Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

RISPERDAL CONSTA 37.5 mg powder and solvent for prolonged-release suspension for intramuscular injection

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

1 vial contains 37.5 mg risperidone.
1 ml reconstituted suspension contains 18.75 mg of risperidone.
Excipient: 1 ml reconstituted suspension contains 3 mg sodium.
For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Powder and solvent for prolonged-release suspension for injection.

Vial with p*owder.*
White to off-white free flowing powder.

Pre-filled syringe of solvent for reconstitution.
Clear, colourless aqueous solution.

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

RISPERDAL CONSTA is indicated for the maintenance treatment of schizophrenia in patients currently stabilised with oral antipsychotics.

4.2 Posology and method of administration

Adults

Starting dose:
For most patients the recommended dose is 25 mg intramuscular every two weeks. For those patients on a fixed dose of oral risperidone for two weeks or more, the following conversion scheme should be considered. Patients treated with a dosage of 4 mg or less oral risperidone should receive 25 mg RISPERDAL CONSTA, while patients treated with higher oral doses should be considered for the higher RISPERDAL CONSTA dose of 37.5 mg.

Where patients are not currently taking oral risperidone, the oral pre-treatment dosage should be considered when choosing the i.m. starting dose. The recommended starting dose is 25 mg RISPERDAL CONSTA every two weeks. Patients on higher dosages of the used oral antipsychotic should be considered for the higher RISPERDAL CONSTA dose of 37.5 mg.

Sufficient antipsychotic coverage with oral risperidone or the previous antipsychotic should be ensured during the three-week lag period following the first RISPERDAL CONSTA injection (see section 5.2).

RISPERDAL CONSTA should not be used in acute exacerbations of schizophrenia without ensuring sufficient antipsychotic coverage with oral risperidone or the previous antipsychotic during the three-week lag period following the first RISPERDAL CONSTA injection.

Maintenance dose:
For most patients 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. 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. No additional benefit was observed with 75 mg in clinical trials. Doses higher than 50 mg every 2 weeks are not recommended.

Elderly

No dose adjustment is required. The recommended dose is 25 mg intramuscularly every two weeks. Where patients are not currently taking oral risperidone, the recommended dose is 25 mg RISPERDAL CONSTA every two weeks. For those patients on a fixed dose of oral risperidone for two weeks or more, the following conversion scheme should be considered. Patients treated with a dosage of 4 mg or less oral risperidone should receive 25 mg RISPERDAL CONSTA, while patients treated with higher oral doses should be considered for the higher RISPERDAL CONSTA dose of 37.5 mg.

Sufficient antipsychotic coverage should be ensured during the three-week lag period following the first RISPERDAL CONSTA injection (see section 5.2). RISPERDAL CONSTA clinical data in elderly are limited. RISPERDAL CONSTA should be used with caution in elderly.

Hepatic and renal 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 every 2 weeks.

Sufficient antipsychotic coverage should be ensured during the three-week lag period following the first RISPERDAL CONSTA injection (see section 5.2).

Paediatric population

RISPERDAL CONSTA is not recommended for use in children below 18 years of age due to a lack of data on safety and efficacy.

Method of administration

RISPERDAL CONSTA should be administered every two weeks by deep intramuscular deltoid or gluteal injection using the appropriate safety needle. For deltoid administration, use the 1-inch needle alternating injections between the two arms. For gluteal administration, use the 2-inch needle alternating injections between the two buttocks. Do not administer intravenously (see section 4.4 and section 6.6).

For instructions on preparation and handling RISPERDAL CONSTA, see section 6.6.

4.3 Contraindications

Hypersensitivity to the active substance or to any of the 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 RISPERDAL CONSTA (see section 4.2).

Elderly patients with dementia

RISPERDAL CONSTA has not been studied in elderly patients with dementia, hence it is not indicated for use in this group of patients. RISPERDAL CONSTA is not licensed for the treatment of dementia-related behavioural disturbances.

Increased Mortality in Elderly People with Dementia

In a meta-analysis of 17 controlled trials of atypical antipsychotic drugs, including RISPERDAL,elderly patients with dementia treated with atypical antipsychotics have an increased mortality compared to placebo. In placebo-controlled trials with oral RISPERDAL in this population, the incidence of mortality was 4.0% for RISPERDAL-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 drug as opposed to some characteristic(s) of the patients is not clear.

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. 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 events (CVAE)

An approximately 3-fold increased risk of cerebrovascular adverse events 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 RISPERDAL in mainly elderly patients (>65 years of age) with dementia showed that CVAEs (serious and non-serious, combined) occurred in 3.3% (33/1009) 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. RISPERDAL CONSTA 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, especially during initiation of treatment. Clinically significant hypotension has been observed postmarketing with concomitant use of risperidone and antihypertensive treatment.

Risperidone should be used with caution in patients with known cardiovascular disease (e.g. heart failure, myocardial infarction, conduction abnormalities, dehydration, hypovolemia, or cerebrovascular disease). The risk/benefit of further treatment with RISPERDAL CONSTA should be assessed if clinically relevant orthostatic hypotension persists.

Tardive dyskinesia/extrapyramidal symptoms (TD/EPS)

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

Neuroleptic malignant syndrome (NMS)

Neuroleptic Malignant Syndrome, 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 antipsychotics, including RISPERDAL CONSTA, should be discontinued.

Parkinson's disease and dementia with Lewy bodies

Physicians should weigh the risks versus the benefits when prescribing antipsychotics, including RISPERDAL CONSTA, 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 RISPERDAL CONSTA. 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. Patient treated with any atypical antipsychotic, including RISPERDAL CONSTA, 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 RISPERDAL CONSTA use. Weight should be monitored regularly.

Hyperprolactinaemia

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. RISPERDAL CONSTA 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 postmarketing. As with other antipsychotics, 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

RISPERDAL CONSTA 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 RISPERDAL CONSTA 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 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 treatment with anticholinergic activity, or being subject to dehydration.

Venous thromboembolism

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

Renal or hepatic impairment

Although oral risperidone has been studied, RISPERDAL CONSTA has not been studied in patients with renal or liver insufficiency. RISPERDAL CONSTA should be administered with caution in this group of patients (see section 4.2).

Administration

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

Excipients

This medicinal product contains less than 1 mmol sodium (23 mg) per dose, i.e., essentially 'sodium-free'.

4.5 Interaction with other medicinal products and other forms of interaction

Interaction studies were performed with oral RISPERDAL.

As with other antipsychotics, caution is advised when prescribing risperidone with medicinal products known to prolong the QT interval, e.g., class Ia antiarrhythmics (e.g., quinidine, dysopiramide, procainamide), class III antiarrhythmics (e.g., amiodarone, sotalol), tricyclic antidepressants (i.e., amitriptyline), tetracyclic antidepressant (i.e., maprotiline), some antihistaminics, other antipsychotics, some antimalarials (i.e., chinice 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.

Potential for RISPERDAL CONSTA to affect other medicinal products

Risperidone 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.

RISPERDAL CONSTA 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.

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

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

Potential for other medicinal products to affect RISPERDAL CONSTA

Carbamazepine has been shown to decrease the plasma concentrations of the active antipsychotic fraction of risperidone. Similar effects may be observed with e.g. rifampicin, phenytoin and phenobarbital which also induce CYP 3A4 hepatic enzyme as well as P-glycoprotein. When carbamazepine or other CYP 3A4 hepatic enzyme/P−glycoprotein (P-gp) inducers are initiated or discontinued, the physician should re-evaluate the dosing of RISPERDAL CONSTA.

Fluoxetine and paroxetine, CYP 2D6 inhibitors, increase the plasma concentration of risperidone, but less so of the active antipsychotic fraction. It is expected that other CYP 2D6 inhibitors, such as quinidine, may affect the plasma concentrations of risperidone in a similar way. When concomitant fluoxetine or paroxetine is initiated or discontinued, the physician should re-evaluate the dosing of RISPERDAL CONSTA.

Verapamil, an inhibitor of CYP 3A4 and P-gp, increases the plasma concentration of risperidone.
Galantamine and donepezil do not show a clinically relevant effect on the pharmacokinetics of risperidone and on the active antipsychotic fraction.

Phenothiazines, tricyclic antidepressants, and some beta-blockers may increase the plasma concentrations of risperidone but not those of the active antipsychotic fraction. Amitriptyline does not affect the pharmacokinetics of risperidone or the active antipsychotic fraction. Cimetidine and ranitidine increase the bioavailability of risperidone, but only marginally that of the active antipsychotic fraction. Erythromycin, a CYP 3A4 inhibitor, does not change the pharmacokinetics of risperidone and the active antipsychotic fraction.

See section 4.4 regarding increased mortality in elderly patients with dementia concomitantly receiving furosemide

4.6 Fertility, pregnancy and lactation

Pregnancy
There are no adequate data from the use of risperidone in pregnant women.
Risperidone was not teratogenic in animal studies but other types of reproductive toxicity were seen (see section 5.3). The potential risk for humans is unknown.

Neonates exposed to antipsychotics (including risperidone) during the third trimester of pregnancy are at risk of adverse reactions including extrapyramidal and/or withdrawal symptoms that may vary in severity and duration following delivery. There have been reports of agitation, hypertonia, hypotonia, tremor, somnolence, respiratory distress, or feeding disorder. Consequently, newborns should be monitored carefully.

RISPERDAL CONSTA should not be used during pregnancy unless clearly necessary.

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 in small quantities. There are no data available on adverse effects in breast-feeding infants. Therefore, the advantage of breast-feeding should be weighed against the potential risks for the child.

4.7 Effects on ability to drive and use machines

RISPERDAL CONSTA has minor or moderate influence on the ability to drive and use machines due to potential nervous system and visual effects (see section 4.8). Therefore, patients should be advised not to drive or operate machinery until their individual susceptibility is known.

4.8 Undesirable effects

The most frequently reported adverse drug reactions (ADRs) (incidence _ 1/10) are: Insomnia, anxiety, headache, upper respiratory tract infection, parkinsonism, depression, and akathisia.

Serious injection site reactions including injection site necrosis, abscess, cellulitis, ulcer, haematoma, cyst, and nodule were reported postmarketing. The frequency is considered not known (cannot be estimated from the available data). Isolated cases required surgical intervention.

The following are all the ADRs that were reported in clinical trials and postmarketing. The following terms and frequencies are applied: very common (≥1/10), common (≥1/100 to <1/10), uncommon (≥1/1000 to <1/100), rare (≥1/10,000 to <1/1,000), very rare (<1/10,000), and not known (cannot be estimated from the available clinical trial data).

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

Adverse Drug Reactions by System Organ Class and Frequency Category

Investigations	
Common	Electrocardiogram abnormal, Blood prolactin increased[a], Hepatic enzyme increased, Transaminases increased, Gamma-glutamyltransferase increased, Weight increased, Weight decreased
Uncommon	Electrocardiogram QT prolonged
Cardiac disorders	
Common	Atrioventricular block, Tachycardia
Uncommon	Bundle branch block, Atrial fibrillation, Bradycardia, Sinus bradycardia, Palpitations
Blood and lymphatic system disorders	
Common	Anaemia
Uncommon	Thrombocytopenia, Neutropenia
Not known	Agranulocytosis
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, Dysgeusia
Eye disorders	
Common	Vision blurred, Conjunctivitis
Not known	Retinal artery occlusion
Ear and labyrinth disorders	
Common	Vertigo
Uncommon	Ear pain
Respiratory, thoracic and mediastinal disorders	
Common	Dyspnoea, Cough, Nasal congestion, Pharyngolaryngeal pain
Rare	Sleep apnea syndrome
Gastrointestinal disorders	
Common	Vomiting, Diarrhoea, Constipation, Nausea, Abdominal pain, Dyspepsia, Toothache, Dry mouth, Stomach discomfort, Gastritis
Rare	Intestinal obstruction, Pancreatitis
Renal and urinary disorders	
Common	Urinary incontinence
Uncommon	Urinary retention
Skin and subcutaneous tissue disorders	
Common	Rash, Eczema
Uncommon	Angioedema, Pruritus, Acne, Alopecia, 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
Endocrine disorders	
Rare	Inappropriate antidiuretic hormone secretion
Metabolism and nutrition disorders	
Common	Hyperglycaemia
Uncommon	Diabetes mellitus[c], Increased appetite, Decreased appetite, Blood cholesterol increased, Blood triglycerides increased
Rare	Hypoglycaemia
Very rare	Diabetic ketoacidosis
Not known	Water intoxication
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
Uncommon	Cystitis, Gastroenteritis, Infection, Localised infection, Subcutaneous abscess
Injury, poisoning and procedural complications	
Common	Fall
Uncommon	Procedural 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
Uncommon	Injection site induration, Induration, Injection site reaction, Chest discomfort, Sluggishness, Feeling abnormal
Rare	Hypothermia
Immune system disorders	
Uncommon	Hypersensitivity
Not known	Anaphylactic reaction
Hepatobiliary disorders	
Rare	Jaundice
Pregnancy, puerperium and perinatal conditions.	
Not known	Drug withdrawal syndrome neonatal (see 4.6)
Reproductive system and breast disorders	
Common	Amenorrhoea, Erectile dysfunction, Galactorrhoea
Uncommon	Sexual dysfunction, Gynaecomastia
Not known	Priapism
Psychiatric disorders	
Very common	Depression, Insomnia, Anxiety
Common	Agitation, Sleep disorder
Uncommon	Mania, Libido decreased, Nervousness

[a] Hyperprolactinemia can in some cases lead to gynaecomastia, menstrual disturbances, amenorrhoea, 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.

[c]In placebo-controlled trials diabetes mellitus was reported in 0.18% in risperidonetreated 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.

The following is a list of additional ADRs associated with risperidone that have been identified as ADRs during clinical trials investigating the oral risperidone formulation (RISPERDAL) but were not determined to be ADRs in the clinical trials investigating RISPERDAL CONSTA.

Additional Adverse Drug Reactions Reported With Oral RISPERDAL but not With RISPERDAL CONSTA by System Organ Class

Investigations
Body temperature increased, Eosinophil count increased, White blood cell count decreased, Haemoglobin decreased, Blood creatine phosphokinase increased, Body temperature decreased

Infections and Infestations
Tonsillitis, Cellulitis, Otitis media, Eye infection, Acarodermatitis, Respiratory tract infection, Onychomycosis, Otitis media chronic

Blood and Lymphatic Disorders
Granulocytopenia

Immune System Disorders
Drug hypersensitivity

Metabolism and Nutrition Disorders
Anorexia, Polydipsia

Psychiatric Disorders
Confusional state, Listless, Anorgasmia, Blunted affect

Nervous System Disorders
Unresponsive to stimuli, Loss of consciousness, Neuroleptic malignant syndrome, Diabetic coma, Cerebrovascular accident, Depressed level of consciousness, Cerebral ischemia, Cerebrovascular disorder, Transient ischemic attack, Dysarthria, Disturbance in attention, Balance disorder, Speech disorder, Coordination abnormal, Movement disorder, Head titubation

Eye Disorders
Ocular hyperemia, Eye discharge, Eye swelling, Dry eye, Lacrimation increased, Photophobia, Visual acuity reduced, Eye rolling, Glaucoma

Ear and Labyrinth Disorders
Tinnitus

Vascular Disorders
Flushing

Respiratory, Thoracic, and Mediastinal Disorders
Wheezing, Pneumonia aspiration, Pulmonary congestion, Respiratory disorder, Rales, Epistaxis, Respiratory tract congestion, Hyperventilation, Dysphonia

Gastrointestinal Disorders
Dysphagia, Faecal incontinence, Faecaloma, Lip swelling, Cheilitis

Skin and Subcutaneous Tissue Disorders
Skin lesion, Skin disorder, Skin discoloration, Seborrheic dermatitis, Hyperkeratosis, Dandruff, Erythema

Musculoskeletal, Connective Tissue, and Bone Disorders
Rhabdomyolysis, Joint swelling, Posture abnormal, Joint stiffness

Renal and Urinary Disorders
Enuresis, Dysuria, Pollakiuria

Reproductive System and Breast Disorders
Ejaculation disorder, Vaginal discharge, Menstrual disorder

General Disorders and Administration Site Conditions
Generalised oedema, Face oedema, Gait disturbance, Thirst, Chills, Peripheral coldness, Drug withdrawal syndrome

Class effects
As with other antipsychotics, very rare cases of QT prolongation have been reported postmarketing with risperidone. Other class-related cardiac effects reported with antipsychotics which prolong QT interval include ventricular arrhythmia, ventricular fibrillation, ventricular tachycardia, sudden death, cardiac arrest and Torsades de Pointes.

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).

Weight gain
In the 12-week double-blind, placebo-controlled trial, 9% of patients treated with RISPERDAL CONSTA, compared with 6% of patients treated with placebo, experienced a weight gain of ≥7% of body weight at endpoint. In the 1-year, open-label study of RISPERDAL CONSTA, changes in body weight in individual patients were generally within ±7% from baseline; 25% of patients had an increase in body weight of ≥7%.

4.9 Overdose

While overdose is less likely to occur with parenteral than with oral medicinal products, information pertaining to oral is presented.

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 oral RISPERDAL and paroxetine.

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

Treatment

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

There is no specific antidote to RISPERDAL. Therefore appropriate supportive measures should be instituted. Hypotension and circulatory collapse should be treated with appropriate measures such as intravenous fluids and/or

sympathomimetic agents. In case of severe extrapyramidal symptoms, anticholinergic medicinal product should be administered. Close medical supervision and monitoring should continue until the patient recovers.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Other antipsychotics, ATC code: N05AX08

Mechanism of action

Risperidone is a selective monoaminergic antagonist with unique properties. It has a high affinity for serotoninergic 5-HT2 and dopaminergic D2 receptors.

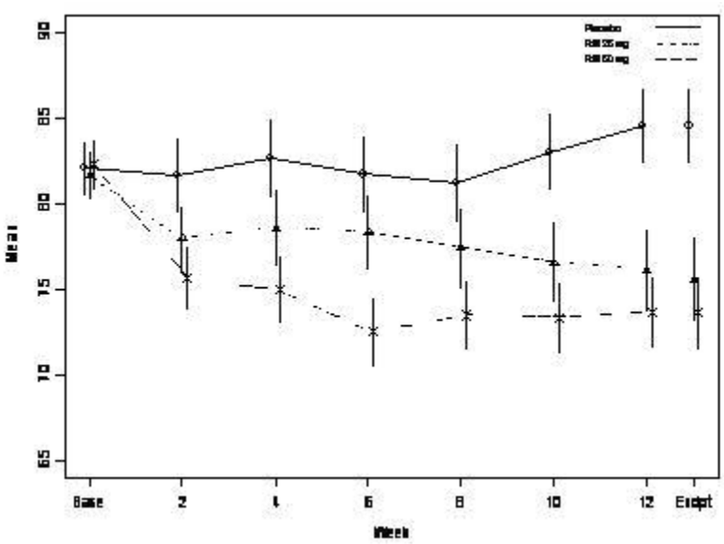
Risperidone binds also to alpha$_1$-adrenergic receptors, and, with lower affinity, to H1-histaminergic and alpha2-adrenergic receptors. Risperidone has no affinity for cholinergic receptors. Although risperidone is a potent D2 antagonist, that is considered to improve the positive symptoms of schizophrenia, it causes less depression of motor activity and induction of catalepsy than classical antipsychotics. 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.

Clinical efficacy

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

In a 12-week comparative trial in stable patients with schizophrenia, RISPERDAL CONSTA was shown to be as effective as the oral tablet formulation. The long−term (50 weeks) safety and efficacy of RISPERDAL CONSTA was also evaluated in an open−label trial of stable psychotic inpatients and outpatients who met the DSM−IV criteria for schizophrenia or schizoaffective disorder. Over time efficacy was maintained with RISPERDAL CONSTA (Figure 1).

Figure 1. Mean in total PANSS score over time (LOCF) in patients with schizophrenia.



5.2 Pharmacokinetic properties

Absorption

The absorption of risperidone from RISPERDAL CONSTA is complete.

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. 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 section 4.2).

The combination of the release profile and the dosage regimen (intramuscular injection every two weeks) results in sustained therapeutic plasma concentrations. Therapeutic plasma concentrations remain until 4 to 6 weeks after the last RISPERDAL CONSTA injection.

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.

No accumulation of risperidone was observed during long term use (12 months) in patients who were injected with 25–50 mg every two weeks.

The above studies were conducted with gluteal intramuscular injection. Deltoid and gluteal intramuscular injections at the same doses are bioequivalent and therefore interchangeable.

Distribution

Risperidone is rapidly distributed. The volume of distribution is 1-2 l/kg. In plasma, risperidone is bound to albumin and $alpha_1$-acid glycoprotein. The plasma protein binding of risperidone is 90%; that of the active metabolite 9−hydroxy-risperidone is 77%.

Biotransformation and elimination

Risperidone is metabolised by CYP 2D6 to 9-hydroxy-risperidone, which has a similar pharmacological activity as risperidone. Risperidone plus 9−hydroxy−risperidone form the active antipsychotic fraction. CYP 2D6 is subject to genetic polymorphism. Extensive CYP 2D6 metabolisers convert risperidone rapidly into 9-hydroxy-risperidone, whereas poor CYP 2D6 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 antipsychotic fraction), after single and multiple doses, are similar in extensive and poor metabolisers of CYP 2D6.

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 CYP 1A2, CYP 2A6, CYP 2C8/9/10, CYP 2D6, CYP 2E1, CYP 3A4, and CYP 3A5. One week after oral risperidone administration, 70% of the dose is excreted in the urine and 14% in the faeces. In urine, risperidone plus 9-hydroxy-risperidone represent 35-45% of the orally administered dose. The remainder is inactive metabolites. The elimination phase is complete approximately 7 to 8 weeks after the last RISPERDAL CONSTA injection.

Linearity

The pharmacokinetics of risperidone are linear in the dose range of 25-50 mg injected every 2 weeks.

Elderly, hepatic and renal impairment

A single-dose pharmacokinetic study with oral risperidone showed on average a 43% higher active antipsychotic fraction plasma concentrations, a 38% longer half-life and a reduced clearance of the active antipsychotic fraction by 30% in the elderly. Higher active antipsychotic fraction plasma concentrations and a reduced clearance of the active antipsychotic fraction by on average 60% were observed in patients with renal insufficiency. Risperidone plasma concentrations were normal in patients with liver insufficiency, but the mean free fraction of risperidone in plasma was increased by about 35%.

Pharmacokinetic/pharmacodynamic relationship

There was no relationship between the plasma concentrations of the active antipsychotic fraction and the change in total PANSS (Positive And Negative Syndrome Scale) and total ESRS (Extrapyramidal Symptom Rating Scale) scores across the assessment visits in any of the phase-III trials where efficacy and safety was examined.

Gender, race and smoking habits

A population pharmacokinetic analysis revealed no apparent effect of gender, race or smoking habits on the pharmacokinetics of risperidone or the active antipsychotic fraction.

5.3 Preclinical safety data

Similar to the (sub)chronic toxicity studies with oral risperidone in rats and dogs, the major effects of treatment with RISPERDAL CONSTA (up to 12 months of intramuscular administration) were prolactin-mediated mammary gland stimulation, male and female genital tract changes, and central nervous system (CNS) effects, related to the pharmacodynamic activity of risperidone. In a toxicity study in juvenile rats treated with oral risperidone, increased pup mortality and a delay in physical development was observed. In a 40-week study with juvenile dogs treated with oral risperidone, sexual maturation was delayed. Based on AUC, long bone growth was not affected in dogs at 3.6-times the maximum human oral exposure in adolescents (1.5mg/day); while effects on long bones and sexual maturation were observed at 15 times the maximum human oral exposure in adolescents.

Risperidone was not teratogenic in rat and rabbit. In rat reproduction studies with risperidone, adverse effects were seen on mating behaviour of the parents, and on birth weight and survival of the offspring.

In rats, intrauterine exposure to risperidone was associated with cognitive deficits in adulthood. Other dopamine antagonists, when administered to pregnant animals, have caused negative effects on learning and motor development in the offspring.

RISPERDAL CONSTA administration to male and female rats for 12 and 24 months produced osteodystrophy at a dose of 40 mg/kg/2 weeks. The effect dose for osteodystrophy in rats was on a mg/m^2 basis 8 times the maximum recommended human dose and is associated with a plasma exposure 2 times the maximum anticipated exposure in humans at the maximum recommended dose. No osteodystrophy was observed in dogs treated for 12 months with RISPERDAL CONSTA up to 20 mg/kg/2 weeks. This dose yielded plasma exposures up to 14 times the maximum recommended human dose.

There was no evidence of genotoxic potential.

As expected for a potent dopamine D2-antagonist, in oral carcinogenicity studies of risperidone in rats and mice, increases in pituitary gland adenomas (mouse), endocrine pancreas adenomas (rat), and mammary gland adenomas (both species) were seen.

In an intramuscular carcinogenicity study with RISPERDAL CONSTA in Wistar (Hannover) rats (doses of 5 and 40 mg/kg/2 weeks), increased incidences of endocrine pancreas, pituitary gland, and adrenal medullary tumours were observed at 40 mg/kg, while mammary gland tumours were present at 5 and 40 mg/kg. These tumours observed upon oral and intramuscular dosing can be related to prolonged dopamine D_2 antagonism and hyperprolactinaemia. Tissue

culture studies suggest that cell growth in human breast tumours may be stimulated by prolactin. Hypercalcemia, postulated to contribute to an increased incidence of adrenal medullary tumours in RISPERDAL CONSTA-treated rats, was observed in both dose groups. There is no evidence to suggest that hypercalcemia might cause phaeochromocytomas in humans.

Renal tubular adenomas occurred in male rats treated with RISPERDAL CONSTA at 40 mg/kg/2 weeks. No renal tumours occurred in the low dose, the NaCl 0.9%, or the microspheres vehicle control group. The mechanism underlying the renal tumours in RISPERDAL CONSTA-treated male Wistar (Hannover) rats is unknown. A treatment-related increase in renal tumour incidence did not occur in the oral carcinogenicity studies with Wistar (Wiga) rats or in Swiss mice administered oral risperidone. Studies conducted to explore the substrain differences in the tumour organ profile suggest that the Wistar (Hannover) substrain employed in the carcinogenicity study differs substantially from the Wistar (Wiga) substrain employed in the oral carcinogenicity study with respect to spontaneous age-related non-neoplastic renal changes, serum prolactin increases, and renal changes in response to risperidone. There are no data suggesting kidney-related changes in dogs treated chronically with RISPERDAL CONSTA.

The relevance of the osteodystrophy, the prolactin-mediated tumours and of the presumed rat substrain-specific renal tumours in terms of human risk is unknown.

Local irritation at the injection site in dogs and rats was observed after administration of high doses of RISPERDAL CONSTA. In a 24-month intramuscular carcinogenicity study in rats, no increased incidence of injection site tumours was seen in either the vehicle or active groups.

In vitro and in vivo, animal models show that at high doses risperidone may cause QT interval prolongation, which has been associated with a theoretically increased risk of torsade de pointes in patients.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Microspheres
poly-(d,l-lactide-co-glycolide)

Solvent
Polysorbate 20
Carmellose sodium
Disodium hydrogen phosphate dihydrate
Citric acid anhydrous
Sodium chloride
Sodium hydroxide
Water for injection

6.2 Incompatibilities

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

6.3 Shelf life

The shelf-life expiry date of this product shall be the date shown on the container and outer packaging of the product on the market in the country of origin.

After reconstitution: Chemical and physical in-use stability has been demonstrated for 24 hours at 25°C.

From a microbiological point of view, the product should be used immediately. If not used immediately, in-use storage times and conditions prior to use are the responsibility of the user and would normally not be longer than 6 hours at 25° C, unless reconstitution has taken place in controlled and validated aseptic conditions.

6.4 Special precautions for storage

The entire dose pack should be stored in the refrigerator (2-8°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.
Store in the original package.

For storage conditions of the reconstituted medicinal product, see section 6.3.

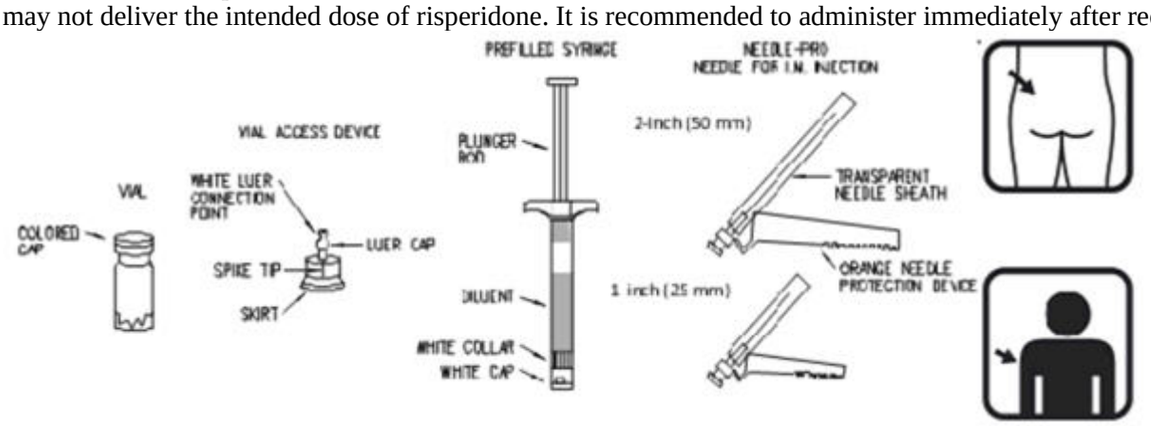
6.5 Nature and contents of container

One vial containing RISPERDAL CONSTA extended release microspheres
One prefilled syringe containing 2 ml solvent for RISPERDAL CONSTA
One Alaris SmartSite Needle-Free Vial Access Device for reconstitution
Two Needle-Pro needles for intramuscular injection (a 21G UTW 1-inch (0.8 x 25 mm) safety needle with needle protection device for deltoid administration, and a 20G TW 2-inch (0.9 x 50 mm) safety needle with needle protection device for gluteal administration).

6.6 Special precautions for disposal and other handling

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

RISPERDAL CONSTA extended release microspheres in the vial must be reconstituted **only** in the solvent in the syringe supplied in the dose pack, and must be administered with **only** the appropriate needle supplied in the dose pack for gluteal (2-inch (50 mm) needle) or deltoid (1-inch (25 mm) needle) administration. Do not substitute any components in the dose pack. To assure that the intended dose of risperidone is delivered, the full contents from the vial must be administered. Administration of partial contents may not deliver the intended dose of risperidone. It is recommended to administer immediately after reconstitution.

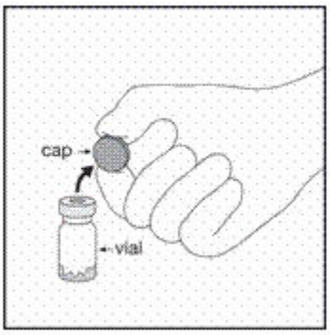


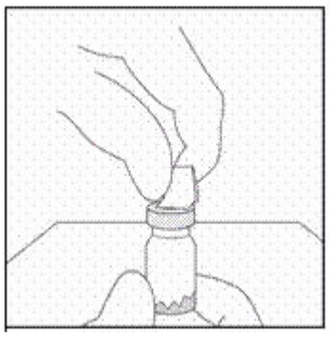
Remove the dose pack of RISPERDAL CONSTA from the refrigerator and allow it to come to room temperature for approximately 30 minutes prior to reconstitution.

Contents of the dose pack:

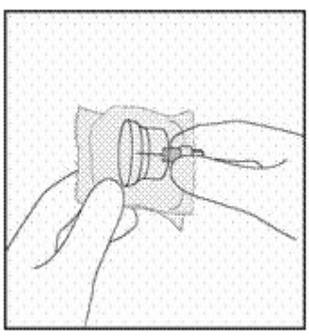
- One vial containing RISPERDAL CONSTA extended release microspheres
- One Alaris SmartSite needle-free vial access device for reconstitution
- One prefilled syringe containing the solvent for RISPERDAL CONSTA
- Two needles for intramuscular injection (a 21G UTW 1-inch (0.8 mm x 25 mm) safety needle with Needle-Pro safety device for deltoid administration and a 20G TW 2-inch (0.9 mm x 50 mm) safety needle with Needle-Pro safety device for gluteal administration)

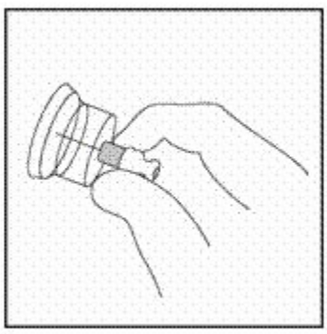
1. Flip off the plastic coloured cap from the vial. Do not remove the grey rubber stopper. Wipe the top of the grey rubber stopper with an alcohol wipe and allow to dry.





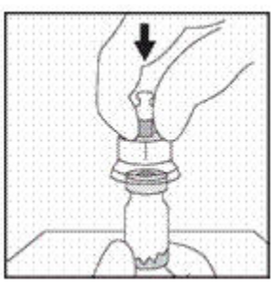
2. Peel back the blister pouch and remove the SmartSite® Needle-Free Vial Access Device by holding between the white luer cap and the skirt.
Do not touch the spike tip of the access device at any time.

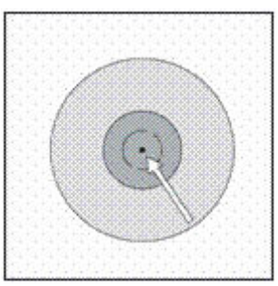




3. It is very important that the SmartSite® Needle-Free Vial Access Device be placed on the vial correctly or the diluent could leak upon transfer to the vial.

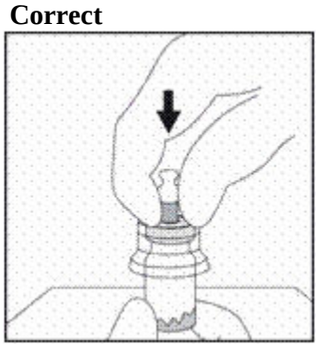
Place the vial on a hard surface. Hold the base of the vial. Orient the SmartSite® Needle-Free Vial Access Device vertically over the vial so that the spike tip is at the center of the vial's rubber stopper.



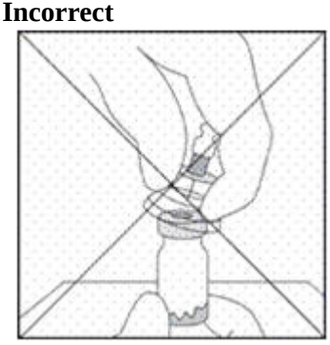


With a straight downward push, press the spike tip of the SmartSite® Needle-Free Vial Access Device through the center of the vial's rubber stopper until the device securely snaps onto the vial top.

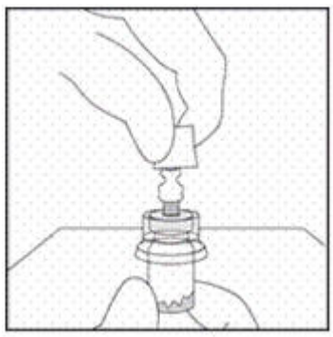
Correct



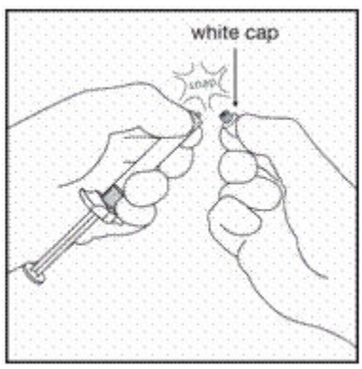
Incorrect



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



5. The prefilled syringe has a white tip consisting of 2 parts: a white collar and a smooth white cap. To open the syringe, hold the syringe by the white collar and **snap** off the smooth white cap **(DO NOT TWIST OFF THE WHITE CAP)**. Remove the white cap together with the rubber tip cap inside.

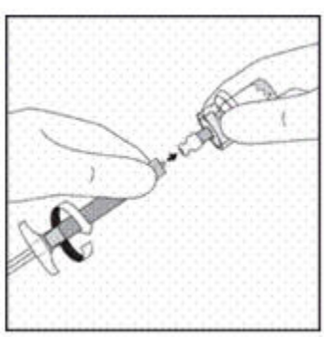


For all syringe assembly steps, hold the syringe only by the white collar located at the tip of the syringe. **Holding the white collar will help to prevent the white collar from getting detached and ensure a good connection to the syringe.** Be careful not to overtighten components when assembling. Overtightening connections may cause syringe component parts to loosen from the syringe body.

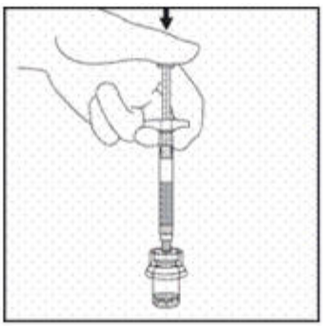
6. While holding the **white collar** of the syringe, insert and **press** the syringe tip into the blue circle of the SmartSite® Needle-Free Vial Access Deviceand **twist** in a clockwise motion to secure the connection of the syringe to the SmartSite® Needle-Free Vial Access Device (avoid over tightening).

Hold the skirt of the vial access device during attachment to prevent it from spinning.

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

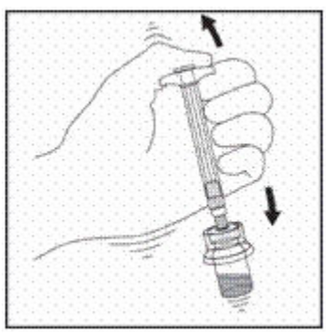


7. Inject the entire contents of the syringe containing the solvent into the vial.



8. Shake the vial vigorously while holding the plunger rod down with the thumb for a minimum of 10 seconds to ensure a homogeneous suspension.

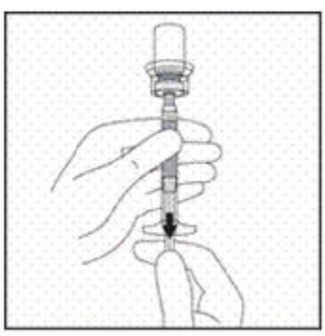
When properly mixed, the suspension appears uniform, thick, and milky in colour. The microspheres will be visible in liquid, but no dry microspheres remain.



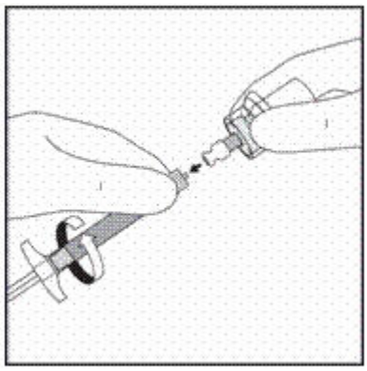
DO NOT STORE THE VIAL AFTER RECONSTITUTION OR THE SUSPENSION MAY SETTLE.

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

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



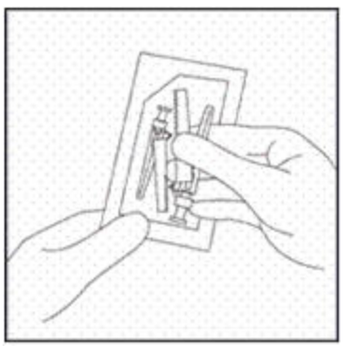
10. While holding the **white collar** of the syringe, unscrew the syringe from the SmartSite® Needle-Free Vial Access Device. Discard both the vial and vial access device appropriately.



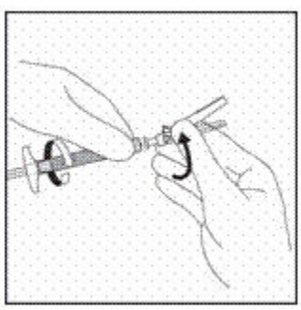
11. Open the needle pack and select the appropriate needle provided with the kit. Do NOT touch the connection part of the needle, only touch the transparent sheath of the needle:

For GLUTEAL injection, select the **20G** TW **2-inch** (0.9 mm x 50 mm) needle (longer needle with **yellow** coloured hub).

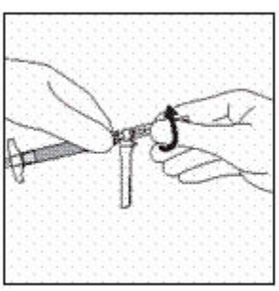
For DELTOID injection, select the **21G** UTW **1-inch** (0.8 mm x 25 mm) needle (shorter needle with **green** coloured hub).



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

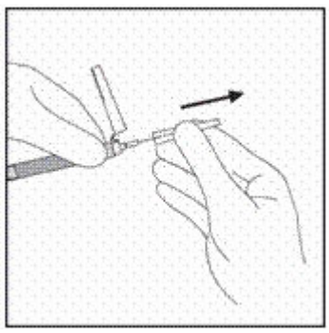


13. While continuing to hold the white collar of the syringe, grasp the transparent needle sheath and seat the needle firmly on the orange Needle-Pro safety device with a push and a clockwise twist. **Seating the needle will help ensure a secure connection between the needle and the orange Needle-Pro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



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

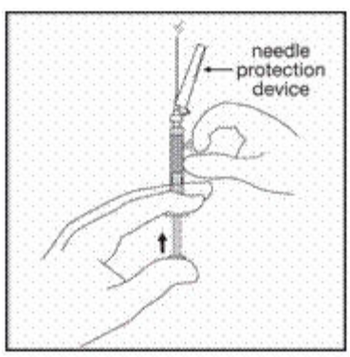
15. While holding the **white collar** of the syringe, pull the transparent needle sheath straight away from the needle. DO NOT TWIST the sheath as the luer connections may be loosened.



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

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

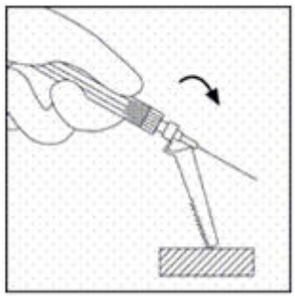
DO NOT ADMINISTER INTRAVENOUSLY.

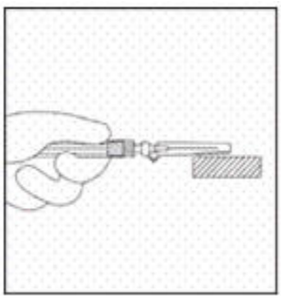


WARNING: To avoid a needle stick injury with a contaminated needle:

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

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





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

Any unused product or waste material should be disposed of in accordance with local requirements.

7 PARALLEL PRODUCT AUTHORISATION HOLDER

Clear Pharmacy
157-173 Roden Street
Belfast BT12 5QA
United Kingdom

8 PARALLEL PRODUCT AUTHORISATION NUMBER

PPA1596/53/2

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 20th January 2012

10 DATE OF REVISION OF THE TEXT

July 2012