treated with furosemide plus risperidone (7.3%; mean age 89

years, range 75-97) when compared to patients treated with risperidone alone (3.1%; mean age 84 years, range 70-96) or furosemide alone (4.1%; mean age 80 years, range 67-90). The increase in mortality in patients treated with furosemide plus risperidone was observed in two of the four clinical trials. Concomitant use of risperidone with other diuretics (mainly thiazide diuretics used in low dose) was not associated with similar findings.

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

Cerebrovascular adverse reactions

An approximately 3-fold increased risk of cerebrovascular adverse events (CVAEs) have been seen in randomised placebo-controlled clinical trials in the dementia population with some atypical antipsychotics. The pooled data from six placebo-controlled studies with risperidone in mainly elderly patients (> 65 years of age) with dementia showed that CVAEs (serious and non-serious, combined) occurred in 3.3% (33/1,009) of patients treated with risperidone and 1.2% (8/712) of patients treated with placebo. The odds ratio (95% exact confidence interval) was 2.96 (1.34; 7.50). The mechanism for this increased risk is not known. An increased risk cannot be excluded for other antipsychotics or other patient populations.

RISVAN should be used with caution in patients with risk factors for stroke.

Orthostatic hypotension

Due to the alpha-blocking activity of risperidone, (orthostatic) hypotension can occur. Some cases of hypotension or orthostatic hypotension have been reported during the clinical development program of RISVAN at doses ranged from 50 mg to 100 mg. Clinically significant hypotension has been observed post-marketing with concomitant use of risperidone and antihypertensive treatment. RISVAN should be used with caution in patients with known cardiovascular disease (e.g., heart failure, myocardial infarction, conduction abnormalities, dehydration, hypovolaemia, or cerebrovascular disease). The risk/benefit of further treatment with RISVAN should be assessed if clinically relevant orthostatic hypotension persists.

Leukopenia, neutropenia, and agranulocytosis

Events of leukopenia, neutropenia and agranulocytosis have been reported with risperidone. 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 RISVAN 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 × 109/L) should discontinue RISVAN and have their WBC followed until recovery.

Tardive dyskinesia/extrapyramidal symptoms (TD/EPS)

Medicines with dopamine receptor antagonistic properties have been associated with the induction of tardive dyskinesia (TD) characterised by rhythmical involuntary movements, predominantly of the tongue and/or face. The onset of extrapyramidal symptoms (EPS) is a risk factor for TD. If signs and symptoms of TD appear, the discontinuation of all antipsychotics should be considered.

Caution is warranted in patients receiving both psychostimulants (e.g., methylphenidate) and risperidone concomitantly, as EPSs could emerge when adjusting one or both medicines. Gradual withdrawal of stimulant treatment is recommended (see Section 4.5 Interactions with Other Medicines and Other Forms of Interactions).

Neuroleptic malignant syndrome (NMS)

Neuroleptic Malignant Syndrome (NMS) characterised by hyperthermia, muscle rigidity, autonomic instability, altered consciousness and elevated serum creatine phosphokinase levels has been reported to occur with antipsychotics. Additional signs may include myoglobinuria (rhabdomyolysis) and acute renal failure. In this event, RISVAN should be discontinued.

Parkinson's disease and dementia with Lewy bodies

Physicians should weigh the risks versus the benefits when prescribing RISVAN to patients with Parkinson's Disease or Dementia with Lewy Bodies (DLB). Parkinson's Disease may worsen with risperidone. Both groups may be at increased risk of Neuroleptic Malignant Syndrome as well as having an increased sensitivity to antipsychotic medicinal products; these patients were excluded from clinical trials. Manifestation of this increased sensitivity can include confusion, obtundation, postural instability with frequent falls, in addition to extrapyramidal symptoms.

Hyperglycaemia and diabetes mellitus

Hyperglycaemia, diabetes mellitus, and exacerbation of pre-existing diabetes have been reported during treatment with risperidone. In some cases, a prior increase in body weight has been reported which may be a predisposing factor. Association with ketoacidosis has been reported very rarely and rarely with diabetic coma. Appropriate clinical monitoring is advisable in accordance with utilised antipsychotic guidelines. Patients treated with RISVAN should be monitored for symptoms of hyperglycaemia (such as polydipsia, polyuria, polyphagia and weakness) and patients with diabetes mellitus should be monitored regularly for worsening of glucose control.

Weight gain

Significant weight gain has been reported with risperidone use. Weight should be monitored regularly.

Hyperprolactinaemia

Hyperprolactinaemia is a common side effect of treatment with risperidone. Evaluation of the prolactin plasma level is recommended in patients with evidence of possible prolactin-related side effects (e.g., gynaecomastia, menstrual disorders, anovulation, fertility disorder, decreased libido, erectile dysfunction, and galactorrhoea).

Tissue culture studies suggest that cell growth in human breast tumours may be stimulated by prolactin. Although no clear association with the administration of antipsychotics has so far been demonstrated in clinical and epidemiological studies, caution is recommended in patients with relevant medical history. RISVAN should be used with caution in patients with pre-existing hyperprolactinaemia and in patients with possible prolactin-dependent tumours.

QT prolongation

QT prolongation has very rarely been reported. Caution should be exercised when risperidone is prescribed in patients with known cardiovascular disease, family history of QT prolongation, bradycardia, or electrolyte disturbances (hypokalaemia, hypomagnesaemia), as it may increase the risk of arrhythmogenic effects, and in concomitant use with medicines known to prolong the QT interval.

Seizures

RISVAN should be used cautiously in patients with a history of seizures or other conditions that potentially lower the seizure threshold.

Priapism

Priapism may occur with RISVAN treatment due to its alpha-adrenergic blocking effects.

Body temperature regulation

Disruption of the body's ability to reduce core body temperature has been attributed to antipsychotic medicines. Appropriate care is advised when prescribing RISVAN 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 treatment 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 medicines or of conditions such as intestinal obstruction, Reye's syndrome, and brain tumour.

Venous thromboembolism

Cases of venous thromboembolism (VTE) have been reported with antipsychotic medicinal products. 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 RISVAN and preventative measures undertaken.

Intraoperative floppy iris syndrome

Intraoperative Floppy Iris Syndrome (IFIS) has been observed during cataract surgery in patients

treated with medicines with risperidone (see Section 4.8 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 alpha1-blocking therapy prior to cataract surgery has not been established and must be weighed against the risk of stopping the antipsychotic therapy.

Hypersensitivity

Although tolerability of oral risperidone should be established prior to initiating treatment in patients who have not been previously treated with risperidone, rarely anaphylactic reactions have been reported during post-marketing experience with parenteral risperidone in patients who have previously tolerated oral risperidone. If hypersensitivity reactions occur, the use of RISVAN should be discontinued, and general supportive measures should be initiated as clinically appropriate, and the patient should be monitored until signs and symptoms resolve.

Reconstitution and administration

A lack of efficacy can occur in case of incorrect reconstitution (see Section 4.2 Dose and method of administration and Section 6.6 Special Precautions for Disposal).

Care must be taken to avoid inadvertent injection of RISVAN into a blood vessel or subcutaneous tissue. If administered intravenously, it is expected that a solid formation will be formed immediately due to the characteristics of RISVAN, producing a blockage of the needle. Consequently, a bleeding could occur at the injection site. In case the administration is subcutaneous, the injection might be more painful, and a slower release of risperidone is expected.

If a dose is incorrectly administered by intravenous or subcutaneous route, the dose should not be repeated since it is difficult to estimate the exposure to the medicine. The patient should be closely monitored and managed as clinically appropriate until the next scheduled 28-day interval injection of RISVAN.

Paediatric use

No data available.

Effects on laboratory tests

No data available.

4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS

The interactions of RISVAN with co-administration of other medicinal products have not been systematically evaluated. The interaction data provided in this section are based on studies with oral risperidone.

Pharmacodynamic-related interactions

Medicinal products known to prolong the QT interval

Caution is advised when prescribing RISVAN with medicinal products known to prolong the QT interval, such as antiarrhythmics (e.g., quinidine, disopyramide, procainamide, propafenone, amiodarone, sotalol), tricyclic antidepressants (i.e., amitriptyline), tetracyclic antidepressants (i.e., maprotiline), some antihistamines, other antipsychotics, some antimalarials (i.e., quinine and mefloquine), and with medicines causing electrolyte imbalance (hypokalaemia, hypomagnesaemia), bradycardia, or those which inhibit the hepatic metabolism of risperidone. This list is indicative and not exhaustive.

Centrally acting medicinal products and alcohol

RISVAN should be used with caution in combination with other centrally acting substances, notably including alcohol, opiates, antihistamines and benzodiazepines due to the increased risk of sedation.

Levodopa and dopamine agonists

RISVAN may antagonise the effect of levodopa and other dopamine agonists. If this combination is deemed necessary, particularly in end-stage Parkinson's disease, the lowest effective dose of each treatment should be prescribed.

Medicinal products with hypotensive effect

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

Psychostimulants

The combined use of psychostimulants (e.g., methylphenidate) with RISVAN can lead to extrapyramidal symptoms upon change of either or both treatments (see Section 4.4 Special warnings and precautions for use).

Paliperidone

Concomitant use of RISVAN with paliperidone is not recommended as paliperidone is the active metabolite of risperidone and the combination of the two may lead to additive active moiety exposure.

Pharmacokinetic-related interactions

RISVAN is mainly metabolised through Cytochrome P (CYP)2D6, and to a lesser extent through CYP3A4. Both risperidone and its active metabolite 9-hydroxy-risperidone are substrates of P-glycoprotein (P-gp). Substances that modify CYP2D6 activity, or substances strongly inhibiting or inducing CYP3A4 and/or P-gp activity, may influence the pharmacokinetics of the risperidone active moiety.

Strong CYP2D6 inhibitors

Co-administration of RISVAN with a strong CYP2D6 inhibitor may increase the plasma concentrations of risperidone, but less so of the active moiety. Higher doses of a strong CYP2D6 inhibitor may elevate concentrations of the risperidone active moiety (e.g., paroxetine, see below). It is expected that other CYP2D6 inhibitors, such as quinidine, may affect the plasma concentrations of risperidone in a similar way. When concomitant paroxetine, quinidine, or another strong CYP2D6 inhibitor, especially at higher doses, is initiated or discontinued, the physician should re-evaluate the dosing of RISVAN.

CYP3A4 and/or P-gp inhibitors

Co-administration of RISVAN with a strong CYP3A4 and/or P-gp inhibitor may substantially elevate plasma concentrations of the risperidone active moiety. When concomitant itraconazole or another strong CYP3A4 and/or P-gp inhibitor is initiated or discontinued, the physician should re-evaluate the dosing of RISVAN.

CYP3A4 and/or P-gp inducers

Co-administration of RISVAN with a strong CYP3A4 and/or P-gp inducer may decrease the plasma concentrations of the risperidone active moiety. When concomitant carbamazepine or another strong CYP3A4 and/or P-gp inducer is initiated or discontinued, the physician should re-evaluate the dosing of RISVAN. CYP3A4 inducers exert their effect in a time-dependent manner and may take at least 2 weeks to reach maximal effect after introduction. Conversely, on discontinuation, CYP3A4 induction may take at least 2 weeks to decline.

Highly protein-bound medicinal products

When risperidone is taken together with highly protein-bound medicinal products, there is no clinically relevant displacement of either medicine from the plasma proteins.
When using concomitant medicinal products, the corresponding label should be consulted for information on the route of metabolism and the possible need to adjust dosage.

<u>Examples</u>

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

Effect of other medicinal products on the pharmacokinetics of risperidone

Antibacterials:

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

Anticholinesterases:

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

Antiepileptics:

- Carbamazepine, a strong CYP3A4 inducer and a P-gp inducer, has been shown to decrease the plasma concentrations of the active moiety. Similar effects may be observed with e.g., phenytoin and phenobarbital which also induce CYP3A4 hepatic enzyme, as well as P-glycoprotein.
- Topiramate modestly reduced the bioavailability of risperidone, but not that of the active moiety. Therefore, this interaction is unlikely to be of clinical significance.

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 moiety 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-hydroxy-risperidone.

Antipsychotics:

- Phenothiazines may increase the plasma concentrations of risperidone but not those of the active moiety.

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 moiety.

Beta-blockers:

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

Calcium channel blockers:

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

Gastrointestinal drugs:

- H_2-receptor antagonists: Cimetidine and ranitidine, both weak inhibitors of CYP2D6 and CYP3A4, increased the bioavailability of risperidone, but only marginally that of the active moiety.

Selective Serotonin Reuptake Inhibitors (SSRIs) and tricyclic antidepressants:

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

Effect of risperidone on the pharmacokinetics of other medicinal products Antiepileptics:

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

Antipsychotics:

- 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.

Digitalis glycosides:

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

Lithium:

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

Concomitant use of risperidone with furosemide

See Section 4.4 Special warnings and precautions for use regarding increased mortality in elderly patients with dementia concomitantly receiving furosemide.

4.6 FERTILITY, PREGNANCY AND 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/m2 basis. The effect appeared to be in females since the oestrus cycle in rats

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

Use in pregnancy – 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 foetal development study in rats, intramuscular administration of risperidone 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 risperidone) 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. RISVAN 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 in 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/m2 basis. A no-effect dose was not determined. It is not known whether these deaths were due to a direct effect on the foetuses or pups or to effects on the dams. In one such study there was an increase in stillborn rat pups at a dose 2.5 times the maximum human dose on a mg/m2 basis.

4.7 EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

RISVAN can have minor or moderate influence on the ability to drive and use machines due to potential nervous system and visual effects (see Section 4.8 Adverse Effects). Therefore, patients should be advised not to drive or operate machinery until their individual susceptibility is known.

4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS)

Summary of the safety profile

The most frequently reported adverse drug reactions (ADRs) that were reported in a phase 3 clinical trial are: blood prolactin increased (11.7%), hyperprolactinaemia (7.2%), akathisia (5.5%), headache (4.8%), somnolence (4.1%), weight increased (3.8%), injection site pain (3.1%) and dizziness (3.1%).

Tabulated list of adverse events

The following table are Treatment-emergent Adverse Events Occurring in ≥ 2% of Risperidone ISM Patients by System Organ Class and Preferred Term – DB Phase (SAF Population) of Clinical study report of Prisma3 clinical trial.

System Organ Class Preferred Term	Placebo N=147	Risperidone ISM 75 mg N=144	Risperidone ISM 100 mg N=146	All Risperidone ISM N=290
	n (%) #[AEs]	n (%) #[AEs]	n (%) #[AEs]	n (%) #[AEs]
Patients with at least one TEAE	65 (44.2) [128]	80 (55.6) [192]	94 (64.4) [225]	174 (60.0) [417]
Cardiac disorders	0	3 (2.1) [3]	6 (4.1) [6]	9 (3.1) [9]
Tachycardia	0	2 (1.4) [2]	4 (2.7) [4]	6 (2.1) [6]
Endocrine disorders	1 (0.7) [1]	8 (5.6) [8]	13 (8.9) [13]	21 (7.2) [21]
Hyperprolactinaemia	1 (0.7) [1]	8 (5.6) [8]	13 (8.9) [13]	21 (7.2) [21]
Gastrointestinal disorders	15 (10.2) [18]	17 (11.8) [18]	10 (6.8) [12]	27 (9.3) [30]
Constipation	2 (1.4) [2]	4 (2.8) [4]	2 (1.4) [2]	6 (2.1) [6]
General disorders and administration site conditions	9 (6.1) [12]	14 (9.7) [17]	8 (5.5) [10]	22 (7.6) [27]
Injection site pain	5 (3.4) [7]	8 (5.6) [10]	4 (2.7) [5]	12 (4.1) [15]
Infections and infestations	7 (4.8) [8]	10 (6.9) [10]	15 (10.3) [21]	25 (8.6) [31]
Nasopharyngitis	0	5 (3.5) [5]	4 (2.7) [4]	9 (3.1) [9]
Investigations	10 (6.8) [16]	28 (19.4) [45]	39 (26.7) [57]	67 (23.1) [102]
Alanine aminotransferase increased	3 (2.0) [3]	4 (2.8) [4]	7 (4.8) [7]	11 (3.8) [11]
Aspartate aminotransferase increased	3 (2.0) [3]	2 (1.4) [2]	4 (2.7) [4]	6 (2.1) [6]
Blood prolactin increased	0	13 (9.0) [15]	21 (14.4) [22]	34 (11.7) [37]
Blood triglycerides increased	1 (0.7) [2]	4 (2.8) [4]	3 (2.1) [3]	7 (2.4) [7]
Weight increased	3 (2.0) [3]	10 (6.9) [10]	8 (5.5) [8]	18 (6.2) [18]
Nervous system disorders	15 (10.2) [19]	33 (22.9) [40]	38 (26.0) [51]	71 (24.5) [91]
Akathisia	3 (2.0) [3]	6 (4.2) [6]	11 (7.5) [13]	17 (5.9) [19]
Dizziness	4 (2.7) [4]	5 (3.5) [5]	6 (4.1) [6]	11 (3.8) [11]
Dystonia	1 (0.7) [1]	4 (2.8) [4]	3 (2.1) [3]	7 (2.4) [7]
Headache	5 (3.4) [6]	15 (10.4) [17]	12 (8.2) [12]	27 (9.3) [29]
Somnolence	4 (2.7) [4]	4 (2.8) [5]	8 (5.5) [8]	12 (4.1) [13]
Psychiatric disorders	18 (12.2) [25]	13 (9.0) [14]	13 (8.9) [19]	26 (9.0) [33]
Insomnia	6 (4.1) [8]	4 (2.8) [4]	6 (4.1) [8]	10 (3.4) [12]

Schizophrenia	8 (5.4) [8]	3 (2.1) [3]	3 (2.1) [4]	6 (2.1) [7]

AE = adverse events, DB = double-blind, SAF = safety population, TEAE = treatment-emergent adverse event. Descriptions of TEAEs are coded using MedDRA version 22.1.

Presented frequencies and the denominator used for percentages are based on patients in the SAF population and the actual treatment received in the DB phase.

Patients with multiple TEAEs within the same system organ class and/or preferred term are only counted once within the respective frequencies.

Tabulated list of adverse reactions

The following are all the ADRs that were reported in clinical trials and post-marketing experience with risperidone by frequency category estimated from risperidone clinical trials.
The following terms and frequencies are applied: 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). Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness.

System Organ Class	Adverse Drug Reaction				
	Frequency				
	Very Common	Common	Uncommon	Rare	Very Rare
Infections and infestations		pneumonia, bronchitis, upper respiratory tract infection, sinusitis, urinary tract infection, ear infection, influenza	respiratory tract infection, cystitis, eye infection, tonsillitis, onychomycosis, cellulitis localised infection, viral infection, acarodermatitis	infection	
Blood and lymphatic system disorders			neutropenia, white blood cell count decreased, thrombocytopenia, anaemia, haematocrit decreased, eosinophil count increased	agranulocytosis[c]	
Immune system disorders			hypersensitivity	anaphylactic reaction[c]	
Endocrine disorders		hyperprolactinaemia[a]		inappropriate antidiuretic hormone secretion, glycosuria	

System Organ Class	Adverse Drug Reaction				
	Frequency				
	Very Common	**Common**	**Uncommon**	**Rare**	**Very Rare**
Metabolism and nutrition disorders		weight increased, increased appetite, decreased appetite	diabetes mellitus, hyperglycaemia, polydipsia, weight decreased, anorexia, blood cholesterol increased, blood triglycerides increased	water intoxication[c], hypoglycaemia, hyperinsulinaemia[c]	diabetic ketoacidosis
Psychiatric disorders	insomnia[d]	sleep disorder, agitation, depression, anxiety	mania, confusional state, libido decreased, nervousness, nightmare	catatonia, somnambulism, sleep-related eating disorder, blunted affect, anorgasmia	
Nervous system disorders	parkinsonism[d], headache	sedation/ somnolence, akathisia[d], dystonia[d], dizziness, dyskinesia[d], tremor	tardive dyskinesia, cerebral ischaemia, loss of consciousness, convulsion[d], syncope, psychomotor hyperactivity, balance disorder, coordination abnormal, dizziness postural, disturbance in attention, dysarthria, dysgeusia, hypoaesthesia, paraesthesia	neuroleptic malignant syndrome, cerebrovascular disorder, diabetic coma, head titubation, unresponsive to stimuli, depressed level of consciousness	
Eye disorders		vision blurred, conjunctivitis	photophobia, dry eye, lacrimation increased, ocular hyperaemia	glaucoma, eye movement disorder, eye rolling, eyelid margin crusting, floppy iris syndrome (intraoperative)[c]	
Ear and labyrinth disorders			vertigo, tinnitus, ear pain		

System Organ Class	Adverse Drug Reaction				
	Frequency				
	Very Common	**Common**	**Uncommon**	**Rare**	**Very Rare**
Cardiac disorders		tachycardia	atrial fibrillation, atrioventricular block, conduction disorder, electrocardiogra m QT prolonged, bradycardia, electrocardiogra m abnormal, palpitations	sinus arrhythmia	
Vascular disorders		hypertension	hypotension, orthostatic hypotension, flushing	pulmonary embolism, venous thrombosis	
Respiratory, thoracic and mediastinal disorders		dyspnoea, pharyngolaryng eal pain, cough, nasal congestion	respiratory tract congestion, wheezing, epistaxis	sleep apnoea syndrome, hyperventilation, rales, pneumonia aspiration, pulmonary congestion, dysphonia, respiratory disorder	
Gastrointestinal disorders		abdominal pain, abdominal discomfort, vomiting, nausea, constipation, diarrhoea, dyspepsia, dry mouth, toothache	faecal incontinence, faecaloma, gastroenteritis, dysphagia, flatulence	pancreatitis, intestinal obstruction, swollen tongue, cheilitis	ileus
Hepatobiliary disorders			transaminases increased, gamma-glutamyltransfer ase increased, hepatic enzyme increased	jaundice	

System Organ Class	Adverse Drug Reaction				
	Frequency				
	Very Common	**Common**	**Uncommon**	**Rare**	**Very Rare**
Skin and subcutaneous tissue disorders		rash, erythema	urticaria, pruritus, alopecia, hyperkeratosis, eczema, dry skin, skin discolouration, acne, seborrhoeiccder matitis, skin disorder, skin lesion	drug eruption, dandruff	Angioedema, Stevens-Johnson syndrome and toxic epidermal necrolysis
Musculoskelet al and connective tissue disorders		muscle spasms, musculoskeleta l pain, back pain, arthralgia	blood creatine phosphokinase increased, posture abnormal, joint stiffness, joint swelling muscular weakness, neck pain	rhabdomyolysis	
Renal and urinary disorders		urinary incontinence	pollakiuria, urinary retention, dysuria		
Pregnancy, puerperium, and perinatal conditions				drug withdrawal syndrome neonatal[c]	

System Organ Class	Adverse Drug Reaction				
	Frequency				
	Very Common	**Common**	**Uncommon**	**Rare**	**Very Rare**
Reproductive system and breast disorders			erectile dysfunction, ejaculation disorder, amenorrhoea, menstrual disorder[d], gynaecomastia, galactorrhoea, sexual dysfunction, breast pain, breast discomfort, vaginal discharge	priapism[c], menstruation delayed, breast engorgement, breast enlargement, breast discharge	
General disorders and administration site conditions		oedema[d], pyrexia, chest pain, asthenia, fatigue, pain	face oedema, chills, body temperature increased, gait abnormal, thirst, chest discomfort, malaise, feeling abnormal, discomfort	hypothermia, body temperature decreased, peripheral coldness, drug withdrawal syndrome, induration[c]	
Injury, poisoning and procedural complications		Fall, injection site pain, injection site swelling	procedural pain, injection site discomfort, injection site erythema		

[a] Hyperprolactinaemia can in some cases lead to gynaecomastia, menstrual disturbances, amenorrhoea, anovulation, galactorrhoea, fertility disorder, decreased libido, erectile dysfunction.

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

[c] Not observed in risperidone clinical studies but observed in post-marketing environment with risperidone.

[d] Extrapyramidal disorder may occur: **Parkinsonism** (salivary hypersecretion, musculoskeletal stiffness, parkinsonism, drooling, cogwheel rigidity, bradykinesia, hypokinesia, masked facies, muscle tightness, akinesia, nuchal rigidity, muscle rigidity, parkinsonian gait, and glabellar reflex abnormal, parkinsonian rest tremor), **akathisia** (akathisia, restlessness, hyperkinesia, and restless leg syndrome), tremor, **dyskinesia** (dyskinesia, muscle twitching, choreoathetosis, athetosis, and myoclonus), dystonia. **Dystonia** includes dystonia, hypertonia, torticollis, muscle contractions involuntary, muscle contracture, blepharospasm, oculogyration, tongue paralysis, facial spasm, laryngospasm, myotonia, opisthotonus, oropharyngeal spasm, pleurothotonus, tongue spasm, and trismus. It should be noted that a broader spectrum of symptoms is included, that do not necessarily have an extrapyramidal origin. **Insomnia** includes initial insomnia, middle insomnia. **Convulsion** includes grand mal convulsion. **Menstrual disorder** includes menstruation irregular, oligomenorrhoea. **Oedema** includes generalised oedema, oedema peripheral, pitting oedema.

Description of selected adverse reactions.

Injection site reactions
The most commonly reported injection site related adverse reaction was pain. In the phase 3 study 14 out of 386 patients (3.6%) reported 18 cases of injection pain reactions after 2,827 injections (0.6%) of RISVAN. The majority of these reactions were reported to be of mild to moderate severity. Subject evaluations of injection site pain based on a visual analogue scale tended to lessen in frequency and intensity over time.

Cardiac disorders
Postural orthostatic tachycardia syndrome

Class effects
Very rare cases of QT prolongation ventricular arrhythmias (ventricular fibrillation, ventricular tachycardia), sudden death, cardiac arrest and Torsades de Pointes have been reported post marketing with risperidone.

Venous thromboembolism
Cases of venous thromboembolism, including cases of pulmonary embolism and cases of deep vein thrombosis, have been reported with antipsychotic drugs (frequency unknown).
Changes in body weight
Data from a 12-week double-blind (DB), placebo-controlled trial indicated that there was a mean increase in weight from baseline of 1.4 (-8 to 18) kg, 0.8 (-8 to 47) kg, and 0.2 (-12 to 18) kg after treatment with the RISVAN 75 mg, RISVAN 100 mg and placebo, respectively.

Paediatric population

No information exists on efficacy and safety of RISVAN in children.

Elder patients

Limited information exists on efficacy and safety of RISVAN in older patients with schizophrenia or dementia. In clinical trials with oral risperidone transient ischaemic attack and Cerebrovascular accident were reported with a frequency of 1.4% and 1.5%, respectively, in older patients with dementia compared to other adults. In addition, the following ADRs were reported with a frequency ≥5% in older patients with dementia and with at least twice the frequency seen in other adult populations: urinary tract infection, peripheral oedema, lethargy, and cough.

Reporting suspected adverse effects

Reporting suspected adverse reactions after registration of the medicinal product is important. It allows continued monitoring of the benefit-risk balance of the medicinal product.
Healthcare professionals are asked to report any suspected adverse reactions at www.tga.gov.au/reporting-problems.

4.9 OVERDOSE

Symptoms

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

known pharmacological effects of risperidone. These include drowsiness and sedation, tachycardia and hypotension, and extrapyramidal symptoms. In overdose, QT prolongation and convulsions have been reported. Torsade de Pointes has been reported in association with combined overdose of risperidone and paroxetine.
In case of acute overdose, the possibility of multiple drug involvement should be considered.

Treatment

A clear airway should be established and maintained, and adequate oxygenation and ventilation should be ensured. Cardiovascular monitoring should commence immediately and should include continuous electrocardiographic monitoring to detect possible arrhythmias.

There is no specific antidote to RISVAN. 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, an anticholinergic medicinal product should be administered. Close medical supervision and monitoring should continue until the patient recovers.

For information on the management of overdose, contact the Poisons Information Centre on 13 11 26 (Australia).

5 PHARMACOLOGICAL PROPERTIES

5.1 PHARMACODYNAMIC PROPERTIES

Mechanism of action

Risperidone is a selective monoaminergic antagonist with a high affinity for serotoninergic 5- HT2 and dopaminergic D2 receptors. Risperidone binds also to alpha1-adrenergic receptors, and with lower affinity, to H1-histaminergic and alpha2-adrenergic receptors. Risperidone has no affinity for cholinergic receptors. 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 D2 receptors and causes release of prolactin, it is less potent than classical neuroleptics for depression of motor activity and for induction of catalepsy in animals.

Balanced central serotonin and dopamine antagonism may reduce extrapyramidal side effect liability and extend the therapeutic activity to the negative and affective symptoms of schizophrenia.

Due to the alpha-blocking activity of 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 serotoninergic 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.

Clinical trials

A therapeutic plasma concentration range of 7.5 ng/mL to 80 ng/mL was used for dose selection rationale during the clinical development plan of RISVAN. This range is based on the expected pharmacodynamic translation of an optimal striatal D2 receptor occupancy (D2RO) of 50%-80%, as suggested by the scientific evidence. The recommended dosage of RISVAN, i.e. 75 mg and 100 mg every 28 days, provides a similar exposure to what it is observed after daily oral administration of risperidone 3 mg and 4 mg, respectively

The efficacy of RISVAN (75 mg and 100 mg) in the treatment of schizophrenia in adults was established in one Phase 3, multicentre, randomised, double-blind, placebo-controlled, parallel groups study. The study admitted patients with an acute exacerbation or relapse of schizophrenia (DSM-5 criteria), who had a Positive and Negative Syndrome Scale (PANSS) score of 80-120. At the screening visit, all risperidone naïve patients received 2 mg/day oral risperidone for 3 days to ensure a lack of any clinically significant hypersensitivity reactions before the trial. Patients with previous history of being treated with risperidone did not receive oral risperidone at the screening and started directly with RISVAN (75 mg or 100 mg) or placebo after randomization. Four hundred and thirty-eight (438) patients were randomised to receive 3 intramuscular doses of RISVAN (75 mg or 100 mg) or placebo every 28 days. The mean age of patients was 42.0 (SD: 11.02) years.

No patients <18 years or >65 years were included. Demographic and other baseline characteristics were similar in each treatment group. No supplemental oral risperidone was permitted during the study.

The primary endpoint was the change in PANSS Total score from baseline to end of study (Day 85). Both RISVAN 75 and 100 mg doses demonstrated a statistically significant improvement compared with placebo based on the primary endpoint (Table 1 and Figure 1). These results support efficacy across the entire duration of treatment and improvement in PANSS and was observed as early as day 4 with significant separation from placebo in the 100 mg and 75 mg groups by day 8 and 15, respectively. Similar to the PANSS Total Score, the three PANSS positive, negative and general psychopathological subscale scores also showed an improvement (decrease) from baseline over time.

Table 1: Mean change in PANSS and CGI-S tTotal score from baseline to the end of study (day 85) (mITT Population)

	Placebo N=132	**RISVAN 75 mg N=129**	**RISVAN 100 mg N=129**
PANSS total score[(a)]			
Mean baseline score (SD)	96.4 (7.21)	96.3 (8.47)	96.1 (8.42)
LS Mean Change, 95% CI [(a)]	-11.0, -14.1 to -8.0	-24.6, -27.5 to -21.6	-24.7, -27.7 to -21.6
Treatment Difference, 95% CI [(b)]		-13.0, -17.3 to -8.8	-13.3, -17.6 to -8.9
P-value		<0.0001	<0.0001
	Placebo N=132	**RISVAN 75 mg N=129**	**RISVAN 100 mg N=129**
CGI-S total score[(c)]			
Mean baseline score (SD)	4.9 (0.52)	5.0 (0.65)	4.9 (0.48)
LS Mean Change, 95% CI [(a)]	-0.6, -0.8 to -0.4	-1.3, -1.5 to -1.2	-1.3, -1.5 to -1.2
Treatment Difference, 95% CI [(b)]		-0.7, -1.0 to -0.5	-0.7, -1.0 to -0.5
P-value		<0.0001	<0.0001

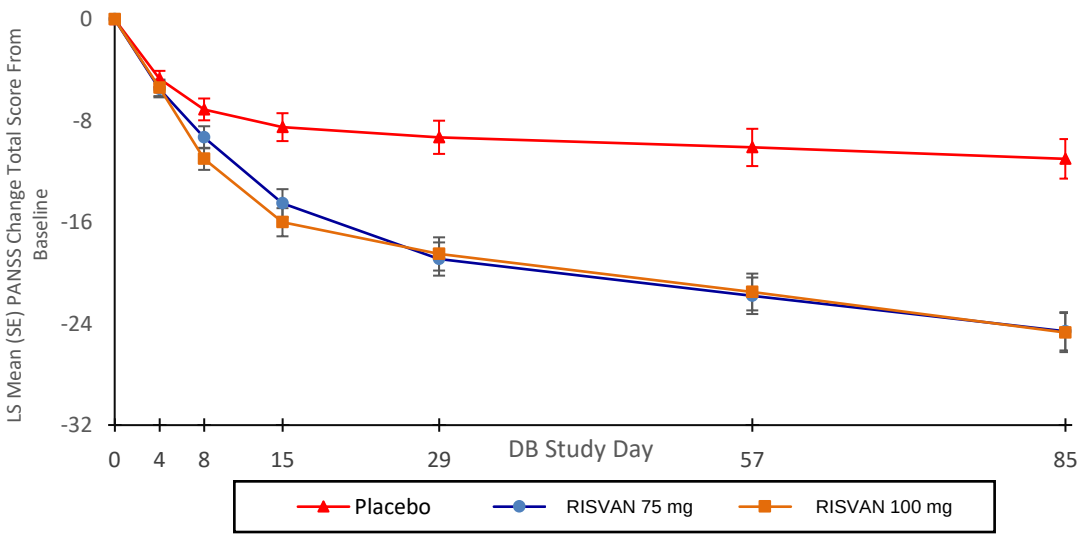
a Data were analyzed using a mixed model repeated measures (MMRM) approach.

b Difference (RISVAN minus placebo) in least squares mean change from baseline adjusted by Lawrence and Hung method.

c The Clinical Global Impression – Severity (CGI-S) score asks the clinician one question: "Considering your total clinical experience with this particular population, how mentally ill is the patient at this time?" which is rated on the following seven-point scale: 1=normal, not at all ill; 2=borderline mentally ill; 3=mildly ill; 4=moderately ill; 5=markedly ill; 6=severely ill; 7=among the most extremely ill patients.

mITT = modified intent-to-treat population; CI = confidence interval.

Figure 1: PANSS Total Score Change from Baseline at Each Time Point in DB Phase (mITT Population)



vs Placebo					
RISVAN 75 mg		***	****	****	****
RISVAN 100 mg	**	****	****	****	****

** p < 0.01, *** p < 0.001, **** p < 0.0001.

The key secondary efficacy endpoint was defined as the mean change from baseline at Day 85 on the Clinical Global Impression – Severity (CGI-S) score. Both RISVAN treatment groups demonstrated statistically significantly better CGI-S scores versus placebo from day 8 onwards (-0.4 (0.05) and -0.6 (0.05) score reduction from baseline for 75 mg and 100 mg, respectively).

Overall Response (PANSS Total score reduction >30% and/or CGI-I of 2 “much improved“ or 1 “very much improved“) rate at endpoint for RISVAN was 56% and showed to be statistically significant from Day 8 and 15 onwards, for both doses in comparison to placebo.

The long-term (12 months) efficacy of RISVAN was evaluated in an open-label extension of the main study in 215 patients with schizophrenia. The extension study was open to enrolment for patients from the DB phase (rollover patients) and stable patients not previously enrolled in the study (de novo patients). The de novo patients were switched from oral risperidone directly to RISVAN 75 mg or 100 mg. Efficacy was maintained over time with a relapse rate 10.7% (95% CI, 6.9% to 15.6%) and a remittance rate 61.0% (95% CI, 53.7% to 68.4%).

5.2 PHARMACOKINETIC PROPERTIES

Risperidone is metabolised to 9-hydroxy-risperidone, which has a similar pharmacological activity to risperidone (see Biotransformation and Elimination).

Absorption

RISVAN contains risperidone in a suspension delivery system that shows a combined absorption process. Following intramuscular injection, a small amount of the drug is immediately released at the moment of the injection that provides immediate plasma levels. After a first peak concentration, mean plasma concentrations decrease sustainedly through Day 14 and then increased again to reach a second peak between approximately Day 21 and Day 24. Following the second peak, plasma concentrations decreased gradually over time. The suspension forms a depot that provides sustained therapeutic plasma concentrations that are maintained over the 28-day interval.

After single IM injection of RISVAN 75 and 100 mg, mean active moiety concentrations of 13 ± 9 and 29 ± 13 ng/mL respectively are achieved at 2 hours after administration. Active moiety plasma concentrations of 17 ± 8 and 21 ± 17 ng/mL respectively one month after administration, and in most of the patients the drug is completely eliminated 75 days after administration, with active moiety values lower than 1 ng/mL.

The mean trough plasma concentrations (C_{trough}) and mean maximum peak plasma concentrations (C_{max}) of active moiety following repeated intramuscular injections with RISVAN are shown in Table 2.

Table 2: Ctrough and Cmax of active moiety following repeated intramuscular injections with RISVAN

Dose	C_{trough} (SD) ng/mL	C_{max} (SD) ng/mL
75 mg[(a)]	17.6	35.9
100 mg(b)	28.9 (13.7)	69.7 (27.8)

a Summary simulated estimates pharmacokinetic (PK) variables following the 3rd dose of RISVAN 75 mg using population (pop) PK model
b Summary statistics PK variables following the 4th dose of RISVAN 100 mg from multiple dose clinical trial SD: standard deviation
Steady state concentrations for the typical subject were attained after the first dose.
The average exposure at steady state was similar for both deltoid and gluteal injection sites.

Distribution

Risperidone is rapidly distributed. The volume of distribution is 1-2 l/kg. In plasma, risperidone is bound to albumin and alpha$_1$~~1~~-acid glycoprotein. The plasma protein binding of risperidone is 90%, that of 9-hydroxy-risperidone is 77%.

Metabolism

Risperidone is metabolised by CYP2D6 to 9-hydroxy-risperidone, which has a similar pharmacological activity as risperidone. Risperidone plus 9-hydroxy-risperidone form the active moiety. CYP2D6 is subject to genetic polymorphism. Extensive CYP2D6 metabolisers convert risperidone rapidly into 9-hydroxy-risperidone, whereas poor CYP2D6 metabolisers convert it much more slowly. Although extensive metabolisers have lower risperidone and higher 9-hydroxy-risperidone concentrations than poor metabolisers, the pharmacokinetics of risperidone and 9-

hydroxy-risperidone combined (i.e., the active moiety), after single and multiple doses, are similar in extensive and poor metabolisers of CYP2D6.

Another metabolic pathway of risperidone is N-dealkylation. *In vitro* studies in human liver microsomes showed that risperidone at clinically relevant concentration does not substantially inhibit the metabolism of medicines metabolised by cytochrome P450 isozymes, including CYP1A2, CYP2A6, CYP2C8/9/10, CYP2D6, CYP2E1, CYP3A4, and CYP3A5.

Excretion

One week after administration, 70% of the dose is excreted in the urine and 14% in the faeces. In urine, risperidone plus 9-hydroxy-risperidone represents 35-45% of the dose. The remainder is inactive metabolites. After oral administration to psychotic patients, risperidone is eliminated with a half-life of about 3 hours. The elimination half-life of 9-hydroxy- risperidone and of the active moiety is 24 hours.

The active moiety is eliminated within 75 days after RISVAN administration, with active moiety values lower than 1 ng/mL in most of the patients.

RISVAN injection versus oral risperidone

Initial plasma levels with RISVAN were within the exposure range observed with 3-4 mg of oral risperidone. Steady state exposure after RISVAN 100 mg compared to 4 mg oral risperidone was 39% higher for AUC and 32% for C_{max} and was similar for C_{min}. Simulations based on population pharmacokinetic modelling shows that RISVAN 75 mg exposure is similar to 3 mg oral risperidone in steady state.

When switching from oral risperidone to RISVAN, the predicted exposure to the active moiety is in a similar range, including peak concentrations.

Linearity/non-linearity

RISVAN has been found to exhibit linear and dose-proportional pharmacokinetics at doses of 75 and 100 mg.

Elderly

RISVAN has not been systematically studied in elderly patients (see Section 4.2 Dose and Method of Administration).

Renal impairment

RISVAN has not been systematically studied in patients with renal impairment. Patients with mild renal impairment (creatinine clearance 60 to 89 mL/min) that received RISVAN administration, showed similar active moiety exposure than patients with normal renal function.
No data is available in moderate renal disease or severe renal disease.

Hepatic impairment

RISVAN has not been systematically studied in patients with hepatic impairment.

Body mass index (BMI)

Population pharmacokinetic simulations have shown potential increases in plasma concentrations

of RISVAN in obese or morbid obese females in comparison with normal weight patients with insignificant clinical impact.

Gender, race and smoking habits

A pop PK analysis revealed no apparent effect of gender, race or smoking habits on the pharmacokinetics of risperidone or the active moiety.

Genotoxicity

No evidence of risperidone genotoxicity was observed in assays for DNA damage, gene mutations or chromosomal damage. RISVAN was not genotoxic in a bacterial reverse mutation assay.

Carcinogenicity

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

Antipsychotic 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 phaeochromocytoma, 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 RISVAN. 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 section 4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS)).

Local irritation at the injection site was observed in dogs and rats after administration of risperidone. 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.

6 PHARMACEUTICAL PARTICULARS

6.1 LIST OF EXCIPIENTS

Pre-filled syringe of powder: polyglactin
Pre-filled syringe of diluent: dimethyl sulfoxide

6.2 INCOMPATIBILITIES

This medicinal product must not be mixed with other medicinal products except those mentioned in Section 6.6 Special Precautions for Disposal.

6.3 SHELF LIFE

RISVAN should be used immediately after reconstitution.
In Australia, information on the shelf life can be found on the public summary of the Australian Register of Therapeutic Goods (ARTG). The expiry date can be found on the packaging.

6.4 SPECIAL PRECAUTIONS FOR STORAGE

Store below 25°C.
Store in the original package in order to protect from moisture.
For storage conditions after reconstitution of the medicinal product, see Section 6.3 Shelf Life.

6.5 NATURE AND CONTENTS OF CONTAINER

Powder prefilled syringe:
Cyclic Olefin Polymer syringe with a nozzle cap and plunger stopper composed of chlorobutyl rubber covered with a polytetrafluoroethylene.

Diluent prefilled syringe:
Cyclic Olefin Polymer syringe with a tip cap composed of chlorobutyl rubber, and a plunger stopper composed of bromobutyl rubber covered with ethylene-tetrafluoroethylene copolymer. The diluent for reconstitution is presented in the following dosage strengths:

- Pre-filled syringe of diluent containing 0.383 mL of dimethyl sulfoxide (diluent for RISVAN 75 mg).

Pre-filled syringe of diluent containing 0.490 mL of dimethyl sulfoxide (diluent for RISVAN 100 mg).

Each kit box of RISVAN contains:

- An aluminium foil pouch with one pre-filled syringe containing powder and a silica gel desiccant sachet.
- An aluminium foil pouch with one pre-filled syringe containing the diluent and a silica gel desiccant sachet.
- One needle for injection 2 inch (0.90 x 51mm [20G]) with safety shield used for gluteus administration.
- One needle for injection 1 inch (0.80 x 25mm [21G]) with safety shield used for deltoid administration.

6.6 SPECIAL PRECAUTIONS FOR DISPOSAL

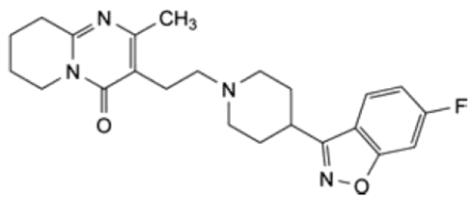
In Australia, any unused medicine or waste material should be disposed of in accordance with local requirements.

6.7 PHYSICOCHEMICAL PROPERTIES

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

6.8 CHEMICAL STRUCTURE

Risperidone is chemically identified as 3-[2-[4-(6-fluoro-1,2-benzisoxazol-3-yl)-1- piperidinyl] ethyl]-6,7,8,9-tetrahydro-2-methyl-4H-pyrido[1,2-a]pyrimidin-4-one.
Structural formula:



Molecular formula of risperidone is $C_{23}H_{27}FN_4O_2$ and molecular mass is 410.48 g/mol.

6.9 CAS NUMBER

106266-06-2

7 MEDICINE SCHEDULE (POISONS STANDARD)

Schedule 4 (Prescription Only Medicine)

8 SPONSOR

Servier Laboratories (Aust.) Pty. Ltd.
www.servier.com.au

Level 4, Building 9
588A Swan Street
Burnley, 3121, Victoria

9 DATE OF FIRST APPROVAL

21 December 2023

10 DATE OF REVISION

15 July 2024

Summary of Changes

Section Changed	Summary of new information
ALL	Trade name changed to RISVAN
8	New Sponsor details