PROFESSIONAL INFORMATION

SCHEDULING STATUS

Schedule 5.

PROPRIETARY NAME AND DOSAGE FORM

RISPERDAL® CONSTA 25 mg prolonged release suspension for intramuscular injection.

RISPERDAL® CONSTA 37,5 mg prolonged release suspension for intramuscular injection.

RISPERDAL® CONSTA 50 mg prolonged release suspension for intramuscular injection.

COMPOSITION

RISPERDAL CONSTA contains 25 mg, 37,5 mg or 50 mg risperidone.

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

Inactive ingredients: The diluent contains carmellose sodium 40mPa.s, citric acid anhydrous disodium hydrogen phosphate dihydrate, polysorbate 20, sodium chloride, sodium hydroxide, water for injection.

PHARMACOLOGICAL CLASSIFICATION

A.2.6.5 Central nervous system depressants. Miscellaneous structures.

PHARMACOLOGICAL ACTION

Pharmacodynamic properties

Risperidone is an antipsychotic of the benzisoxazol derivatives. It is a selective monoaminergic antagonist. Risperidone has affinity for serotonin-5-HT_2, dopamine-D_2, H_1-histamine, α_1- and α_2-adrenergic receptors. Risperidone has no affinity for cholinergic receptors. It is a potent D_2-antagonist.

Pharmacokinetic properties

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

After repeated intramuscular injections with 25 or 50 mg RISPERDAL CONSTA every two weeks, median trough and peak plasma concentrations of the active antipsychotic fraction fluctuated between 9,9-19,2 ng/mℓ and 17,9 – 45,5 ng/mℓ respectively. The pharmacokinetics of risperidone are linear in the dose range of 25 - 50 mg injected every 2 weeks. No accumulation of risperidone was observed during long-term use (12 months) in patients who were injected with 25 - 50 mg every two weeks.

A single dose study showed higher active plasma concentrations and a reduced clearance of the active antipsychotic fraction by 30 % in the elderly and 60 % in patients with moderate renal insufficiency. In

patients with severe renal insufficiency the clearance was one third that of normal. The plasma concentrations of risperidone were normal in patients with liver insufficiency, but the mean free fraction of risperidone in plasma was increased by about 35 %.

Absorption

The absorption of risperidone from RISPERDAL CONSTA is complete.

Distribution

Risperidone is rapidly distributed. The volume of distribution is 1-2 ℓ/kg.

In plasma, risperidone is bound to albumin and alpha1-acid glycoprotein. The plasma protein binding of risperidone is about 90 % and that of the active metabolite 9-hydroxy-risperidone is 77 %.

Metabolism

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

Elimination

The active antipsychotic fraction and risperidone clearances were 5,0 and 13,7 ℓ /h in extensive metabolisers, respectively, and 3,2 and 3,3 ℓ /h in poor metabolisers of CYP2D6, respectively.

The combination of the release profile and the dosage regimen (intramuscular injection every two weeks) result in sustained therapeutic plasma concentrations.

Therapeutic plasma concentrations remain until 4 to 6 weeks after the last RISPERDAL CONSTA injection. The elimination phase is complete approximately 7 to 8 weeks after the last injection.

INDICATIONS

RISPERDAL CONSTA is indicated for the treatment of acute and chronic schizophrenia. RISPERDAL CONSTA is also indicated as monotherapy or adjunctive therapy for the maintenance treatment to prevent the recurrence of manic episodes of bipolar I disorder in patients who have previously responded to oral antipsychotics or other anti-manic treatments.

CONTRAINDICATIONS

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

Not for children under 18 years as efficacy and safety in children under the age of 18 years have not been studied.

Hepatic and renal impairment

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

Parkinson's disease and Lewy body dementia (see WARNINGS and SPECIAL PRECAUTIONS)

WARNINGS and SPECIAL PRECAUTIONS

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

Elderly Patients with Dementia

Overall Mortality

Elderly patients with dementia treated with atypical antipsychotic medicines have an increased mortality compared to placebo in a meta-analysis of 17 controlled trials of atypical antipsychotic medicines, including risperidone. In placebo-controlled trials with oral risperidone in this population, the incidence of mortality was 4,0 % for risperidone-treated patients compared to 3,1 % for placebo-treated patients. The mean age (range) of patients who died was 86 years (range 67-100).

Concomitant use with Furosemide

In the oral RISPERDAL placebo-controlled trials in elderly patients with dementia, a higher incidence of mortality was observed in patients treated with furosemide plus risperidone (7,3 %; mean age 89 years, range 75-97) when compared to patients treated with risperidone alone (3,1 %; mean age 84 years, range 70-96) or furosemide alone (4,1 %; mean age 80 years, range 67-90). The increase in mortality in patients treated with furosemide plus risperidone was observed in two of the four clinical trials.

No pathophysiological mechanism has been identified to explain this finding, and no consistent pattern for cause of death observed.

Nevertheless, caution should be exercised and the risks and benefits of this combination should be considered prior to the decision to use.

There was no increased incidence of mortality among patients taking other diuretics as concomitant medication with risperidone. Irrespective of treatment, dehydration was an overall risk factor for mortality and should therefore be carefully avoided in elderly patients with dementia.

Cerebrovascular Adverse Events (CAE)

In placebo-controlled trials in elderly patients with dementia, there was a higher incidence of cerebrovascular adverse events, (cerebrovascular accidents and transient ischemic attacks), including fatalities, in patients treated with oral risperidone compared to patients receiving placebo (mean age 85 years; range 73-97).

Orthostatic Hypotension

Due to the alpha-blocking activity of RISPERDAL CONSTA, (orthostatic) hypotension can occur, especially during the initial dose-titration period. (See INTERACTIONS). RISPERDAL CONSTA should be used with caution in patients with known cardiovascular disease, and the dosage should be gradually titrated as recommended. A dose reduction should be considered if hypotension occurs.

Leukopaenia, Neutropaenia, and Agranulocytosis

Events of leukopaenia, neutropaenia and agranulocytosis have been reported with RISPERDAL CONSTA. Agranulocytosis has been reported during postmarketing surveillance.

Patients with a history of a clinically significant low white blood cell count (WBC) or a medicine-induced leukopaenia/neutropaenia should be monitored during 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 neutropaenia should be carefully monitored for fever or other symptoms or signs of infection and treated promptly if such symptoms or signs occur. Patients with significant neutropaenia (absolute neutrophil count < 1 X $10^9/\ell$) should discontinue RISPERDAL CONSTA and have their WBC followed until recovery.

Venous thromboembolism

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

Tardive Dyskinesia/Extrapyramidal Symptoms (TD/EPS)

RISPERDAL CONSTA has been associated with the induction of tardive dyskinesia (TD) characterised by potentially irreversible rhythmical involuntary movements, predominantly of the tongue and/or face. It has been reported that the occurrence of extrapyramidal symptoms is a risk factor for the development of tardive dyskinesia. Tardive dyskinesia appears to be more prominent in the elderly especially elderly females. RISPERDAL CONSTA has a potential to induce extrapyramidal symptoms. If signs and symptoms of tardive dyskinesia appear, the discontinuation of RISPERDAL CONSTA should be considered.

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

Neuroleptic Malignant Syndrome (NMS)

Neuroleptic Malignant Syndrome is a potentially fatal symptom complex, 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, all antipsychotic medicines, including RISPERDAL CONSTA, should be discontinued. After the last administration of RISPERDAL CONSTA, plasma levels of risperidone are present for up to (a minimum) of 6 weeks.

Parkinson's disease/ Lewy body dementia and NMS

Patients with Parkinson's Disease or Dementia with Lewy bodies (DLB) have an increased risk of Neuroleptic Malignant Syndrome as well as having an increased sensitivity to antipsychotic medications.(see CONTRAINDICATIONS). Manifestation of this increased sensitivity can include confusion, obtundation, postural instability with frequent falls, in addition to extrapyramidal symptoms.

In addition, in clinical trials, elderly patients have a higher mortality than placebo-treated patients (see CONTRAINDICATIONS).

Hypersensitivity reactions

Although tolerability with oral risperidone should be established prior to initiating treatment with RISPERDAL CONSTA, very rare cases of

anaphylactic reaction has been reported during postmarketing experience in patients who have previously tolerated oral risperidone (see DOSAGE AND DIRECTIONS FOR USE and SIDE EFFECTS).

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

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 RISPERDAL CONSTA.

Patients with an established diagnosis of diabetes mellitus who are started on RISPERDAL CONSTA 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 RISPERDAL CONSTA should be monitored for symptoms of hyperglycaemia including polydipsia, polyuria, polyphagia, and weakness. Patients who develop symptoms of hyperglycaemia during treatment with RISPERDAL CONSTA should undergo fasting blood glucose testing. In some cases, hyperglycaemia has resolved when RISPERDAL CONSTA was discontinued: however, some patients required continuation of anti-diabetic treatment despite discontinuation of RISPERDAL CONSTA.

Weight gain

Significant weight gain has been reported. Monitoring weight gain is advisable when RISPERDAL CONSTA is being used. Patients may be advised to refrain from overeating in view of the possibility of weight gain.

QT Interval

Caution should be exercised when RISPERDAL CONSTA is prescribed in patients with a history of cardiac dysrhythmias, in patients with congenital long QT syndrome, and in concomitant use with medicines known to prolong the QT interval.

Priapism

Medicines with alpha-adrenergic blocking effects have been reported to induce priapism. Priapism has been reported with risperidone during postmarketing surveillance (see SIDE EFFECTS).

Body Temperature Regulation

Disruption of the body's ability to reduce core body temperature may occur. 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 medicines or of conditions such as intestinal obstruction, Reye's syndrome, and brain tumour.

Seizures

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.

IFIS may increase the risk of eye complications during and after the operation. Current or past use of RISPERDAL CONSTA should be made known to the ophthalmic surgeon in advance of surgery. The potential benefit of stopping RISPERDAL CONSTA prior to cataract surgery has not been established and must be weighed against the risk of stopping RISPERDAL CONSTA therapy.

Administration

Care must be taken to avoid inadvertent injection of RISPERDAL CONSTA into a blood vessel.

Ability to drive or use machinery

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

INTERACTIONS

The risk of using RISPERDAL CONSTA in combination with other medicines has not been systematically evaluated.

Centrally-Acting Medicines and Alcohol

Given the primary CNS depressive effect of RISPERDAL CONSTA, it should be used with caution in combination with other centrally acting medicines or alcohol.

Levodopa and Dopamine Agonists

RISPERDAL CONSTA may antagonise the effect of levodopa and other dopamine agonists.

Psychostimulants

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

(See WARNINGS and SPECIAL PRECAUTIONS)

Medicines with Hypotensive Effects

Clinically significant hypotension has been observed postmarketing with concomitant use of risperidone and antihypertensive treatment (see WARNINGS and SPECIAL PRECAUTIONS).

Medicines known to prolong the QT interval

Caution is advised when prescribing RISPERDAL CONSTA with medicines known to prolong the QT interval.

Pharmacokinetic-related Interactions

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

Strong CYP2D6 Inhibitors

Co-administration of RISPERDAL CONSTA with a strong CYP2D6 inhibitor may increase the plasma concentrations of risperidone, but less so of the active antipsychotic fraction. Higher doses of a strong CYP2D6 inhibitor may elevate concentrations of the risperidone active antipsychotic fraction (e.g., paroxetine, 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

When concomitant itraconazole or another strong CYP3A4 and/or P-gp inhibitor is initiated or discontinued, the medical practitioner should re-evaluate the dosing of RISPERDAL CONSTA.

CYP3A4 and/or P-gp Inducers

When concomitant carbamazepine or another strong CYP3A4 and/or P-gp inducer is initiated or discontinued, the medical practitioner should re-evaluate the dosing of RISPERDAL CONSTA.

Highly Protein-bound Medicines

When RISPERDAL CONSTA is taken together with other highly protein-bound medicines (e.g. diazepam, warfarin, digitoxin, imipramine and propranolol), there is no clinically relevant displacement of either agent from the plasma proteins.

Examples

Examples of medicines that potentially interact or that were shown not to interact with RISPERDAL CONSTA 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 P-gp inducer, has been shown to decrease the plasma levels of the active antipsychotic fraction of risperidone.
- Topiramate modestly reduced the bioavailability of risperidone, but not that of the active antipsychotic fraction. Therefore, this interaction is unlikely to be of clinical significance.
- RISPERDAL CONSTA 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 concentration of risperidone but not those of the active antipsychotic fraction.
- Apriprazole, 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 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:

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

Diuretics:

- There is an increased mortality in elderly patients with dementia concomitantly receiving furosemide and RISPERDAL CONSTA. (See WARNINGS and SPECIAL PRECAUTIONS)

Gastrointestinal Medicines:

- 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 antipsychotic fraction.

Lithium:

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

SSRIs and Tricyclic Antidepressants:

- Fluoxetine a strong CYP2D6 inhibitor increases the plasma concentration of risperidone but less so of the active anti-psychotic 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 anti-psychotic fraction. However, higher doses of paroxetine may elevate concentrations of risperidone active antipsychotic fraction.
- Tricyclic antidepressants may increase the plasma concentration of risperidone but not those of the active antipsychotic fraction.
- Dosages higher than 100 mg/day of sertraline or fluvoxamine may elevate concentrations of the risperidone active antipsychotic fraction.
- Venlafaxine administered under steady-state conditions at 150 mg/day slightly inhibited the CYP2D6-mediated metabolism of risperidone (administered as a single 1 mg oral dose) to its active metabolite, 9-hydroxyrisperidone, resulting in an approximate 32 % increase in risperidone AUC. However, venlafaxine co-administration did not significantly alter the pharmacokinetic profile of the total active antipsychotic fraction.

HUMAN REPRODUCTION

Pregnancy

The safety of RISPERDAL CONSTA for use in human pregnancy has not been established.

A retrospective observational cohort study based on a US claims database compared the risk of congenital malformations for live

births among women with and without antipsychotic use during the first trimester of pregnancy. The risk of congenital malformations with risperidone, after adjusting for confounder variables available in the database, was elevated compared to no antipsychotic exposure (relative risk = 1,26, 95 % CI: 1,02-1,56). No biological mechanism has been identified to explain these findings and teratogenic effects have not been observed in non-clinical studies. Based on the findings of this single observational study, a causal relationship between *in utero* exposure to risperidone and congenital malformations has not been established.

Although, in experimental animals, risperidone did not show direct reproductive toxicity, some indirect, prolactin- and CNS-mediated effects were observed.

Neonates exposed to antipsychotic medicines (including RISPERDAL CONSTA) during the third trimester of pregnancy are at risk for extrapyramidal and/or withdrawal symptoms that may vary in severity following delivery. These symptoms in the neonates may include agitation, hypertonia, hypotonia, tremor, somnolence, respiratory distress, or feeding disorder.

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

Lactation

In animal studies, risperidone and 9-hydroxy-risperidone are excreted in the milk. It has been demonstrated that risperidone and 9-hydroxy-

risperidone are also excreted in human breast milk. Therefore, women receiving RISPERDAL CONSTA should not breastfeed.

DOSAGE AND DIRECTIONS FOR USE

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

When starting RISPERDAL CONSTA, the patient must receive an oral antipsychotic medicine simultaneously for at least three weeks, as therapeutic concentrations of RISPERDAL CONSTA are only reached after a three week period.

RISPERDAL CONSTA should be administered every two weeks by deep intramuscular deltoid or gluteal injection using the enclosed safety needle. For deltoid administration, use the 2,5 cm needle alternating injections between the two arms. For gluteal administration, use the 5,08 cm needle alternating injections between the two buttocks. Do not administer intravenously (see WARNINGS and SPECIAL PRECAUTIONS and Instructions for use and handling).

Adults (older than 18 years of age)

The recommended dose is 25 mg intramuscular every two weeks.

Some patients may benefit from the higher doses of 37,5 mg or 50 mg.

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.

Sufficient antipychotic coverage should be ensured during the three-week lag period following the first RISPERDAL CONSTA injection.

Doses higher than 50 mg every 2 weeks are not recommended.

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

Paediatric (18 years of age and younger)

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

Elderly (65 years of age and older)

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

Renal and hepatic impairment

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

If hepatically or renally impaired patients require treatment with RISPERDAL CONSTA, a starting dose of 0,5 mg twice daily oral risperidone is recommended during the first week. The second week 1 mg, twice daily or 2 mg once daily can be given. If an oral total daily dose of at least 2 mg is well tolerated, an injection of 25 mg RISPERDAL CONSTA can be administered evry 2 weeks.

Instructions for use and handling

Important information

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

Wait 30 minutes

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

Do not warm any other way.

Use components provided

The components in this dose pack are specifically designed for use with RISPERDAL CONSTA 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.

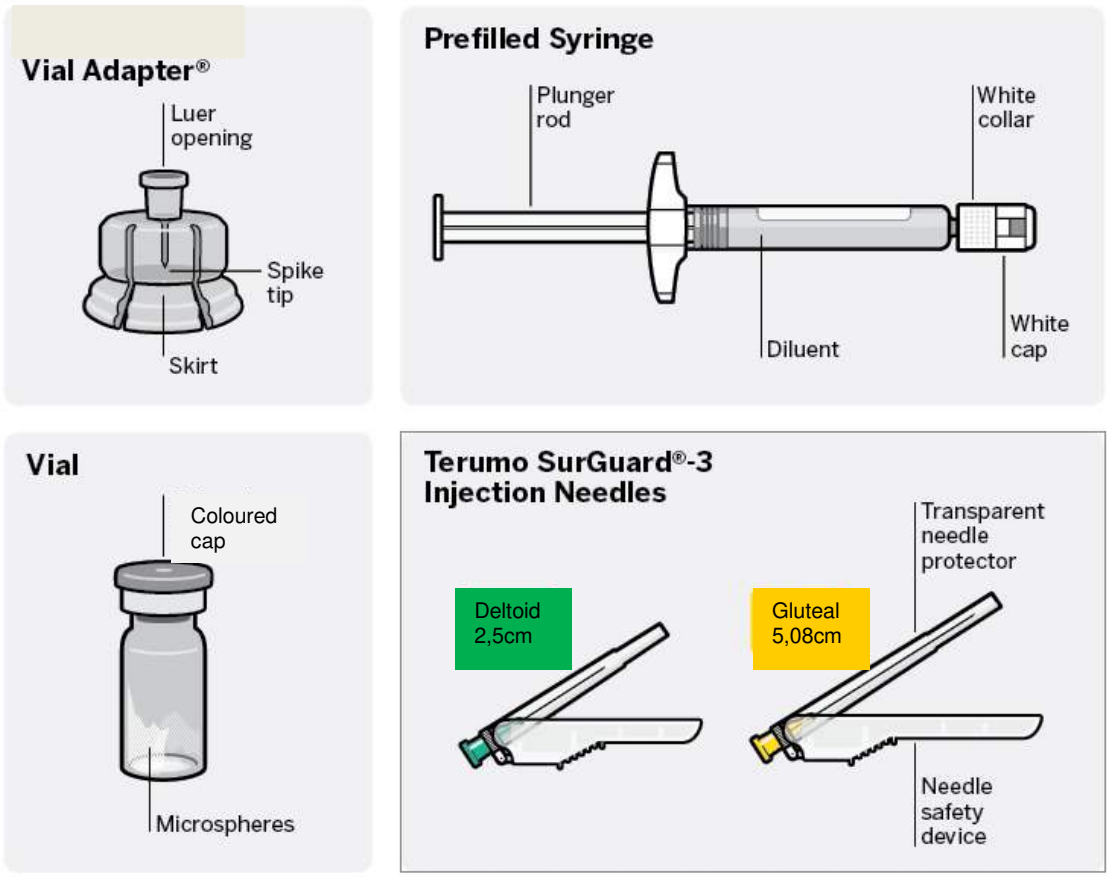
Proper dosing

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.

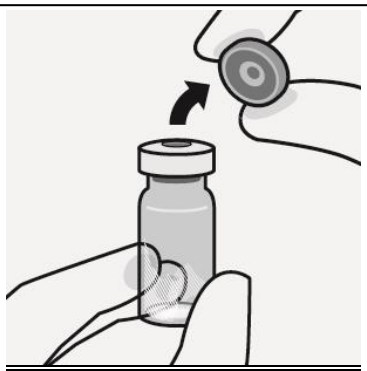
Dose pack contents



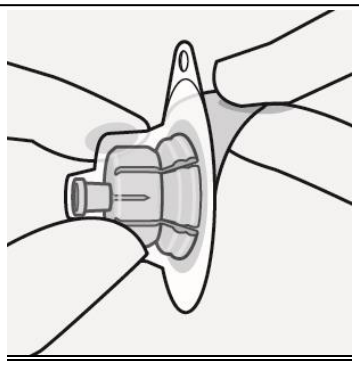
Step 1

Assemble components

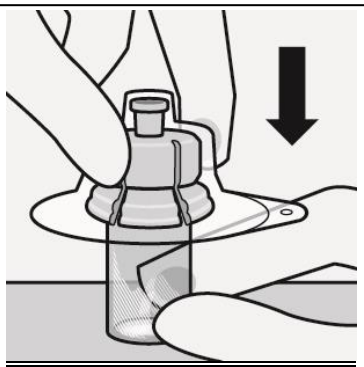
Connect vial adapter to vial



Remove cap from vial
Flip off coloured cap from vial.



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



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

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

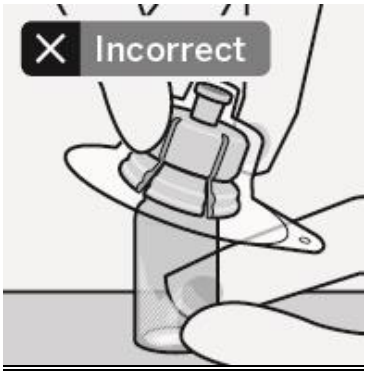
Do not remove grey rubber stopper.

Do not remove vial adapter from blister.

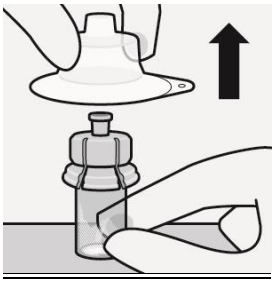
Do not touch spike tip at any time. This will result in contamination.

adapter straight down onto vial top until it snaps securely into place.

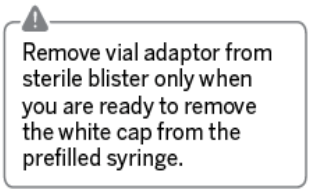
Do not place vial adapter on at an angle or diluent may leak upon transfer to the vial.



Connect prefilled syringe to vial adapter



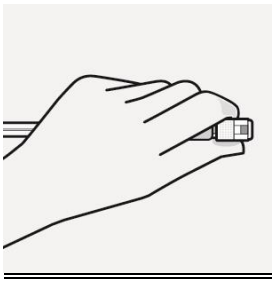
Remove sterile blister



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

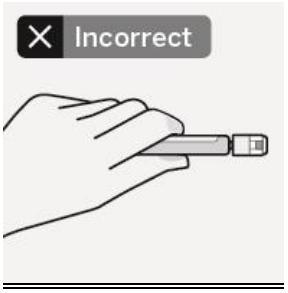
Do not shake.

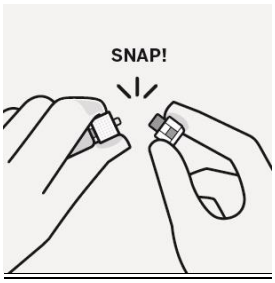
Do not touch exposed luer opening on vial adapter. This will result in contamination.



Use proper grip
Hold by white collar at the tip of the syringe.

Do not hold syringe by the glass barrel during assembly.

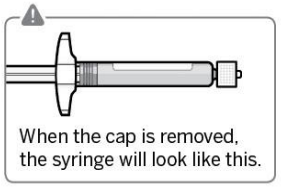




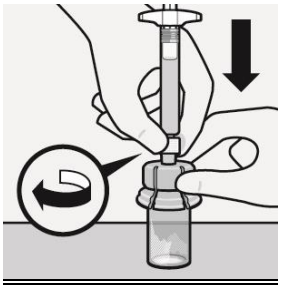
Remove cap
Holding the white collar, snap off the white cap.

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.

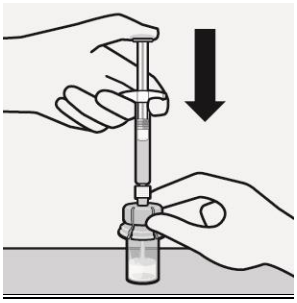
Do not hold the glass syringe barrel. This may cause the white collar to loosen or detach.

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



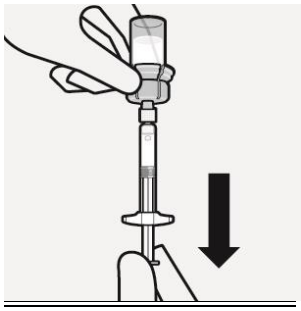
Inject diluent
Inject entire amount of diluent from syringe into the vial.

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

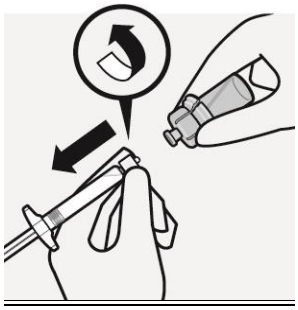
Suspend microspheres in diluent
Continuing to hold down the plunger rod, shake vigorously for at least 10 seconds, as shown.

Check the suspension. When properly mixed, the suspension appears uniform, thick and milky in color. 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.



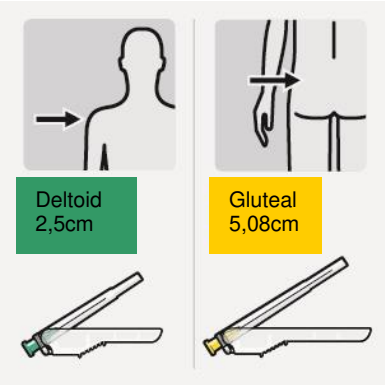
Remove vial adapter
Hold white collar on the syringe and unscrew from vial adapter.

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

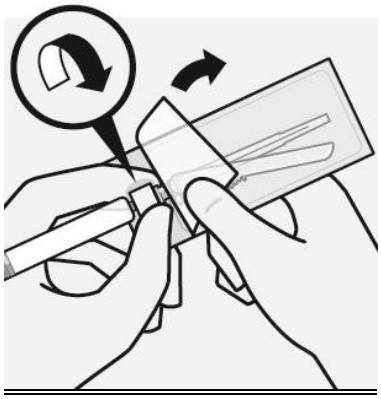
Discard both vial and vial adapter appropriately.

Step 3

Attach needle



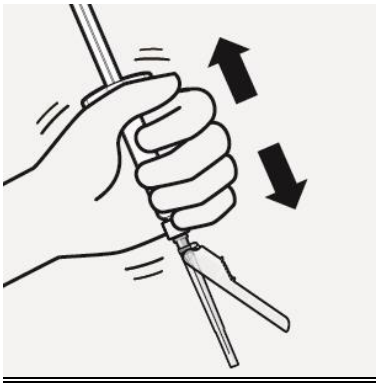
Select appropriate needle
Choose needle based on injection location (gluteal or deltoid).



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.



Resuspend microspheres

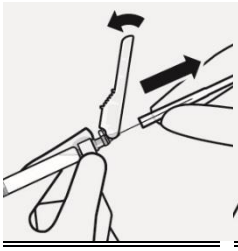
Fully remove the blister pouch.

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

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

Step 4

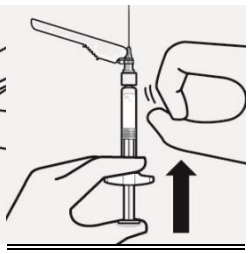
Inject dose



Remove transparent needle protector

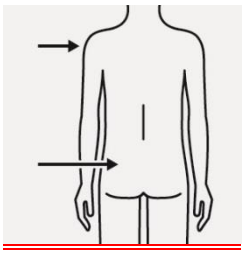
Move the needle safety device back towards the syringe, as shown. Then hold white collar on syringe and carefully pull the transparent needle protector straight off.

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



Remove air bubbles

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

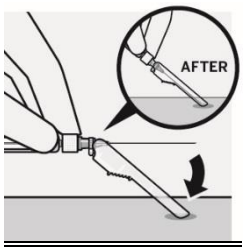


Inject

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

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

Do not administer intravenously.



Secure needle in safety device

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

Avoid needle stick injury:

Do not use two hands.

Do not intentionally disengage or mishandle the needle safety device.

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

Properly dispose of needles

Check to confirm needle safety device is fully engaged. Discard in an approved sharps container.

Also discard the unused needle provided in the dose pack.

SIDE EFFECTS

Clinical trial data

The most frequently reported adverse reactions (ARs) in clinical trials (incidence 1/10) are: Insomnia, anxiety, headache, upper respiratory tract infection, parkinsonism, depression, and akathisia.

The following are all the AR's that were reported in 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) and very rare (< 1/10 000)

Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness.

Investigations

Common:	Abnormal electrocardiogram, increased[a] blood prolactin, increased blood glucose, increased hepatic enzyme, increased transaminases, increased gamma-glutamyltransferase, increased weight, decreased weight.
Uncommon	Prolonged electrocardiogram QT.

Cardiac disorders

Common	Atrioventricular block, tachycardia.
Uncommon	Bundle branch block, bradycardia, sinus bradycardia, palpitations.

Blood and lymphatic system disorders

Common	Anaemia
Uncommon	Neutropaenia

Nervous system disorders

Very common	Parkinsonism[b], akathisia[b], headache.
Common	Dizziness, sedation, somnolence, tremor, dystonia[b], tardive dyskinesia, dyskinesia[b].
Uncommon	Convulsion, syncope, dizziness postural, hypoaesthesia, paraesthesia, lethargy, hypersomnia.

Eye disorders

Common	Blurred vision, conjunctivitis.

Ear and labyrinth disorders

Common	Vertigo.
Uncommon	Ear pain.

Respiratory, thoracic and mediastinal disorders

Common	Dyspnoea, cough, nasal congestion, pharyngolaryngeal pain.

Gastrointestinal disorders

Common	Vomiting, diarrhoea, constipation, nausea, abdominal pain, dyspepsia, toothache, dry mouth, stomach discomfort, gastritis.

Renal and urinary disorders

Common	Urinary incontinence.
Uncommon	Urinary retention.

Skin and subcutaneous tissue disorders

Common	Rash, eczema.
Uncommon	Pruritus, acne, dry skin.

Musculoskeletal and connective tissue disorders

Common	Arthralgia, back pain, pain in extremity, myalgia.
Uncommon	Muscular weakness, neck pain, buttock pain, musculoskeletal chest pain.

Metabolism and nutrition disorders

Common	Hyperglycaemia.
Uncommon	Increased appetite, decreased appetite.

Infections and infestations

Very common	Upper respiratory tract infection.
Common	Pneumonia, influenza, lower respiratory tract infection, bronchitis, urinary tract infection, ear infection, sinusitis, viral infection, rhinitus, pharyngitis.
Uncommon	Cystitis, gastroenteritis, infection, localised infection, subcutaneous abscess.

Injury, poisoning and procedural complications

Common	Fall
Uncommon	Injection site pain.

Vascular disorders

Common	Hypertension, hypotension.
Uncommon	Orthostatic hypotension.

General disorders and administration site conditions

Common	Pyrexia, peripheral oedema, chest pain, fatigue, pain, injection site pain, asthenia, influenza-like illness, malaise.
Uncommon	Injection site induration, induration, chest discomfort, sluggishness, feeling abnormal.

Immune system disorders

Uncommon	Hypersensitivity.

Reproductive system and breast disorders

Common	Amenorrhoea, erectile dysfunction, galactorrhoea, oligomenorrhea, breast discomfort, ejaculation disorder.
Uncommon	Sexual dysfunction, gynaecomastia.

Psychiatric disorders

Very common	Depression, insomnia, anxiety.
Common	Agitation, sleep disorder.
Uncommon	Decreased libido, nervousness.

a) Hyperprolactinaemia can in some cases lead to gynaecomastia, menstrual disturbances, amenorrhoea, and galactorrhea.

b) 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), akathisia (akathisia, restlessness,

hyperkinesia, and restless leg syndrome), tremor, dyskinesia (dyskinesia, muscle twitching, choreoathetosis, athetosis, and myoclonus), dystonia. Dystonia includes dystonia, muscle spasms, hypertonia, torticollis, muscle contractions involuntary, muscle contracture, blepharospasm, oculogyration, tongue paralysis, facial spasm, laryngospasm, myotonia, opisthotonus, oropharyngeal spasm, pleurothotonus, tongue spasm, and trismus. Tremor includes tremor and Parkinsonian rest tremor. It should be noted that a broader spectrum of symptoms are included, that do not necessarily have an extrapyramidal origin.

Postmarketing Data

Adverse events first identified as adverse reactions during postmarketing experience with RISPERDAL CONSTA.

Blood and Lymphatic Disorders

Agranulocytosis, thrombocytopaenia.

Endocrine Disorders

Inappropriate antidiuretic hormone secretion.

Metabolism and Nutrition Disorders

Diabetic ketoacidosis, diabetes mellitus, hypoglycaemia, water intoxication, increased blood cholesterol, increased blood triglycerides.

Psychiatric Disorders

Catatonia, Mania,

Sleep-related eating disorder, somnabulism.

Nervous System Disorders

Dysgeusia.

Eye Disorders

Retinal artery occlusion[a].

Floppy iris syndrome (intraoperative)

Cardiac Disorders

Atrial fibrillation.

Vascular Disorders

Deep vein thrombosis, pulmonary embolism.

Respiratory, Thoracic, and Mediastinal Disorders

Sleep apnoea syndrome.

Gastrointestinal Disorders

Pancreatitis.

Paralytic Ileus

Hepatobiliary Disorders

Jaundice.

Skin and Subcutaneous Tissue Disorders

Angioedema, alopecia.

Renal and Urinary Disorders

Urinary retention.

Pregnancy, Puerperium and Perinatal Conditions

Neonatal drug withdrawal syndrome.

Reproductive System and Breast Disorders

Priapism.

General Disorders

Hypothermia, injection site abscess, injection site cellulites, injection site cyst, injection site haematoma, injection site necrosis, injection site ulcer.

[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)

Hypersensitivity

Cases of anaphylactic reaction after injection with RISPERDAL CONSTA have been reported during postmarketing experience in patients who have previously tolerated oral risperidone.

KNOWN SYMPTOMS OF OVERDOSAGE AND PARTICULARS OF ITS TREATMENT

Symptoms*:*

Reported signs and symptoms have been those resulting from an exaggeration of the medicines known pharmacological effects.
Symptoms of acute overdosage include drowsiness, sedation, hypotension, tachycardia and extrapyramidal symptoms. In overdose, QT-prolongation and convulsions have been reported. Torsades de pointes has been reported in association with combined overdose of oral RISPERDAL and paroxetine. In the case of acute overdosage, the possibility of multiple medicine 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 dysrhythmias.
Since there is, no known antidote if accidental poisoning or overdosage is suspected, 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.

IDENTIFICATION

Clear, colourless, glass vial with a grey rubber stopper, tightly crimped, coloured flip-off cap* containing a white, free flowing powder, free from visible foreign material, suspending readily without clumping or visible foreign material.

* The colour of the flip-off cap is verified- the colour varies by dosage strengths as follows:

Pink: 25 mg risperidone per vial

Green: 37,5 mg risperidone per vial

Blue: 50 mg risperidone per vial

Pre-filled syringe of diluent for reconstitution.

Clear, colourless, aqueous solution free from visible foreign materials.

PRESENTATION

- One 5 mℓ vial containing RISPERDAL CONSTA extended release microspheres, powder for suspension for injection.

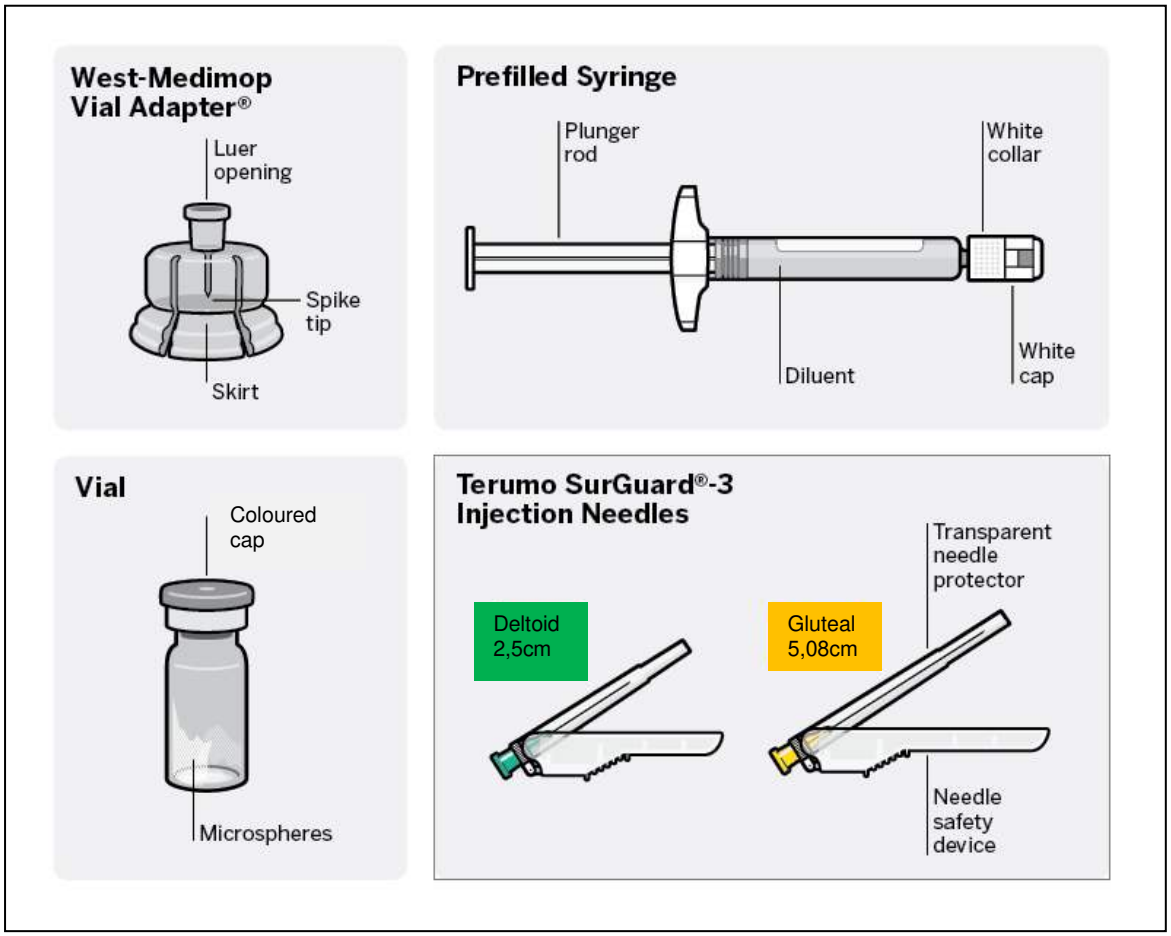
- One 3 mℓ prefilled syringe containing 2 mℓ diluent for RISPERDAL CONSTA.

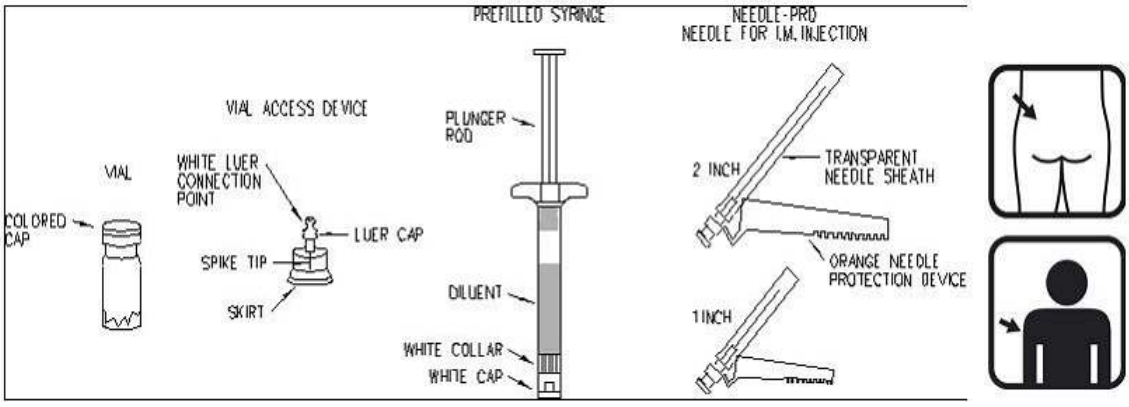
- One Vial Adapter for reconstitution (referred as Vial Adapter).

- Two Terumo SurGuard® 3 Needles for intramuscular injection (a 21G UTW 2,5 cm safety needle with needle protection device for deltoid aministration and a 20G TW 5,08 cm safety needle with Needle-Pro safety device for gluteal administration).

("Rx- only"=device to be sold with prescription medicines only).

Dose pack contents





STORAGE INSTRUCTIONS

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

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

KEEP OUT OF REACH OF CHILDREN.

REGISTRATION NUMBER

RISPERDAL CONSTA 25, 37,5 & 50 mg: 37/2.6.5/0142 – 4

Nam. Reg. No.:
RISPERDAL CONSTA 25, 37,5 & 50 mg:
06/2.6.5/0023/4/5
NS 3

NAME AND BUSINESS ADDRESS OF THE HOLDER OF THE CERTIFICATE OF REGISTRATION

JANSSEN PHARMACEUTICA (PTY) LTD

(Reg. No.: 1980/011122/07)

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RA-JACZA-MedInfo@its.jnj.com

DATE OF PUBLICATION OF THE PROFESSIONAL INFORMATION INSERT

- The date on the registration certificate of the medicine: 29 July 2005

- The date of the most recently revised professional information insert as approved by Advisory Clinical Committee: 02 May 2019